APPENDIXES

Appendix A: Peer Reviewers and Acknowledgments

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Appendix B: Search Strings

#2	Search ("Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH])	82356
#3	Search ("Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]) Limits: All Adult: 19+ years, English, Publication Date from 1990, Humans	16462
#5	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	190820
#6	Search #3 AND #5	686
#7	Search #3 AND #5 Limits: Editorial, Letter, Practice Guideline	18
#8	Search #6 NOT #7	668
#18	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	28712
#28	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin"[Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	8701
#29	Search #3 AND #18	1365
#30	Search #3 AND #28	777
#31	Search #3 AND #18 Limits: Editorial, Letter, Practice Guideline	237
#32	Search #29 NOT #31	1128
#33	Search #3 AND #28 Limits: Editorial, Letter, Practice Guideline	178
#34	Search #30 NOT #33	599
#35	Search #8 OR #30 OR #34	1405

2 were discarded as clearly out of scope, so PUBMED = 1403
Cochrane Reviews = 84 = 24 New, unduplicated
EMBASE =1808 = 469 New, unduplicated
Unduplicated = 1986

Appendix C: Studies in an Included Meta-Analysis

1. Abe T, Takeuchi T, Miyasaka N, Hashimoto H, Kondo H, Ichikawa Y, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol 2006;33(1):37-44.

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Appendix D: Excluded Studies

Not Published in English

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Wrong Outcome

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Drug Not Included

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Appendix E: Evidence Tables

Abbreviations used in the evidence tables

ACR	American College of Rheumatology
ADA	adalimumab
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
AIMS	Arthritis Impact Measurement Scales
ANA	anakinra
ARA	American Rheumatism Association criteria (pre-1987)
AS	ankylosing spondylitis
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)
AUC	area under the curve
BUD	budesonide
Ccs	corticosteroids
CFS	chronic fatigue syndrome
CHF	coronary heart failure
Cm	centimeters
Combo	combination therapy
CI	confidence interval
CHD	coronary heart disease
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CVD	cardiovascular disease
CXT	cyclophosamide
CYP	cyclosporine
Ds	days
DM	diabetes mellitus
DAS	Disease Activity Score
DMARD	disease modifying antirheumatic drug
D-HAQ	Dutch version of the Health Assessment Questionnaire (HAQ)
EQ-5D–	Quality of Life Questionnaire
ESR	erythrocyte sedimentation rate
ETA	etanercept
EULAR	European League against Rheumatism
EuroQol EQ-5D	European Quality of Life Questionnaire
EuroQOL VAS	European Quality of Life Visual Analogue Scale
GI	gastrointestinal
HAQ	Health Assessment Questionnaire
HAQ-DI	Disability Index of the Heath Assessment Questionnaire (HAQ)
HIV	Human immunodeficiency virus
HLA-DR4	Human immune-response, D-related antigen encoded by the D locus on chromosome 6
HR	hazard ratio
HRQOL	health related quality of life
ICD	International Classification of Diseases

INF	infliximab
ISRs	injection site reactions
ITT	intention to treat
JRA	juvenile rheumatoid arthritis
HCQ	hydroxychloroquine
JSN	joint space narrowing
LEF	leflunomide
MTX	methotrexate
Mg	milligrams
mSharp Scale	Modified Sharp Method for Scoring Radiographs
mos	months
MHAQ	Modified Health Assessment Questionnaire
NSAIDs	non-steroidal anti-inflammatory drugs
NSFHS	National Survey of Functional Health Status
NA	not applicable
NMSC	non-melanoma skin cancer
NR	not reported
NS	not significant
NYHA	New York Heart Association
OA	osteoarthritis
OR	odds ratio
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PASI	Psoriasis Area and Severity Index
PNL	prednisolone
PRED	prednisone
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Scale
Pt	patient
PY	person-year
QOL	quality of life
RCT	randomized controlled trial
RAI	Ritchie Articular Index
RA	rheumatoid arthritis
RDS	radiological damage score
RF	rheumatoid factor
RIT	rituximab
RR	risk ratio
SAEs	serious adverse events
SAARDs	slow-acting anti-rheumatic drugs
SCC	squamous cell carcinoma
SD	standard deviation
SF-36	Medical Outcomes Study Short Form 36 Health Survey
SJC	swollen joint count
SHS	Sharp/van der Heijde Method (SHS) for Scoring Radiographs
SIR	standardized incidence ratio
SLE	Systemic Lupus Erythematosus

SMR	standardized morbidity ratio
SSZ	sulfasalazine
SSTG	South Swedish Arthritis Treatment Group
TB	Tuberculosis
TIM	targeted immune modulator
TJC	tender joint count
TNF	tumor necrosis factor
Txt	treatment
URTI	upper respiratory tract infection
UTI	urinary tract infection
vs.	versus
yrs	years
w/	with
w/in	with in
w/o	with out

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study **Country, Setting:** US, clinics **Funding:** Immunex **Research Objective:** To compare ETA and MTX in pts with early RA **Study Design:** RCT **Overall N:** 632 (468 extension) **Study Duration:** 12 mos (1 year open label extension; 2 more years, total of 5 yrs)	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: < 3 yrs • Positive serum test for RF or at least 3 bone erosions evident on radiographs of hands, wrists, or feet • At least 10 swollen joints and at least 12 tender or painful joints • ESR ≥ 28 mm per hour • Serum CRP concentration of at least 2.0 mg per deciliter • Morning stiffness that lasted at least 45 minutes • Stable doses of NSAIDS and PRE allowed **Exclusion Criteria:** • Prior txt with MTX • No other important concurrent illnesses	**Interventions, dose:** **D1:** MTX (19 mg/wk) **D2:** ETA (10 mg twice wkly) **D3:** ETA (25 mg twice wkly) **N:** **D1:** 49 **D2:** 50 **D3:** 51 **Mean age, yrs:** **D1:** 49 **D2:** 50 **D3:** 51 **Sex, % female:** **D1:** 75 **D2:** 75 **D3:** 74 **Race, % white:** **D1:** 88 **D2:** 84 **D3:** 86	**Mean disease duration, yrs:** **D1:** 12 mos **D2:** 11 mos **D3:** 12 mos **TJC, mean:** **D1:** 30 (16.1) **D2:** 31 (15.5) **D3:** 31 (15.8) **SJC, mean:** **D1:** 24 (11.9) **D2:** 24 (11.7) **D3:** 24 (11.9) **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 41 **D2:** 42 **D3:** 39 **MTX naive, %:** **D1:** 100 **D2:** 100 **D3:** 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** **D1:** 100 **D2:** 100 **D3:** 100 **Baseline DAS, mean:** NR	**First 12 weeks** Mean changes in SF-36, HAQ, and ASHI significantly better in with ETA vs. MTX ($P < 0.0001$) **16 to 52 weeks** No significant difference in SF-36, HAQ, and ASHI scores between groups **At 6 months** Significantly more pts on ETA (25 mg) than on MTX achieved ACR50 and ACR70 responses (data NR, $P < 0.05$) **At 12 months** **ACR 20 response rates, %:** **D1**: 65 **D3**: 72 *(P* = 0.16) **Mean increase in Sharp score** **D1**: 1.00 **D3**: 1.59 *(P* = 0.11) **Erosion score change** **D1**: 1.03 **D3**: 0.47 *(P* = 0.002) Despite improvement, QoL measures remained below general population ($P < 0.0001$); at start QoL measures were significantly below that of general population ($P < 0.0001$) **24 month open-label extension**:	**At year 2** **SAEs:** 20.6 **Cardiovascular Events:** 1.8 MI **Malignancies:** 3% overall Total events: 18 Breast: 3 Prostate: 3 Colon: 3 Lung: 12 Malignant melanoma: l2 Leukemia: 1 Kidney: 1 Hodgkins: 1 Adenocarcinoma: 1 **URTI:** Pnuemonia 2 Overall SAE rate of 0.093 events per pt-year comparable to rate observed in first year of efficacy study, events per pt-year MTX: 0.109 ETA: 0.091	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study (continued)				**ACR20,%** **D1:** 59 **D3:** 72 (*P* = 0.005); **ACR50, %** **D1:** 49 **D3:** 42 **ACR 70,%** **D1:** 29 **D2:** 24 **HAQ improvement of at least 0.5 units, %:** **D1:** 55 **D2:** 37 (*P* < 0.001) **Total modified Sharp score change** **D1**: 1.3 **D3**: 3.2 *(P* = 0.001) **Erosion score change** **D1**: 0.7 **D3**: 1.9 *(P* = 0.001)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study **Country, Setting:** Netherlands and Belgium, multicenter **Funding:** Netherland **Research Objective:** Comparing efficacy and radiographic outcomes of combination of SSZ, MTX and PNL with SSZ alone **Study Design:** RCT **Overall N:** 155 (148) **Study Duration:** 56 wks; (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 69 • Diagnosed with RA according to ACR criteria • Duration of condition < 2 yrs • NSAID txt at least 3 mos, 6 or more active inflamed joints AND presence of 2 or more (9 or more tender joints, morning stiffness 45 min or more, EST of 28 or more in first hour **Exclusion Criteria:** • Pregnant or lactating: adequate contraception • Prior txt with: DMARDS except HCQ or steroids • Past TB • Impaired renal or hepatic system serious comorbidity surgery in past 3 mos • Unable to comply with protocol • Allergy to study med • Alcohol or substance abuse	**Interventions, dose:** **D1:** Combined txt (SSZ, MTX, PNL) **D2:** SSZ Only SSZ: 2g/d MTX: 7.5 mg/wk, weaned after 40 wks PNL: 60 mg/d wk 1 40 mg/d wk 2 25 mg/d wk 3 20 mg/d wk 4 15 mg/d wk 5 10 mg/d wk 6 then 7.5 mg/d until wk 28 then weaned off **N:** **D1:** 76 **D2:** 79 **Mean age, yrs:** NR **Sex, % female:** **D1:** 66% **D2:** 52% **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 4 mos **D2:** 4 mos **TJC, mean:** NR **SJC, mean:** NR **Antimalarial use (%):** **D1:** 21 **D2:** 24 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Erosions on hand or foot xrays, %:** **D1:** 74 **D2:** 79	**At week 28** **Mean pooled index** **D1:** - 1.4 (95% CI, 1.2-1.6) **D2:** - 0.8 (95% CI, 0.6-1.0) (*P* < 0.0001) **ACR20, %:** **D1:** 72 **D2:** 49 (*P* = 0.006) **ACR50, %:** **D1:** 49 **D2:** 27 (*P* = 0.007) **DAS median change:** **D1:** -2.1 (SD 1.2) **D2:** -1.3 (SD 1.2) (*P* < 0.0001) **HAQ mean change:** **D1:** -1.1 (SD 0.8) **D2:** -0.6 (SD 0.6) (*P* < 0.0001) **Sharp mean change**: **D1:** 1 **D2:** 4 (*P* < 0.001) **At week 56** **Mean pooled index:** **D1:** 1.1 (SD 0.8) **D2:** 0.9 (SD 0.8) (*P* =0.20) **DAS median change:** **D1:** 1.4 (SD 1.2) **D2:** 1.3 (SD 1.4) (*P* = 0.78) **HAQ mean change:** **D1:** 0.8 (SD 0.8) **D2:** 0.6 (SD 0.7) (*P* < 0.06)	**Overall:** **D1:** 72.3 **D2:** 62.0 **SAEs:** **D1:** 2.6 **D2:** 7.6 **Infections:** **D1:** 15.8 **D2:** 7.6 **Cardiovascular Events:** **D1:** 7.9 **D2:** 5.1 **Hepatotoxicity:** **D1:** 2.6 **D2:** 0	**Overall Attrition Rate, %:** 3.2 **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **At week 80** **Sharp mean change**: **D1:** 4 **D2:** 12 (*P* < 0.01) **Five yr follow up** **Sharp score mean change:** **D1:** 5.6 (95% CI, 4.3, 7.1) (*P* = 0.001) **D2:** 8.6 (95%CI, 6.2-11) (*P* = 0.001) **Time averaged DAS28, points/yr**: **D1:** -0.07 **D2:** **-0.17**		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study **Country, Setting:** Multinational (Europe, North America, Australia), multicenter (133) **Funding:** Abbott Laboratories **Research Objective:** To compare efficacy and safety of ADA + MTX vs. MTX or ADA in pts with early, aggressive RA (RA) who had not previously received MTX txt **Study Design:** RCT **Overall N:** 799 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: 3 yrs or less • MTX naive pts • > 8 swollen joints, > 10 tender joints, and an erythrocyte sedimentation rate of > 28 • Folic acid only other med allowed **Exclusion Criteria:** • Prior txt with: MTX, cyclophosphamide, cyclosporine, azathioprine	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ADA (40 mg/biwkly) **D3:** ADA (40 mg/biwkly) + MTX (20 mg/wk) **N:** **D1:** 257 **D2:** 274 **D3:** 268 **Mean age, yrs:** **D1:** 52 **D2:** 52.1 **D3:** 51.9 **Sex, % female:** **D1:** 73.9 **D2:** 77.4 **D3:** 72 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** .8 **D2:** .7 **D3:** .7 **TJC, mean:** **D1:** 32.3 **D2:** 31.8 **D3:** 30.7 **SJC, mean:** **D1:** 22.1 **D2:** 21.8 **D3:** 21.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 35.4 **D2:** 36.5 **D3:** 35.8 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.3 **D2:** 6.4 **D3:** 6.3 **HAQ:** **D1:** 1.5 **D2:** 1.6 **D3:** 1.5 **Erosion score:** **D1:** 13.6 **D2:** 11.3 **D3:** 11.0	**At 6 months** **Radiographic progression; change in Sharp scores:** **D1:** 3.5 **D2:** 2.1 (*P* < 0.001) **At 1 yr** **Radiographic progression; change in Sharp scores:** **D1:** 5.7 **D2:** 3.0 (*P* < 0.001) **HAQ DI improvement, mean units +/- sd:** **D1**: -0.8 +/- 0.7 **D2:** -0.8 +/- 0.6 **D3**: -1.1 +/- 0.6 **D2** vs. **D1**, *P* = NR **D3** vs. **D1**: *P* < 0.001 **D3** vs. **D2**: *P* = 0.002) **At 2 yrs** **ACR50 response, %:** **D1:** 43 **D2:** 37 **D3:** 59 **D3** vs. **D2** or **D1**: *P* < 0.001 **D1** vs. **D2**: *P*= NS **Clinical remission, %:** **D1:** 25 **D2:** 25 **D3:** 49 (both *P* < 0.001) **Radiographic progression; change in Sharp scores:** **D1:** 10.4 **D2:** 5.5 (*P* < 0.001)	**SAEs:** **D1:** 18.5 **D2:** 21.1 **D3:** 15.9 **Infections:** **D1:** 123 **D2:** 110 **D3:** 119 **Serious Infections:** **D1:** 2.9 **D2:** 0.7 **D3:** 1.6 **Malignancies:** **D1:** 0.4 **D2:** 0.9 **D3:** 0.9 **Withdrawal because of adverse events:** **D1:** 7% **D2:** 10% **D3:** 12%	**Overall Attrition Rate, %:** 32% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study	Inclusion and	Characteristics	Baseline Disease	Health Outcomes	Adverse	Analysis and

Characteristics	Exclusion Criteria	and Interventions	and Treatment Characteristics		Events, %	Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study				**Withdrawal because of lack of efficacy, %:** **D1:** 18 **D2:** 19 **D3:** 4.9 **HAQ DI improvement, mean units +/- sd:** **D1**: -0.9 +/- 0.6 **D2:** -0.9 +/- 0.7 **D3**: -1.0 +/- 0.7 **D2** vs. **D1**, *P* = NR **D3** vs. **D1;** *P* < 0.05 **D3** vs. **D2**; *P* = 0.058 **% with HAQ DI score of zero:** **D1**: 19 **D2:** 19 **D3**: 33 **D3** vs. **D2**, *P* < 0.001 **D3** vs. **D1**: *P* < 0.001 **% with HAQ DI improvement of ≥ 0.22 units from baseline:** **D1**: 63 **D2:** 58 **D3**: 72 **D3** vs. **D2**, *P* < 0.05 **D3** vs. **D1**: *P* < 0.05		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 **Country, Setting:** Scotland, 8 NHS sites **Funding:** Wyeth and Pharmacia - drugs Arthritis Research Campaign **Research Objective:** If a combination of SSZ and MTX is superior to either alone in RA pts with supoptimal response to 6 mos of SSZ **Study Design:** RCT **Overall N:** 165 **Study Duration:** Phase I: 6 mos; Phase 2: 12 additional mos for those with DAS > 2.4 after 6 mos	**Inclusion Criteria:** • Age: 18 to 80 • Duration of condition: < 10 yrs • Active disease defined by DAS > 2.4 after 6 mos SSZ txt were eligble for phase II • NSAIDs and other medications were continued • Intra-articular or intramuscular corticosteroid was permitted but not within 1 mo of 6, 12, & 18 mo assessments **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: MTX or SSZ • Impaired renal or hepatic system: creatinine > 150 mmol/dl, ALT, aspertate aminotransferase > 80 IU/l, alkaline phosphatase > 700 IU/l, gamma GT x3 • Other: abnormal white cell count (< 4 x 10*9/l)	**Interventions, dose:** **D1:** SSZ + MTX **D2:** SSZ + placebo **D3:** MTX + placebo Phase I MTX: 7.5 mg/w (3 x 2.5 mg) increasing by 2.5 mg/mo until max of 25 mg or toxicity SSZ: enteric coated 500 mg/d increased by 500 mg/wkly until 40 mg/kg per d to a max of 4g/d for initial 6 mos Placebo: Folic Acid 5 mg/wk given 3 days after MTX and MTX + placebo **N:** **D1:** 56 **D2:** 55 **D3:** 54 Overall: 687 **Mean age, yrs:** **D1:** 56 **D2:** 55 **D3:** 53 Overall: 55 **Sex, % female:** **D1:** 75 **D2:** 75 **D3:** 79 Overall: 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 1.9 **D2:** 1.6 **D3:** 1.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** All **Txt resistant, %:** All **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 3.63 **D2:** 3.67 **D3:** 3.5 **Sharp:** **D1:** 17.0 **D2:** 14.0 **D3:** 12.0	**Median change 18 mos:** **DAS:** **D1:** -0.67 **D2:** -0.30 **D3:** -0.26 (**D1** vs. **D2**; *P* = 0.039) (**D1** vs. **D3**; *P* = 0.023) (**D2** vs. **D3**; *P* = 0.79) **HAQ:** **D1:** -0.50 **D2:** -0.25 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.51) (**D1** vs. **D3**; *P* = 0.57) (**D2** vs. **D3**; *P* = 0.99) **SJC:** **D1:** -3.00 **D2:** -3.00 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.94) (**D1** vs. **D3**; *P* = 0.81) (**D2** vs. **D3**; *P* = 0.74) **ACR20, % :** **D1:** 29 **D2:** 18 (OR 1.25 (95% CI, 0.56-2.79) ; *P* = 0.68) **D3:** 15 (OR 2.01 (95% CI, 0.85-4.76), *P* = 0.14) **ACR50, %:** **D1:** 11 **D2:** 6 (OR 1.43 (95% CI, 0.43-4.81), *P* = 0.76) **D3:** 7 (OR 1.79 (95% CI, 0.49-6.49), *P* = 0.53)	NR	**Overall Attrition Rate, %:** 28.5 • 687 pts entered phase I (6 mos) • At 6 mos, 165 were not eliglbe to enter phase II (discontinued SSZ because of side effects: 19%, did not attend: 3.6%, died: 0.4%) • Another 191 were not randomized because DAS score was < 2.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **D2:** 2 (OR 1.50 (95% CI, 0.24-9.34), *P* = 1.00) **D3:** 2 (OR 3.00 (95% CI, 0.30-29.78), *P* = 0.62)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 **Country, Setting:** Europe, multicenter **Funding:** Wyeth **Research Objective:** To compare efficacy and safety of ETA and SSZ, alone and in combination, in pts with active RA despite SSZ txt **Study Design:** RCT **Overall N:** 260 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • Diagnosed according to ACR criteria; • Functional class of: I-III • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Duration of condition < 20 yrs • Stable doses of oral corticosteroids (10 mg/d of PRE or equivalent), one NSAID, simple analgesics with no anti-inflammatory action or daily doses of aspirin (300 mg) **Exclusion Criteria:** • Prior txt with: (1) ETA or other TNF antagonists or (2) received a DMARD other than SSZ within 3 mos. Or any biologic or cyclophosphamide within 6 mos, corticosteroids within 4 wks	**Interventions, dose:** **D1:** SSZ (2,2.5, or 3 g /d) + placebo **D2:** ETA (25 mg SC twice wkly) + placebo **D3:** ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) **N:** **D1:** 50 **D2:** 103 **D3:** 101 Overall: 254 **Mean age, yrs:** **D1:** 53.3 **D2:** 51.3 **D3:** 50.6 Overall: 51.4 **Sex, % female:** **D1:** 82.0 **D2:** 78.6 **D3:** 80.2 Overall: 79.9 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 5.6 (sd 4.4) **D2:** 7.1 (sd 5.2) **D3:** 6.5 (sd 5.1) **TJC, mean:** **D1:** 14.0 **D2:** 14.7 **D3:** 14.1 **SJC, mean:** **D1:** 11.1 **D2:** 10.1 **D3:** 10.4 **DMARD use, %:** **D1:** 58.0 **D2:** 69.9 **D3:** 58.4 **Corticosteroid use, %** **D1:** 40.0 **D2:** 59.2 **D3:** 44.6 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D1:** 28.0 **D2:** 73.8 **D3:** 74.0 ($P < 0.01$) **ACR50, %:** **D1:** 14.0 **D2:** 46.6 **D3:** 52.0 ($P < 0.01$) **ACR70, %:** **D1:** 2.0 **D2:** 21.4 **D3:** 25.0 ($P < 0.01$) In groups receiving ETA, significant differences in ACR core components were observed by wk 2 compared with those receiving SSZ alone ($P < 0.01$) **DAS improvement, %:** **D1:** 19.6 **D2:** 48.2 **D3:** 49.7 ($P < 0.01$) **Mean HAQ improvement, %:** **D1:** 9.2 **D2:** 35.3 **D3:** 40.2 ($P < 0.01$)	**Infections:** **D1:** 13 **D2:** 47 **D3:** 31 **Infusion or injection reaction:** **D1:** 3 **D2:** 38 **D3:** 21 **Abdominal Pain:** **D1:** 0 **D2:** 7 **D3:** 8 **Headache:** **D1:** 4 **D2:** 5 **D3:** 15 **Nausea:** **D1:** 3 **D2:** 3 **D3:** 12 **URTI:** **D1:** 5 **D2:** 10 **D3:** 11	**Overall Attrition Rate, %:** 13 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **Country, Setting:** Finland, France, Germany (France only for 5 yr), multicenter **Funding:** Pharmacia Upjohn **Research Objective:** Clinical benefit of MTX + SSZ compared to either drug alone early, active RA pts fulfilling some criteria of poor potential long term outcome **Study Design:** RCT **Overall N:** 209 (146) **Study Duration:** 52 wks (5 yrs)	**Inclusion Criteria:** • Diagnosed according to ACR criteria • Duration < 1 yr • Presence of active disease as defined by DAS ≥ 3 (calculation based on Ritchie articular index, 44 SJC, and ESR) and presence of RF and/or HLA DR 1/4 • Concommitant drugs allowed were analgesics and NSAIDS **Exclusion Criteria:** • Prior txt with steroids, DMARDS, or any drugs to treat RA other than analgesic or NSAIDS • Pts with contraindications to use of SSZ or MTX	**Interventions, dose:** **D1:** SSZ + placebo **D2:** MTX + placebo **D3:** SSZ + MTX MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate SSZ: increased to 2 grams daily by d #9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate Other?: combo MTX + SSZ **N:** **D1:** 68 **D2:** 69 **D3:** 68 **Mean age, yrs:** **D1:** 52 **D2:** 50 **D3:** 52 **Sex, % female:** **D1:** 71 **D2:** 74 **D3:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 2.9 mos since diagnosis, 10.8 since onset **D2:** 2.3 mos from diagnosis, 18.4 from onset **D3:** 3.4 mos from diagnosis, 10.6 from onset **TJC, mean:** NR **SJC, mean:** **D1:** 10.5 **D2:** 9.4 **D3:** 9.4 **DMARD use, %:** All groups: 0 **Corticosteroid use, %** All groups: 0 MTX naive, %: All groups: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** All groups: 100	**DAS change:** **D1:** -1.15 **D2:** -0.87 **D3:** -1.26 (*P* = 0.019 from inter-group comparisons using analysis of variance) **RAI changes:** **D1:** -7.1 **D2:** -4.2 **D3:** -9.4 (*P* = 0.001) **ACR response, %:** **D1:** 59 **D2:** 59 **D3:** 65 (*P* = NR) **At 5 years** Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared to monotherapy with either drug used alone **Mean DAS:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9)	**Overall:** **D1:** 75 **D2:** 75 **D3:** 91 **Abdominal Pain:** **D1:** 9 **D2:** 6 **D3:** 13 **Dizziness:** **D1:** 6 **D2:** 1 **D3:** 3 **Headache:** **D1:** 9 **D2:** 4 **D3:** 12 **Nausea:** **D1:** 32 **D2:** 23 **D3:** 49	**Overall Attrition Rate, %:** 27% (28.8) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 **Country, Setting:** Multinational, multicenter (26 rheumatology centers) **Funding:** Roche **Research Objective:** To confirm role of B cells in RA by evaluating effect of RIT in pts with active RA according to ACR and EULAR criteria **Study Design:** RCT **Overall N:** 161 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 21 • Diagnosed according to 1987 ACR criteria • Failed previous MTX treatment • > MTX 10 mg/wk and active disease • RF-positive • NSAIDS at stable doses or Css at doses < 12.5 mg per d of PNL • All received 17-d txt with Css and a 10 mg dose of leucovorin **Exclusion Criteria:** • Autoimmune disorder other than RA (except Srjogen's) • Functional class IV • Active rheumatoid vasculitis • Systemic diseases associated with arthritis • CFS • Serious, uncontrolled diseases • Active infection	**Interventions, dose:** **D1:** MTX (≥10 mg/wk) **D2:** RIT (1000 mg on ds 1 and 15) **D3:** RIT (1000 mg on ds 1 and 15) + CYP (750 mg d 3,17) **D4:** RIT (1000 mg on ds 1 and 15) + MTX (≥10 mg/wk) **N:** **D1:** 40 **D2:** 40 **D3:** 41 **D4:** 40 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 53 **D4:** 54 **Sex, % female:** **D1:** 80 **D2:** 73 **D3:** 83 **D4:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 9 **D3:** 10 **D4:** 12 **TJC, mean:** **D1:** 32 **D2:** 34 **D3:** 33 **D4:** 32 **SJC, mean:** **D1:** 19 **D2:** 21 **D3:** 19 **D4:** 23 **DMARD use (#):** **D1:** 2.6+/- 1.3 **D2:** 2.5+/-1.6 **D3:** 2.6+/-1.4 **D4:** 2.5+/-1.4 **Corticosteroid use, %** NR **MTX naive, %:** 0 **Txt resistant, %:** 100 **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D2:** 65 **D4:** 73 (*P* = NR) **ACR50, %:** **D2:** 33 **D4:** 43 (*P* = NR) **ACR70, %:** **D2:** 15 **D4:** 23 (*P* = NR) **Rates of moderate or good EULAR responses, %:** **D2:** 85 **D4:** 83 (*P* = NR) **DAS:** **D2:** -2.2 **D4:** -2.6 **At 48 weeks** **ACR20, %:** **D2:** 33 **D4:** 65 (*P* = NR) **ACR50, %:** **D2:** 15 **D4:** 35 (*P* = NR) **ACR70, %:** **D2:** 10% **D4:** 15% (*P* = NR)	**Overall:** **D1:** 80 **D2:** 80 **D3:** 73 **D4:** 85 **SAEs:** **D1:** 8.0 **D2:** 5.0 **D3:** 4.9 **D4:** 8.0 **Infusion or injection reaction:** **D1:** 30 **D2:** 45 **D3:** 32 **D4:** 33 **Nausea:** **D1:** 3 **D2:** 5 **D3:** 10 **D4:** 0 **URTI:** **D1:** 15 **D2:** 10 **D3:** 5 **D4:** 10	**Overall Attrition Rate, %:** at 24 wks 6.2% at 48 wks 37.8% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 (continued)	• History of recurrent infection or recurrent bacterial infections with encapsulated organisms • Primary of secondary immunodeficiency • History of cancer		**Baseline DAS, mean:** **D1:** 6.9 **D2:** 6.8 **D3:** 6.9 **D4:** 6.8			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 **Country, Setting:** Multinational, 117 centers **Funding:** NR **Research Objective:** To compare both short and long-term (up to 2 yr) clinical efficacy and safety of LEF and MTX for txt of RA **Study Design:** RCT **Overall N:** 999 **Study Duration:** 1 yr, optional second yr	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria: Active Disease • Previous use of DMARDs: only if discontinued 28 ds before trial • Duration of condition: for at least 4 mos, but no longer than 10 yrs • NSAIDs and steroids were allowed provided a stable dose of NSAIDs or steroid (≤ 10 mg/d) PNL for at least 28 ds prior to study entry • Women of childbearing age were required to use adequate contraception **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: Intra-articular corticosteriod injections w/in 6 wks of efficacy assessment	**Interventions, dose:** **D1:** LEF Yr 1 **D2:** MTX Yr 1 **D3:** LEF Yr 2 **D4:** MTX Yr 2 MTX: 7.5 to 15 mg/wk LEF: loading dose of 100 mg/d for 3 ds, followed by maintenance dose 20/ mg/d **N:** **D1:** 501 **D2:** 498 **D3:** 292 **D4:** 320 **Mean age, yrs:** **D1:** 58.3 **D2:** 57.8 **D3:** 57.7 **D4:** 57.0 **Sex, % female:** **D1:** 70.7 **D2:** 71.3 **D3:** 71.2 **D4:** 71.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.7 **D2:** 3.8 **D3:** 3.5 **D4:** 3.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 66.3 **D2:** 66.9 **D3:** 64.7 **D4:** 66.9 **Corticosteroid use, %** **D1:** 36.3 **D2:** 33.5 **D3:** 14.0 **D4:** 11.3 **MTX naive, %:** NR **DMARD Txt resistant, %:** **D1:** 1.1 **D2:** 1.1 **D3:** 1.0 **D4:** 1.1 **Pts with Early RA (≤ 3 yrs):** NR	**At year 1** **ACR20:** **D1:** 50.5% **D2:** 64.8% ($P < 0.001$) **HAQ improvement:** Minimal quantitative difference between groups, but statistically significant (shown in figure only; $P < 0.05$) **Radiograph change, Larsen Scores:** **D1** and **D2**: 0.03 increase (P =NS, NR) **Primary clinical efficacy endpoints**: **TJC:** **D1:** -8.3 **D2:** - 9.7 **SJC:** **D1:** -6.8 **D2:** -9.0 **Physician global assessment:** **D1:** -0.9 **D2:** -1.2 **Pt global assessment:** **D1:** -0.9 **D2:** -1.2 **At year 2** **ACR20, %:** **D1:** 64.3 **D2:** 71.7 (P = NS, NR)	**SAEs:** **D1:** 7% **D2:** 8% **Headache:** **D1:** 6.2 **D2:** 4.8 **Hepatotoxicity:** **D1:** 5.4 **D2:** 16.3 **D3:** 2.7 **D4:** 5.9 **Nausea:** **D1:** 11.2 **D2:** 15.7 **URTI:** **D1:** 5.2 **D2:** 5.0 **D3:** 4.5 **D4:** 5.6 **Deaths** MTX: 2	**Overall Attrition Rate, %:** • 26.3% (263/999) during yr 1 • Combined 2 yrs, attrition 50.3% (502/999) of those initially starting study at baseline • During yr 2, attrition 18.8% (115/612) of those agreeing to continue study for 2nd yr **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek, 2002 **Country, Setting:** Sweden, primary care clinics, unversity clinic **Funding:** NR **Research Objective:** To assess efficacy and safety of ETA, INF, and LEF in a population-based setting **Study Design:** Nonrandomized open-label trial **Overall N:** 369 (33 pts tried 2 different txts and 1 tried all 3; 404 txts) **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18+ • Previous use of DMARDs: required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX • Diagnosis of RA according to clinical judgment of treating doctor • All pts included were required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX • Pts were selected on basis of current disease activity and/or unacceptable steroid requirement as judged by treating doctor, but had different backgrounds concerning previous txt, concomitant diseases, and functional impairment and disability	**Interventions, dose:** **D1:** ETA (25 mg/twice wkly) **D2:** INF (3 mg/kg or higher) **D3:** LEF (20 mg/d) **N:** **D1:** 166 **D2:** 135 **D3:** 103 **Mean age, yrs:** **D1:** 54 **D2:** 55.4 **D3:** 61.3 **Sex, % female:** **D1:** 78 **D2:** 79 **D3:** 82 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 14.9 **D2:** 14.1 **D3:** 14.9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 100 **D2:** 100 **D3:** 100 **Corticosteroid use, %** **D1:** 83 **D2:** 81 **D3:** 73 **MTX naive, %:** **D1:** 0 **D2:** 0 **D3:** 0 **Txt resistant, %:** **D1:** 100 **D2:** 100 **D3:** 100 **Pts with Early RA (≤3 yrs):** NR	**At 3 months** **ACR20/50:** INF significantly higher than LEF (data NR; $P < 0.01$) ETA higher ACR 20 response rate than INF (data NR; $P < 0.02$) ETA had a significantly higher ACR50 response rate than INF (data NR; $P < 0.05$) **At 6 months** **ACR 20/50:** ETA better than LEF (data NR; $P < 0.01$) ETA higher ACR 20 response rate than INF (data NR; $P < 0.02$) **At 12 months** No significant difference between ETA and INF ETA and INF led to significant reduction in prednisolone use starting at 2 wks No reduction in prednisolone use for LEF	**Infusion reaction:** 3.7% of INF pts experienced an infusion reaction	**Overall Attrition Rate, %:** N/A **ITT Analysis:** No **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek, 2002 (continued)	• Other meds allowed **Exclusion Criteria:** NR		**Baseline DAS, mean:** **D1:** 5.8 **D2:** 5.6 **D3:** 5.4 **HAQ:** **D1:** 1.55 **D2:** 1.47 **D3:** 1.46			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004 **Country, Setting:** US, multicenter, specialty clinic **Funding:** Amgen, Inc., Thousand Oaks, CA **Research Objective:** To determine potential for additive or synergistic effects of combination therapy with selective anti-TNF-alpha agent ETA and anti-IL1 agent AKA **Study Design:** RCT **Overall N:** 242 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • RA according to ACR criteria • Duration of condition: > 6 mos • 6+ swollen joints • 9+ tender/painful joints • At least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of > 1.5 mg/dl, or ESR > 28 mm/hr; and, MTX > 16 wks, stable dose of 10-25 mg/wk > 8 wks; continued txt with stable doses of MTX and other stable medications, such as corticosteroids **Exclusion Criteria:** • Any DMARD other than MTX within past 4 wks • Txt with AKA or any protein-based TNF-alpha inhibitor	**Interventions, dose:** **D1:** ETA (25 mg twice wkly) **D2:** ETA (12.5 mg once wkly) + AKA (100 mg/d) **D3:** ETA (25 mg twice wkly) + AKA (100 mg/d) **N:** **D1:** 80 **D2:** 81 **D3:** 81 **Mean age, yrs:** **D1:** 54.4 **D2:** 53.8 **D3:** 55.7 **Sex, % female:** **D1:** 82.5 **D2:** 71.6 **D3:** 77.8 **Race, % white:** **D1:** 86.3 **D2:** 77.8 **D3:** 75.3	**Mean disease duration, yrs:** **D1:** 9.7 **D2:** 9.5 **D3:** 10.6 **TJC, mean:** **D1:** 31 **D2:** 31 **D3:** 35.9 **SJC, mean:** **D1:** 21.4 **D2:** 19.8 **D3:** 23.4 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 48.8 **D2:** 54.3 **D3:** 44.4 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**At week 24** **ACR20, %:** **D1:** 68 **D2:** 51 **D3:** 62 **D1** vs. **D2** (*P* = 0.037) All others NS **ACR50, %:** **D1:** 41 **D2:** 39 **D3:** 31(*P* = 0.914) OR (ETA + AKA vs. ETA alone) 0.64 (90% CI, 0.37-1.09); sensitivity analysis yielded similar results **ACR70, %:** **D1:** 21 **D2:** 24 **D3:** 14 (*P* = NR) **Sustained ACR20 response:** Between 43% and 54% of subjects in each group (specifics NR) **EULAR response, %:** **D1:** 79 **D2:** 66 **D3:** 73 (*P* = NR) **Mean % reduction in DAS:** **D1:** 39 **D2:** 41 **D3:** 40 (*P* = NR)	**Overall:** **D1:** 90 **D2:** 95.1 **D3:** 93.8 **SAEs:** **D1:** 2.5 **D2:** 4.9 **D3:** 14.8 **Infections:** **D1:** 40 **D2:** 37 **D3:** 46.9 **Serious Infections:** **D1:** 0 **D2:** 3.7 **D3:** 7.4 **Infusion or injection reaction:** **D1:** 40 **D2:** 67.9 **D3:** 70.4 **URTI:** **D1:** 20 **D2:** 11.1 **D3:** 13.6	**Overall Attrition Rate, %:** 15.7 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004 (continued)	• Received any intraarticular or systemic corticosteroid injections within past 4 wks • Recent history of significant infection or other important concurrent illness		**MTX use, %:** Overall: 100 **HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.6			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age > 18 yrs • RA according to ACR criteria • Duration of condition < 2 yrs • Active disease with at least 6 of 66 swollen joints • At least 6 of 68 tender joints • ESR > 28 mm/hr OR global health score greater than or equal to 20mm on 0 to 100 VAS • Concomittant NSAIDS and intraarticular steroids **Exclusion Criteria:** • Pregnant • Prior txt with: DMARDS other than antimalarials • Impaired renal or hepatic system	**Interventions, dose:** **D1:** sequential monotherapy **D2:** step-up combination therapy **D3:** initial combination with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 **Country, Setting:** Netherlands, 1 academic and 6 peripheral clinics **Funding:** Pharmachemie BV; Pharmacia AB **Research Objective:** Compare efficacy and safety of SSZ, MTX, and combination of both in pts with early RA **Study Design:** RCT **Overall N:** 105 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed with RA according to ACR criteria: ACR criteria • RF positive and/or HLA-DR4 positive and/or HLA DR1 positive • Functional class of: DAS ≥ 3.0 • Duration of condition: < 12 mos • Analgesica and NSAIDS allowed **Exclusion Criteria:** • Prior txt with: DMARDS other than analgesics and NSAIDS • Other: contraindications to SSZ or MTX	**Interventions, dose:** **D1:** SSZ (1 g/day; max 3 g/day) **D2:** MTX (7.5 mg/wk; max 15 mg/wk) **D3:** MTX (7.5 mg/wk; max 15 mg/wk) + SSZ (1 g/day; max 3 g/day) **N:** **D1:** 34 **D2:** 35 **D3:** 36 **Mean age, yrs:** **D1:** 56.8 **D2:** 54.9 **D3:** 57.0 **Sex, % female:** **D1:** 61.8 **D2:** 65.7 **D3:** 66.7 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.1 mos **D2:** 3.0 mos **D3:** 2.6 mos **TJC, mean:** **D1:** 20.8 **D2:** 20.6 **D3:** 24.8 **SJC, mean:** **D1:** 17.0 **D2:** 19.9 **D3:** 20.8 **DMARD use, %:** Overall: 0 **Corticosteroid use, %** Overall: 0 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.6 **D2:** 4.7 **D3:** 5.0	No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable **At 52 weeks** **DAS mean change:** **D1:** -1.6 (95% CI, -2.0 to -1.2) **D2:** -1.7 (95% CI, -2.0 to -1.4) **D3:** -1.9 (95% CI, -2.2 to -2.3) **Ritchie mean change:** **D1:** -8.6 (95% CI, -10.7 to -6.5) **D2:** -8.2 (95% CI, -10.1 to -6.4) **D3:** -9.4 (95% CI, -11.1 to -7.7) **Swollen joints mean change**: **D1:** SSZ -7.9 (95% CI, -10.1 to -5.7) **D2:** -10.2 (95% CI, -12.5 to -8.0) **D3:** -11.3 (95% CI, -13.5 to -9.2)	**Overall:** **D1:** 88.2 **D2:** 77.1 **D3:** 88.9 **SAEs:** **D1:** 8.8 **D2:** 0 **D3:** 0 **Abdominal Pain:** **D1:** 26.5 **D2:** 20 **D3:** 36 **Cardiovascular Events (Dyspnea):** **D1:** 5.9 **D2:** 0 **D3:** 5.6 **Dizziness:** **D1:** 17.6 **D2:** 8.6 **D3:** 27.8 **Headache:** **D1:** 17.6 **D2:** 11.4 **D3:** 11.1 **Nausea:** **D1:** 29.4 **D2:** 25.7 **D3:** 63.9 **URTI** **D1:** 17.6 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from baseline:** **D1:** -0.32 (95% CI, -0.53 to -0.10) **D2:** -0.46 (95% CI, -0.68 to -0.25) **D3:** -0.51 (95% CI, -0.76 to -0.26) **Number of pts with a response according to ACR criteria at end of study:** **D1:** 25 **D2:** 25 **D3:** 28 **Number of pts with good response according to EULAR definition:** **D1:** 14 **D2:** 15 **D3:** 14		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Hyrich et al., 2006 **Country, Setting:** Great Britain, multiclinic **Funding:** Schering Plough, Wyeth, Abbott, A mgen British Society for Rheumatology Biologics Register **Research Objective:** Compare outcome at 6 mos in unselected real-world RA pts treated with ETA or INF alone or with MTX or another DMARD **Study Design:** Prospective cohort study	**Inclusion Criteria:** • Age > 16 yrs • Diagnosed with RA according to 1987 ACR criteria; starting either ETA or INF as first biologic drug • Other meds were allowed **Exclusion Criteria:** NR	**Interventions, dose:** **D1:** ETA (25 mg 2x wk) **D2:** ETA + DMARD **D3:** ETA + MTX **D4:** INF (3 mg/kg wks 0,2,6 then every 8wks) **D5:** INF + DMARD **D6:** INF + MTX Some doses NR **N:** **D1:** 763 **D2:** 245 **D3:** 250 **D4:** 128 **D5:** 121 **D6:** 1204 **Mean age, yrs:** **D1:** 58 **D2:** 55 **D3:** 54 **D4:** 59 **D5:** 58 **D6:** 55 **Sex, % female:** **D1:** 80 **D2:** 79 **D3:** 76 **D4:** 79 **D5:** 74 **D6:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 16 **D2:** 15 **D3:** 13 **D4:** 16 **D5:** 14 **D6:** 14 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 54 **D2:** 51 **D3:** 44 **D4:** 69 **D5:** 59 **D6:** 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	**At 6 months** **EULAR response:** **D3** vs. **D1:** (OR 1.98, 95% CI, 1.45-2.71) **D2** vs. **D1** (OR 1.20, 95% CI, 0.89-1.61) **D3** vs **D2** (OR 1.66, 95% CI, 1.14-2.42) A better EULAR response in both MTX (OR 1.35 [95% CI, 0.92-2.00]) and DMARD (OR 1.26 [95% CI, 0.75-2.13]) subgroups as compared with INF monotherapy **DAS28**: **D1:** 4.8 +/-.4 **D2:** 4.6 +/- 1.5 **D3:** 4.3 +/- 1.5 **D4:** 5.0 +/- 1.6 **D5:** 4.9 +/- 1.6 **D6:** 4.6 +/- 1.6	**Adherence:** Drug survival at 6 mos: ETA 20% INF 21% ETA subgroups (22% mono, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy , vs. 22% DMARD co-therapy)	**Overall Attrition Rate, %:** 21 **ITT Analysis:** N/A **Quality; Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Hyrich et al., 2006 (continued) **Overall N:** 2711 **Study Duration:** 6 mos			**Baseline DAS, mean:** **D1:** 6.8 **D2:** 6.6 **D3:** 6.6 **D4:** 6.8 **D5:** 6.8 **D6:** 6.7			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kirwan et al., 2004 **Country, Setting:** Belgium, Sweden, and United Kingdom, multicenter (16) **Funding:** Astra-Zeneca **Research Objective:** To compare BUD, a locally acting glucocorticoid with minimal systemic exposure, with conventional glucocorticoid txt and placebo in RA **Study Design:** RCT **Overall N:** 143 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 80 yrs • Diagnosed according to ACR criteria • Functional class I-III • Stable doses of NSAIDs (30 ds) and/or DMARDs (90 ds) **Exclusion Criteria:** • Pregnant or lactating • Glucocorticoids by any route for at least 30 ds • Systemic lupus erythematosus • Polymyalgia rheumatica • Psoriatic arthropathy • Spondylo-arthropathy • Smyloidosis • Active peptic ulcer disease • Uncontrolled DM • Other significant disease • Local or systemic infection • Allergy to BUD or other glucocorticoids; txt w/ live viruses	**Interventions, dose:** **D1:** BUD (3 mg/d) **D2:** BUD (9 mg/d) **D3:** PNL (7.5 mg/d) **D4:** Placebo **N:** **D1:** 37 **D2:** 36 **D3:** 39 **D4:** 31 **Mean age, yrs:** **D1:** 54.2 **D2:** 57.8 **D3:** 53.4 **D4:** 54.7 **Sex, % female:** **D1:** 70 **D2:** 77 **D3:** 62 **D4:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 13.1 **D2:** 8.5 **D3:** 7.0 **D4:** 7.2 **TJC, mean:** **D1:** 14.2 **D2:** 11.8 **D3:** 12.3 **D4:** 12.6 **SJC, mean:** **D1:** 12.9 **D2:** 9.8 **D3:** 11.6 **D4:** 11.8 **DMARD use, %:** **D1:** 76 **D2:** 69 **D3:** 67 **D4:** 65 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Functional capacity and health related quality of life are secondary outcomes for this study **ACR20, %:** **D1:** 22 **D2:** 42 **D3:** 56 **D4:** 25 D2 vs D3, *P* = 0.11 **TJC:** **D1:** 2.23 (-0.63 to 5.1) **D2:** 3.65 (0.75 to 6.54) (*P* < 0.05) **D3:** 4.83 (2.01 to 7.65) (*P* < 0.001) **SJC:** **D1:** 1.53 (0.92 to 3.98) **D2:** 3.81 (1.3 to 6.52) (*P* < 0.01) **D3:** 3.67 (1.25 to 6.09) (*P* < 0.01) **Pain:** **D1:** 6.6 (-5.8 to 18.9) **D2:** 11.4 (-1.3 to 24) **D3:** 22.3 (10 to 34.6) (*P* < 0.001) **DAS, patient:** **D1:** 7.9 (-4.7 to 20.5) **D2:** 16.4 (3.6 to 29.3) (*P* < 0.05) **D3:** 24.5 (12.1 to 37) (*P* < 0.001)	**Overall:** **D1:** 89 **D2:** 94 **D3:** 85 **D4:** 90 **SAEs:** **D1:** 5 **D2:** 0 **D3:** 5 **D4:** 6 **Abdominal Pain:** **D1:** 11 **D2:** 8 **D3:** 10 **D4:** 6 **Headache:** **D1:** 11 **D2:** 14 **D3:** 15 **D4:** 3 **URTI:** **D1:** 19 **D2:** 11 **D3:** 15 **D4:** 3	**Overall Attrition Rate, %:** 16 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kirwan et al., 2004 (continued)	• (i.e., polio) or live bacteria (i.e., tubercle bacilli) during previous 90 days • Undergone resection of stomach or more than 100 cm of small bowel		**HAQ:** **D1:** 1.61 **D2:** 1.57 **D3:** 1.51 **D4:** 1.52	**DAS, physician:** **D1:** 0.25 (-0.12 to 0.62) **D2:** 0.45* (0.07 to 0.82) (*P* < 0.05) **D3:** 0.66 (0.3 to 1.03) *(P* < 0.001) **HAQ:** **D1:** 0.009 (-0.19 to 0.21) **D2:** 0.107 (-0.31 to 0.09) **D3:** 0.383 (0.188 to 0.578) (*P* < 0.001) Diffrence: D3 vs. D1: 0.393; *P* < 0.001 D3 vs. D2: 0.276; *P* < 0.01 **SF-36:** **D1:** 2 (-2 to 6) **D2:** 3.7 (-0.4 to 7.8) **D3:** 7.4 (3.5 to 11.4) *(P* < 0.001) **SF-36 Mental Subscale** **D1:** 4.8 (-0.8 to 10.4) **D2:** 6.0 (0.4 to 11.7) (D3 vs D1; *P* < 0.05) **D3:** 7.2 (1.7 to 12.8) (D3 vs D2; *P* < 0.001)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004; van der Heijde, 2006 TEMPO study **Country, Setting:** Multinational (Europe), multicenter **Funding:** Wyeth Research **Research Objective:** To compare safety and efficacy of combination of ETA and MTX with monotherapies in pts with RA who had failed previous DMARD txt **Study Design:** RCT **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**Inclusion Criteria:** • Age ≥ 18 • Diagnosed according to ACR criteria • Functional class I-III • Less than satisfactory response to at least 1 DMARD other than MTX • Duration 6 mos to 20 yrs • RA defined as > 10 swollen and > 12 painful joints and at least one of: ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs **Exclusion Criteria:** • TNF antagonist, any immuno-suppressive drugs w/in 6 mos • Any investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ETA (25 mg 2x wkly) **D3:** ETA (25 mg 2x wkly) + MTX (7.5 titrated to 20 mg/wk) **N:** **D1:** 228 (152) **D2:** 223 (163) **D3:** 231 (188) Overall (at 2yrs): 503 **Mean age, yrs:** **D1:** 53 **D2:** 53.2 **D3:** 52.5 Overall (at 2yrs): 52.1 **Sex, % female:** **D1:** 79 **D2:** 77 **D3:** 74 Overall (at 2yrs): 76 **Race, % white:** **D1:** 98 **D2:** 99 **D3:** 98 Overall (at 2yrs): 99	**Mean disease duration, yrs:** **D1:** 6.8 **D2:** 6.3 **D3:** 6.8 **TJC, mean:** **D1:** 33.1 **D2:** 35 **D3:** 34.2 **SJC, mean:** **D1:** 22.6 **D2:** 23 **D3:** 22.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 64 **D2:** 57 **D3:** 62 **MTX naive, %:** **D1:** 58 **D2:** 58 **D3:** 56 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**At 24 weeks** **AUC of ACR-N, %-yrs:** **D1:** 12.2 **D2:** 14.7 **D3:** 18.3 (*P* < 0.0001) **ACR20, %:** **D1:** 75 **D2:** 76 **D3:** 85 (*P* = 0.0151) **ACR50, %:** **D1:** 43 **D2:** 48 **D3:** 69 (*P* < 0.0001) **ACR70, %:** **D1:** 19 **D2:** 24 **D3:** 43 (*P* < 0.0001) **At 52 weeks** **DAS < 1.6 remission, %:** **D1:** 13 **D2:** 16 **D3:** 35 (**D3** vs. **D2:** *P* < 0.0001; **D2** vs. **D1:** *P* = 0.5031) **HAQ, decline:** **D1:** 0.65 **D2:** 0.7 **D3:** 1.0 (*P* < 0.05) **D3** therapy significantly more likely to attain HAQ DI similar to population norms (< 0.5) than monotherapy	**Overall:** **D1:** 81 (87) **D2:** 86 (92) **D3:** 81 (86) **Infections:** **D1:** 64 (75) **D2:** 59 (71) **D3:** 67 (76) **Serious Infections:** **D1:** 4 (7) **D2:** 4 (6) **D3:** 4 (6) **Infusion or injection reaction:** **D1:** 2 (2) **D2:** 21 (21) **D3:** 10 (11) **Abdominal Pain:** **D1:** 18 **D2:** 12 **D3:** 18 **Hypertension:** **D1:** 5 **D2:** 13 **D3:** 9 **Headache:** **D1:** 14 **D2:** 15 **D3:** 15 **Nausea:** **D1:** 32 (39) **D2:** 10 (13) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**Radiograhic outcomes** **Total Sharp Score change:** **D1:** 0.28 **D2:** 0.52 **D3**: -0.54; D3 vs D2; *P* = 0.0006 D2 vs D1; *P* =0.047 **Erosion score change:** **D1:** 1.68 **D2:** 0.21 **D3**: -0.30; D3 vs D2; *P* = 0.0001 D2 vs D1; *P* =0.008 **JSN score change:** **D2:** 0.32 **D3**: -0.23; *P* = 0.0007 **At 2 years** **Total Sharp score change:** **D1:** 1.12 **D2:** 1.10 **D3**: -0.56; *P* = 0.05 D3 vs D2; *P* = 0.05 D2 vs D1; *P* = NR **Erosion score change** **D2:** 0.36 **D3:** -0.76 P < 0.05 **JSN score change** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006 **Country, Setting:** Sweden, multicenter **Funding:** Osterlund and Kock Foundations, 80-yr Fund of King Gustav V, and Reumatikerfor-bundet **Research Objective:** LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA pts treated in clinical practice **Study Design:** Prospective cohort study **Overall N:** 949 **Study Duration:** Varied (results reported for 3 yrs)	**Inclusion Criteria:** • Unsuccessful txt with 2 DMARDS including MTX • Pts diagnosed with RA according to clinical judgment of treating physician • Treated at 8 centers in Southern Sweden during March 1999 through January 2004 • Meds allowed, NR **Exclusion Criteria:** • Prior txt with biologic therapy	**Interventions, dose:** **D1:** ETA (25 mg s.c. twice wkly) **D2:** INF (≥3 mg/kg at 0, 2, 6, and 12 wks and then every 8 wks) **N:** **D1:** 309 **D2:** 640 **Mean age, yrs:** **D1:** 55.1 **D2:** 56.2 **Sex, % female:** **D1:** 82 **D2:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 14.7 **D2:** 12.7 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.9 **D2:** 5.6 **MTX use, %:** **D1:** 31 **D2:** 73 **HAQ:** **D1:** 1.6 **D2:** 1.4	**At 3 months** **D1:** 63 **D2:** 45 ($P < 0.001$) **At 6 months** **D1:** 61 **D2:** 47 (P = NS) **At 12 months** **LUNDEX values** (index of drug efficacy in clinical practice)**:** **D1:** ~ 55% (~ 4 0% at 3 yrs) **D2:** ~ 45% (~ 30% at 3 yrs) **ACR20, %:** **D1:** 69 **D2:** 53 (P = 0.001) **At 24 months** **ACR20, %:** **D1:** 65 **D2:** 56 (P = NS) **At 36 months** **ACR20, %:** **D1:** 63 **D2:** 61 (P = NS) **ACR50, %:** **D1:** 39 **D2:** 39 (P = NS) **ACR 70, %:** **D1:** 16 **D2:** 18 (P = NS)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006 (continued)				**EULAR (moderate), %:** **D1:** 46 **D2:** 29 (*P* = NS) **EULAR (good), %:** **D1:** 36 **D2:** 45 (*P* = NS) **Intermediate Outcome Measures:** INF had significantly lower adherence compared to ETA (*P* < 0.001)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2006 **Country, Setting:** Germany Registry Data **Funding:** Pharmas: Essex, Wyeth, A mgen, Abbott **Research Objective:** To investigate frequency of remission and improved functional status in pts with 2 or more DMARD failures who have received new txt with biologics **Study Design:** Prospective cohort study **Overall N:** 1,083 **Study Duration:** 1 yr	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed with RA according to ACR criteria • Failed at least 2 prior treatments with DMARDs **Exclusion Criteria:** • Only 1 DMARD failure • No failure of MTX • Rec'd new txt ≥ 1 days before study entry • DAS < 3.2 at baseline	**Interventions, dose:** **D1:** Biologics (ADA, ANA, ETA, INF) (dose NR) **D2:** DMARDs as a class (dose NR) **N:** **D1:** 818 **D2:** 265 **Mean age, yrs:** **D1:** 53.7 **D2:** 57.4 **Sex, % female:** **D1:** 76.6 **D2:** 83.8 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 10 **D2:** 9 **TJC, mean:** **D1:** 12.9 **D2:** 10.5 **SJC, mean:** **D1:** 10.5 **D2:** 8.2 **DMARD use, %:** Overall: 100 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.1 **D2:** 5.5 **# previous DMARDs:** **D1:** 4.0 **D2:** 2.8	Biologics had double chance of remission compared to conventional DMARD therapies, via multivariate regression (OR: 1.95; 95% CI, 1.20-3.19) Severely disabled pts (≤ 50% of full function) in D1 (biologics) significantly more likely to achieve physical independence (≥ 67% of full function) than D2 (DMARDs/controls) (OR 3.88, 95% CI, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in D1 (biologics)than in D2 (DMARDs/controls) (OR 2.18 95% CI, 1.04-4.6) **At 12 months** **DAS28 remission, %:** **D1:** 24.9 **D2:** 12.4 ($P < 0.004$) **ARA remission, %:** **D1:** 16.1 **D2:** 8.3 ($P < 0.036$) **Pts in remission by DAS Criteria, %:** **D1:** 16.3 **D2:** 15.3	NR	**Overall Attrition Rate, %:** 14% **ITT Analysis:** No **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2006 (continued)				**Pts in ARA Remission, %:** **D1:** 13.2 **D2:** 10.2 Approximately half of pts in remission at 6 mos relapsed until 12 mos, %: **D1:** 55 **D2:** 58 Patients with moderate disease acitvitiy (DAS28, 3.2-5.1) at start of treatment, had high remission rates in biologics group: DAS 30.6 ARA 16.9% Sustained remission at 6 and 12 months achieved in <10 % of patients		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study **Country, Setting:** Finland, NR **Funding:** Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital **Research Objective:** Efficacy and tolerability of combo of DMARDs vs. a single DMARD **Study Design:** RCT **Overall N:** 199 randomized, 187 completed 2 yrs, 160 at 5 yrs **Study Duration:** 24 mos (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 65 • Diagnosed with RA according to ACR criteria: active disease, 1987 criteria • Duration of condition: < 2 yrs **Exclusion Criteria:** • Previous use of DMARDs • Underwent glucocorticoid glucocorticoid therapy within the previous • 2 weeks • serious comorbidity • suspected inabilty to • comply with the protocol • hypersensitivity to any study medication • history of cancer • pregnant women • women of childbearing age who were not using reliable methods of contraception	**Interventions, dose:** **D1:** Combo: MTX + HCQ + SSZ + PNL **D2:** Single DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 months **N:** **D1:** 97 **D2:** 98 **Mean age, yrs:** **D1:** 45 **D2:** 46 **Sex, % female:** **D1:** 58 **D2:** 66 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.3 mos **D2:** 8.6 mos **TJC, mean:** **D1:** 18 **D2:** 20 **SJC, mean:** **D1:** 14 **D2:** 14 **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Larsen Score:** **D1:** 0 **D2:** 2	**At 2 years** **Eroded joints, number:** **D1:** 2 **D2:** 3 (*P* = 0.006) btw groups Progression of radiological joint damage lower in combination versus monotherapy **Larsen Erosion Score improvement:** **D1:** 2 **D2:** 10 (*P* = 0.002) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **Clinical remission, %:** **D1:** 37.9 **D2:** 18.4 (*P* = 0.011) **ACR50, %:** **D1:** 71 **D2:** 58 (*P* = 0.058) Median work disability per pt-observation yr, days: **D1:** 12.4 **D2:** 32.2 (*P* = 0.008) **At 5 years** **Eroded joints, number:** **D1:** 3 **D2:** 6	**Overall:** **D1:** 70 **D2:** 71 **SAEs:** **D1:** 3 **D2:** 5 **Cardiovascular Events:** **D1:** 1 MI **D2:** 2 MIs **Malignancies:** 1 prostate cancer; 1 multiple myeloma **URTI:** 1 pneumonia	**Overall Attrition Rate, %:** 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **5 year Remiission** D1: 28 D2: 22 (*P* = NS) **Increase in Larsen score** D1: lower than (*P* =0.004)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: O'Dell et al., 1996 **Country, Setting:** US, multicenter (Rheumatology clinics) **Funding:** Lederle, Sanofi, Winthrop, and Pharmacia provided study drugs **Research Objective:** To determine whether DMARDs were effective as combination therapy for RA and whether combinations studied had better efficacy than MTX alone **Study Design:** RCT **Overall N** 102 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age 19-70 • Diagnosed w/ ACR criteria > 6 mos • Poor response to at least 1 DMARD • At least 3 of: ESR ≥ 28 mm/hr, morning stiffness ≥ 45 mins, ≥ 8 tender joints, ≥ 3 swollen joints; stable therapy w/ Css ≤ 10 mg/day; • NSAIDs allowed **Exclusion Criteria:** • Pregnant or lactating • Prior combo treatment with any 2: gold, HCQ, penicil-lamine, SSZ, MTX • Impaired renal or hepatic system • Stage IV disease • Allergy to study drugs • Pulmonary or CVD • Visual	**Interventions:** **D1:** MTX (7.5 to 17.5 mg/week) **D2:** SSZ (1 g/day) + HCQ (400 mg/day) **D3:** MTX + SSZ+HCQ **N** **D1:** 36 **D2:** 35 **D3:** 31 **Mean age, yrs:** **D1:** 50 **D2:** 49 **D3:** 50 **Sex, % female:** **D1:** 69 **D2:** 74 **D3:** 65 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 10 **D2:** 6 **D3:** 10 **TJC, mean:** **D1:** 31 **D2:** 32 **D3:** 29 **SJC, mean:** **D1:** 31 **D2:** 31 **D3:** 27 **DMARD use, %:** All groups: 100 **Current Corticosteroid use, %)** **D1:** 53% **D2:** 46% **D3:** 52% **MTX naive, %:** **D1:** 92 **D2:** 89 **D3:** 87 **Treatment resistant, %:** All 100 **Pts with Early RA (≤3 yrs):** All groups: 0 **Baseline DAS, mean:** NR	Outcome improved by at least 50%, as determined by whether 3 following requirements had been fulfilled (modified Paulus composite criteria): • morning stiffness of less than 30 minutes' duration, decreased by 50%; • joint tenderness decreased by 50%; • joint swelling decreased by 50%; • ESR < 30 mm per hour in women and < 20 mm per hour in men Comparison between MTX + SSZ+HCQ and each of other groups with respect to good responses was statistically significant (P = 0.003 by log-rank test) **At 2 years** Maintenance of at least 50% improvement at 9 mos to end of 2-year treatment period (total n=50): **D1:** 33%, 12/36 pts **D2:** 40%, 14/35 pts **D3:** 77%, 24/31 pts (D3 vs D2, P = 0.003 and D3 vs. D1, P < 0.001 for respective comparisons between **D3** (3-drug group) and **D2**; **D3** vs **D1**)	Similar withdrawal rates due to Adverse Events across groups Treatment with all 3 drugs did not produce more toxic effects than did MTX alone **D1**: discontinued treatment because of toxic effects: • 2 w/ pneumonia; • 1 each had stomatitis, diarrhea, nausea, and vertigo; • 1 pt had sepsis and died. **D2**: 3 discontinued due to pneumonia, diarrhea, and Crohn's disease; **D3:** 3 in 3-drug group discontinued due to nausea, cervical cancer, and weight gain. No pt had serum aspartate aminotransferase values more than twice upper limit of normal **D3:** higher serum creatinine values than D2 or D1 at nine mos (P = 0.03)	**Overall Attrition Rate, %:** 51% **ITT Analysis:** Yes **Quality Rating:** Fair for KQ1 Good for KQ3

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: O'Dell et al., 1996 (continued)	difficulties • Retinal disease • Macular degeneration • Active peptic ulcer disease		**Duration of morning stiffness (minutes):** **D1:** 190 **D2:** 156 **D3:** 135 **RF:** **D1:** 89% **D2:** 85% **D3:** 84%			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2002 **Country, Setting:** US, multicenter (7) **Funding:** Pharmacia & Upjohn, Mylan,Sanofi-Winthrop- meds. Albert G. and Bernice F. Hansen Foundation **Research Objective:** Efficacy of combination therapy with MTX, HCQ, and SSZ to MTX + HCQ and to MTX + SSZ in txt of RA **Study Design:** RCT **Overall N:** 171 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 19-80 yrs • Diagnosed with RA according to ACR criteria • Duration of condition: > 6 mos • Active disease with at least 3 of 4 following features: ESR > 28 mm/hour, duration of morning stiffness ≥ 45 minutes, ≥ 8 tender joints, and ≥ 3 swollen joints **Exclusion Criteria:** • Previous combination therapy with any medications studied • Significant liver or renal disease • Stage IV disease • Allergy to any study drugs • women of childbearing age not using adequate contraception • Significant hematologic, pulmonary, or CVD	**Interventions, dose:** **D1:** MTX and HCQ **D2:** MTX and SSZ **D3:** MTX, HCQ, and SSZ: All pts MTX: accelerated from 7.5 mg/wk to 17.5 mg/wk in all pts not in remission SSZ: escalated from 500 mg twice daily to 1gram twice daily in pts not in remission HCQ: 200 mg twice daily **N:** **D1:** 58 **D2:** 55 **D3:** 58 Overall: 171 **Mean age, yrs:** **D1:** 50.9 **D2:** 52.5 **D3:** 48.9 Overall: 50.9 **Sex, % female:** **D1:** 78 **D2:** 84 **D3:** 76 Overall: 79 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.9 +/- 10 **D2:** 5.8 +/- 5.9 **D3:** 6.9 +/- 8.4 **TJC (mean +/- SD):** **D1:** 15.7 +/- 8.2 **D2:** 15.6 +/- 7.4 **D3:** 19.7 +/- 9.2 **SJC, mean:** **D1:** 21.1 +/- 8.3 **D2:** 19.1 +/- 7.9 **D3:** 24.0 +/- 8.8 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 71 **D2:** 56 **D3:** 50 **MTX naive, %:** **D1:** 43.1 **D2:** 54.5 **D3:** 41.4 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**At 2 years** **ACR 20, %:** **D1:** 60, 35/58 pts **D2:** 49 27/55 pts **D3:** 78, 45/58 pts (**D3** vs **D2**; *P* = 0.002) (**D3** vs. **D1**; (*P* = 0.05) **ACR 50, %:** **D1:** 40 **D2:** 29 **D3:** 55 (**D3** vs **D2**; *P* = 0.005) (**D3** vs. **D1**, *P* = 0.10) **ACR 70, %:** **D1:** 26 **D2:** 18 **D3:** 16 (*P* = NS) Changes in values for ACR core set, improvement in triple therapy group was greater than either of other 2 txt groups. TJC differences were statistically significant, D3 vs D1 (*P* ≤ 0.005)	**Overall:** **D1:** 8.6 **D2:** 9.1 **D3:** 6.9 **Infections:** **D2:** 1.8 **Serious Infections:** **D1:** 1.7 **Cardiovascular Events:** **D1:** 1.7 (1 MI) **Headache:** **D2:** 1.8 **Hepatotoxicity:** **D3:** 1.7 **Malignancies:** **D3:** 1.7 (1 non-Hodgkins lymphoma)	**Overall Attrition Rate, %:** 14.6% (25/171 subjects) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2002 (continued)			**% RF positive:** **D1:** 88 **D2:** 88 **D3:** 89 **ESR:** **D1:** 28.5 +/- 20.3 **D2:** 34.1 +/- 26.5 **D3:** 30.1 +/- 21.0	**Reduced morning stiffness, minutes:** **D1:** -59.2 +/- 103.3 **D2:** -53.2 +/- 89.5 **D3:** -109.3 +/- 86.4 minutes (**D3** vs. **D1**; *P* = 0.01) (**D3** vs. **D2**; *P* = 0.006)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial **Country, Setting:** Multinational, unversity hospitals **Funding:** Centocor **Research Objective:** To compare benefits of initiating txt with MTX and anti-TNFá with those of MTX txt alone in pts with RA of < 3 yrs duration **Study Design:** RCT **Overall N:** 1049 **Study Duration:** 54 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3 mos and < 3 yrs • > 10 swollen joints, and > 12 tender joints • 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS • 20 mg MTX (required) **Exclusion Criteria:** • Prior txt with: MTX, received other DMARDs within 4 wks of entry • Used ETA, INF, ADA or other anti-TNF-á agent • History of TB; HIV, hepatitis B or C virus, CHF, or lymphoma or other malignancy	**Interventions, dose:** **D1:** MTX (20 mg/wk) + placebo **D2:** MTX + INF (3 mg/kg/wk) **D3:** MTX + INF (6 mg/kg/wk) **N:** **D1:** 282 **D2:** 359 **D3:** 363 **Mean age, yrs:** **D1:** 50 **D2:** 51 **D3:** 50 **Sex, % female:** **D1:** 75 **D2:** 71 **D3:** 68 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 0.9 **D2:** 0.8 **D3:** 0.9 **TJC, mean:** **D1:** 34 **D2:** 32 **D3:** 33 **SJC, mean:** **D1:** 22 **D2:** 21 **D3:** 22 **DMARD use, %:** **D1:** 35 **D2:** 29 **D3:** 32 **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** NR **JSN:** **D1:** 3.0 **D2:** 2.9 **D3:** 2.9	**At weeks 30 to 54** **HAQ:** **D1:** 0.68 **D2:** 0.80 **D3:** 0.88; (**D2** vs. **D1**; *P* = 0.03) (**D3** vs. **D1**; *P* < 0.001) **At 54 weeks** **HAQ > 0.22, %:** **D1:** 65.2 **D2:** 76.0 **D3:** 75.5 (**D2** vs. **D1**; *P* = 0.003) (**D3** vs. **D1**; *P* < 0.004) **ACR20, %:** **D1:** 53.6 **D2:** 62.4 **D3:** 66.2 (**D2** vs. **D1**; *P* = 0.028) (**D3** vs. **D1**; *P* < 0.001) **ACR50, %:** **D1:** 32.1 **D2:** 45.6 **D3:** 50.4 (**D2** vs. **D1**; *P* = 0.001) (**D3** vs. **D1**; *P* < 0.001) **ACR70, %:** **D1:** 21.2 **D2:** 32.5 **D3:** 37.2 (**D2** vs. **D1**; *P* = 0.002) (**D3** vs. **D1**; *P* < 0.001)	**SAEs:** **D1:** 11 **D2:** 14 **D3:** 14 **Serious Infections:** **D1:** 2.1 **D2:** 5.6 **D3:** 5.0 **Infusion or injection reaction:** **D1:** 7 **D2:** 21 **D3:** 15 **TB:** **D1:** 0 **D2:** 0.8 **D3:** 0.3 **Nausea:** **D1:** 18 **D2:** 20 **D3:** 17 **URTI:** **D1:** 21 **D2:** 25 **D3:** 28	**Overall Attrition Rate, %:** 14.9 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **D3:** 46.7 (*P* < 0.001) **Modified Sharp:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 (*P* < 0.001) **Increase in radiographic score, %:** INF: 39 vs. MTX 61 (*P* < 0.001) **Employability:** INF+MTX (OR 2.4, *P* < 0.001) MTX (*P* = 0.56) Combo has higher probability of improvement than MTX alone **Net increase in employability:** MTX+INF: 8% MTX-only: 2% **Employability status changed from employable to unemployable, %:** INF: 8 MTX-only: 14 (*P* = 0.05) **SF-36 Physical component summary scores** **D1:** 11.7 **D2:** 13.2 **D3:** 10.1 D3 vs. D1, *P* =0.10 D3 vs. D2; *P* =0.003		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 *P* < 0.001 **Erosion Score change:** **D1:** 3.0 **D2:** 0.3 **D3:** 0.1 *P* < 0.001 **JSN Score change:** **D1:** 0.6 **D2:** 0.1 **D3:** 0.2 *P* < 0.001		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Smolen et al., 1999; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **Study Design:** RCT **Overall N:** 266 (358 including placebo arm) **Study Duration:** 24 wks (12 and 24 month followup)	**Inclusion Criteria:** • Age: ≥ 18 • Active RA defined by: ≥ 6 tender and swollen joints, based on a 28-joint count, physician and pt global assessments of RA activity of "fair, poor, or very poor", CRP > 2.0 mg/dL or ESR > 28 mm/h • Functional class I – III • Other DMARDs discontinued ≥ 4 wks • Stable doses of NSAIDS permitted -acetylsalicylic acid, oral steroids (prednisolone ≤ 10 mg/day), and up to 3 intra-articular steroid injections, not exceeding 60 mg triamcinolone • Intra-articular steroid injections not permitted during first 6 mos **Exclusion Criteria:** • Pregnant or lactating	**Interventions:** **D1:** LEF **D2:** SSZ **N:** **D1:** 133 **D2:** 133 **Mean age, yrs:** **D1:** 58.3 **D2:** 58.9 **Sex, % female:** **D1:** 75.9 **D2:** 69.2 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.6 **D2:** 7.4 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 60.2 **D2:** 48.9 **Corticosteroid use, %:** **D1:** 28.6 **D2:** 27.8 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF positive:** **D1:** 79% **D2:** 80%	**At 24 weeks** **ACR 20, %:** **D1:** 55 **D2:** 56 **ACR 50, %:** **D1:** 33 **D2:** 30 **Improving HAQ scores, change (%):** **D1:** -0.50 (45) **D2:** -0.29 (29) (*P* = 0.0086) **Change in Sharp; number, change (SD):** **D1:** 87 1.23 (2.85) **D2:** 84 2.32 (10.11) **Larsen score change:** **D1:** 0.01 **D2:** 0.01 (*P* = NS) **At 1 year** **Change in Sharp; number, change (SD):** **D1:** 60 0.97 (6.11) **D2:** 53 1.38 (2.88) **Larsen score change:** **D1:** 0.02 **D2:** 0.02 (*P* = NS) **At 2 years** **Larsen score change:** **D1:** -0.07 **D2:** -0.02 (*P* = NS) Similar ACR20 response rates D1: 48; D2: 44; *P*=NR	**SAEs:** **D1:** 5 **D2:** 7 **Headache:** **D1:** 7 **D2:** 11 **Nausea:** **D1:** 10 **D2:** 17 **URTI:** **D1:** 14 **D2:** 15 **Diarrhea:** **D1:** 17 **D2: 9** **Alopecia:** **D1:** 8 **D2: 5** **Rash:** **D1:** 10 **D2: 9** **Withdrawal due to AEs:** **D1:** 14 **D2: 19** 2 cases of reversible agranulocytosis in SSZ	**Overall Attrition Rate, %:** 33% at 24 wks **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 **Country, Setting:** US and Canada, multicenter (47 university & private rheumatology practices) **Funding:** Hoescht Marion Roussel **Research Objective:** Efficacy and safety of LEF with placebo and MTX in active RA **Study Design:** RCT **Overall N:** 482 (active arms-364) **Study Duration:** 12 mos (w/ 1 year followup)	**Inclusion Criteria:** • Age: 18 or older • Diagnosed according to ACR criteria; DMARDs discontinued at least 30 days prior • Duration of condition at least 6 mos • 10 mg stable prednisone (or equivalent) • NSAIDs if dosages stable at least 30 days prior to enrollment **Exclusion Criteria:** • Pregnant or lactating • Prior treatment with: MTX • Inflammatory joint disease not caused by RA, • History of clinically significant drug or alcohol abuse, or admitted to consumption of more than 1 alcoholic drink per day	**Interventions:** **D1:** LEF (20 mg/week) **D2:** MTX (7.5 to 15 mg/week) **N:** **D1:** 182 **D2:** 182 **Mean age, yrs:** **D1:** 54.1 **D2:** 53.3 **Sex, % female:** **D1:** 72.5 **D2:** 75.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.0 **D2:** 6.5 **TJC, mean:** **D1:** 15.5 **D2:** 15.8 **SJC, mean:** **D1:** 13.7 **D2:** 13.0 **DMARD use, %:** **D1:** 55.5 **D2:** 56.0 **Corticosteroid use, %:** **D1:** 53.8 **D2:** 52.7 **MTX naive, %:** Both groups 100 **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **NR** **RF positive:** **D1:** 64.8 **D2:** 59.4 **MHAQ:** **D1:** 0.8 **D2:** 0.8	**At 12 mos** **ACR 20, %** **D1:** 52 **D2:** 46 **ACR 50, %** **D1:** 34 **D2:** 23 **ACR 70, %** **D1:** 20 **D2:** 9 **MHAQ mean change** **D1:** -0.3 **D2:** -0.2 **Sharp score change** **D1:** 0.53 (n:131) **D2:** 0.88 (n= 138) (*P* = 0.05) **Mean change HAQ-DI** **D1:** -0.45 (n= 164) **D2:** -0,26 (n= 168) (*P* ≤ 0.01) **Mean change SF-36 physical component** **D1:** 7.6 (n= 157) **D2:** 4.6 (n=162) **Work productivity mean change** **D1:** 9.8 (n= 138) **D2:** 7.5 (n= 148) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**SAEs:** **D1:** 1.1 **D2:** 2.7 **Infections:** **D1:** 56.6 **D2:** 59.9 **Abdominal Pain:** **D1:** 13.7 **D2:** 15.4 **Nausea:** **D1:** 20.9 **D2:** 19.2 **Back pain:** **D1:** 8 **D2:** 2 **Diarrhea:** **D1:** 36.8 **D2:** 21.6 **Oral Ulcers:** **D1:** 6.8 **D2:** 10.5 **GI Events:** **D1:** 5.5 **D2:** 1.7 **Elevated Transaminases:** **D1:** 7.1 **D2:** 4.4 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al 2005 **Country, Setting** Sweden, multicenter **Funding:** Swedish Rheumatism Association and others **Research Objective** Efficacy of low-dose PNL on joint damage and disease activity in pts with early RA being treated concomitantly with DMARDs **Study Design:** RCT **Overall N:** 250 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age 18 to 80 yrs • Diagnosed according ARA 1987 revised criteria • Duration ≤ 1 yr: pt in BARFOT study • DAS28 score >3.0 • Started by treating rheumatologist on first DMARD • Concomitant NSAIDS txt permitted • Intraarticular steroid injections allowed except 2 wks prior to any clinical evaluation **Exclusion Criteria:** • Pregnant or lactating • Glucocorticoids, DMARDs • Contraindication for glucocorticoid therapy • Previous fragility fractures, pts < 65 years with T score < -2.5 on bone mineral densitometry	**Interventions, dose:** **D1:** DMARD (SSZ 2 g/day or MTX mean dose 10 mg/week, dosages NR) + PNL (7.5 mg/d) **D2:** DMARD only **N:** **D1:** 119 **D2:** 131 **Mean age, yrs:** **D1:** 51 **D2:** 59 **Sex, % female:** **D1:** 65 **D2:** 63 **Race, % white:** **D1:** NR **D2:** NR	**Mean disease duration, yrs:** **D1:** 6.5 mos **D2:** 5.8 mos **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** Overall: 100 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 5.28 **D2:** 5.42 **HAQ:** **D1:** 1.01 **D2:** 0.98 **SOFI:** **D1:** 8 **D2:** 9	**At 2 yrs:** **DAS < 2.6 disease remission, % achieved** **D1**: 55.5 **D2**: 32.8 (*P* = 0.0005) **DAS28, scores over time ± SD** **D1**: 5.3 ± 1.1 at baseline to 2.7 ± 1.5 after 1 yr and 2.7 ± 1.3 after 2 yrs **D2**: 5.4 ± 1.0, 3.3 ± 1.5, and 3.2 ± 1.4 **HAQ scores mean decrease over time :** **D1**: 1.0 at baseline to 0.4 at 1 year and 0.5 **D2**: 1.0, 0.6, and 0.7 (*P* value NR) **Improvement in mean SOFI index** **D1:** mean decreased from 8 at baseline to 4 at 1 year and 4 after 2 years **D2:** 9, 6, and 7 respectively (*P* value NR) **Total sharp score ,median IQR change** i D1: 1.8 (IQR 0.5-6.0) D2: 3.5 (IQR 0.5-10.0) (*P* = 0.019) **Newly eroded joints per pt, median** D1: 0.5 (IQR 0-2) D2: 1.25 (IQR 0-3.25) (*P* = 0.007)	NR	**Overall Attrition Rate, %:** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al 2005 (continued)	• 65 or older with Z score ≤ 1			**Radiographic progression beyond smallest detectable difference, %** **D1:** 25.9 **D2:** 39.3 (*P* = 0.033) **Joint space narrowing score, median change** **D1:** 1 **D2:** 2 (*P* = 0.08)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: van Riel et al., 2006 **Country, Setting:** Multinational, multicenter **Funding:** Wyeth **Research Objective:** Evaluate efficacy and safety of ETA monotherapy vs. ETA + MTX in RA pts with inadequate response to MTX **Study Design:** RCT, open-label **Overall N:** 315 **Study Duration:** 16 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed according to ACR criteria • Functional class of: I-III • Previous use of DMARDs • Inadequal control of RA symptoms on MTX ≥ 12.5 mg/wk for ≥3 mos **Exclusion Criteria:** • DMARDS other than MTX within 12 wks of screening; prednison ≥10 mg/d • Corticosteroid injections within 6 wks • 'Significant' concurrent medical illness	**Interventions, dose:** **D1:** ETA (25 mg s.c. twice wkly) **D2:** ETA (25 mg s.c. twice wkly) + MTX (≥12.5 mg/wk) **N:** **D1:** 159 **D2:** 155 **Mean age, yrs:** **D1:** 53 **D2:** 54 **Sex, % female:** **D1:** 79.2 **D2:** 76.8 **Race, % white:** **D1:** 99.4 **D2:** 98.7	**Mean disease duration, yrs:** **D1:** 10.0 **D2:** 9.8 **TJC, mean:** **D1:** 14.6 **D2:** 14.7 **SJC, mean:** **D1:** 11.2 **D2:** 11.9 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 49.1 **D2:** 55.5 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.2 **D2:** 6.3 **HAQ:** **D1:** 1.6 **D2:** 1	**DAS28 improvement of > 1.2 units, %:** D1: 72.8 D2: 75.2 Difference -2.3 (95% CI, -13.1-8.2; *P* = 0.658) **EULAR response maintained, %:** **D1**: 80.0 **D2:** 82.4 (*P* = NR) **ACR 20, %:** **D1**: 71.0 **D2**: 67.1 Difference 3.9 (95% CI, -6.4-14,2; *P* = 0.46) **ACR 50, %:** **D1**: 41.9 **D2:** 40.1 Difference 1.8,(95% CI, -9.2-12.8 ; *P* = 0.75) **ACR 70, %:** D1: 17.4 D2 : 18.4 Difference -1.0 (95% CI, -9.6-7.6; *P* = 0.82)	**Overall:** **D1:** 62.9 **D2:** 70.3 **SAEs:** **D1:** 5.0 **D2:** 4.5 **Infections:** **D1:** 24.5 **D2:** 32.3 **Serious Infections:** **D1:** 0.6 **D2:** 0.3 **Infusion or injection reaction:** **D1:** 6.3 **D2:** 6.5 **Dizziness:** **D1:** 0.6% **D2:** 0 **Headache:** **D1:** 8.8 **D2:** 6.5 **URTI:** **D1:** 8.2 **D2:** 12.9	**Overall Attrition Rate, %:** 17.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 **Country, Setting:** US, Rheumatology practices (509) **Funding:** Immunex Corporation **Research Objective:** To evaluate effectiveness of select biologics, MTX (MTX), and other DMARDs in management of adult RA in routine clinical practice **Study Design:** Prospective cohort study **Overall N:** 5,397 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18 or older • Diagnosed with RA according to ACR criteria: 1987 ACR • Pts requiring a change in RA txt **Exclusion Criteria:** • Pregnant or lactating • Active infection, • Concurrent enrollment in a clinical trial	**Interventions, dose:** **D1:** MTX (10 to 15 mg/wk) **D2:** ETA (50 mg/wk) **D3:** ETA (50 mg/wk) +MTX **D4:** INF (3.8 mg/8wks) **D5:** INF (3.8 mg/8wks) + MTX (15 mg/wk) **D6:** LEF (20 mg/d) **D7:** LEF (20 mg/d) +MTX (15 mg/wk) **D8:** MTX (15 mg/wk) +HCQ (400 mg/d) **D9:** MTX (15 mg/wk) +HCQ (400 mg/d) +SSZ (2000 mg/d) **N:** **D1:** 941 **D2:** 1251 **D3:** 1783 **D4:** 120 **D5:** 540 **D6:** 204 **D7:** 191 **D8:** 325 **D9:** 42 **Mean age, yrs:** **D1:** 56.8 **D2:** 53.2 **D3:** 52.6 **D4:** 60.2 **D5:** 58.5 **D6:** 57.7 **D7:** 55.5 **D8:** 53.8 **D9:** 47.8	**Mean disease duration, yrs:** **D1:** 3.5 **D2:** 9.2 **D3:** 7.7 **D4:** 10.6 **D5:** 9.5 **D6:** 10.1 **D7:** 7.4 **D8:** 4.6 **D9:** 7.2 **TJC, mean:** **D1:** 13 **D2:** 13.4 **D3:** 13.3 **D4:** 14.8 **D5:** 3.9 **D6:** 12.8 **D7:** 12.2 **D8:** 11.8 **D9:** 10.1 **SJC, mean:** **D1:** 11.3 **D2:** 11.1 **D3:** 11.5 **D4:** 13.9 **D5:** 12.0 **D6:** 11.8 **D7:** 11.4 **D8:** 9.2 **D9:** 10.2	**mACR20, %:** **D1:** 37 **D2:** 41 **D3:** 43 **D4**: 26 **D5:** 35 **Adjusting for baseline covariates** **D3:** vs. **D1**(OR 1.29, 95% CI, 1.09-1.52; *P* < 0.01) **D2** vs. **D1** (OR 1.23, 95% CI, 1.02-1.47; *P* < 0.05) **D1** vs. **D5** (OR 0.96 CI 0.76-1.21 p = 0.72) **D1** vs. **D4** (OR 0.66, 95% CI, 0.43-1.02; *P* = 0.06) **Mean change HAQ improvement, %** **D1:** 7 **D2:** 17 (*P* < 0.001) **D3:** 17 (*P* < 0.001) **mACR20 response** **D5** vs. **D1**: (OR 0.68, 95% CI, 0.48-0.96; *P* < 0.05) **D6** vs. **D1** (OR 0.76, 95% CI, 0.54-1.06; *P* = 0.11) **D8** vs, **D1**: (OR 0.94, 95% CI, 0.72-1.23; *P* = 0.64) **D9** vs. **D1**: (OR 0.57, 95% CI, 0.27-1.18; *P* = 0.13) **SJC % improvement** **D1** vs **D1**: 34 (N/A) **D2** vs. **D1**: 53 (*P* < 0.0001) **D4** vs. **D1**: 29 (*P* = NS) **D3** vs. **D1**: 55 (*P* < 0.0001) **D5** vs **D1**:48 (*P* < 0.01)	NR	**Overall Attrition Rate, %:** 33.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)		**Sex (% female** **D1:** 75 **D2:** 75 **D3:** 79 **D4:** 71 **D5:** 77 **D6:** 76 **D7:** 78 **D8:** 80 **D9:** 79 **Race, % white:** **D1:** 77 **D2:** 81 **D3:** 81 **D4:** 78 **D5:** 81 **D6:** 78 **D7:** 82 **D8:** 83 **D9:** 79	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **D7:** 95 **D8:** 78 **D9:** 88 **Corticosteroid use, %** **D1:** 53 **D2:** 48 **D3:** 51 **D4:** 63 **D5:** 57 **D6:** 48 **D7:** 56 **D8:** 50 **D9:** 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**TJC % improvement** D1: 34(N/A) D2 vs. D1: 53% (*P* < 0.001) D4 vs D1: 29% (*P* = NS) D3 vs D1: 55% (*P* < 0.0001) D5 vs D1: 48% (*P* = NS) **HAQ % improvement amongst pts < 65 yrs** **D2:** 22 **D4:** 4 (*P* = NR)		

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005 **Country, Setting:** Germany, clincal **Funding:** Essex Pharma, Wyeth Pharma, Amgen, and Abbott **Research Objective:** To compare drug continuation rates in pts. with RA who start on a biological agent or on a DMARD after previous DMARD failure **Study Design:** Retrospective cohort study **Overall N:** 1,523 **Study Duration:** 1 yr	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed with RA according to ACR criteria • Previous use of DMARDs: at least 2 **Exclusion Criteria:** NR	**Interventions (dose):** **D1:** ETA **D2:** INF **D3:** AKA **D4:** Total Control Group **D5:** LEF **D6:** LEF + MTX Dosages NR **N:** **D1:** 511 **D2:** 343 **D3:** 70 **D4:** 599 **D5:** 120 **D6:** 141 **Mean age, yrs:** **D1:** 53.7 **D2:** 53.6 **D3:** 54.3 **D4:** 56.5 **D5:** 58 **D6:** 57.4 **Sex, % female:** **D1:** 77.9 **D2:** 71.1 **D3:** 77.1 **D4:** 82.8 **D5:** 85.8 **D6:** 78.0 **Race, % white:** NR	**Mean disease duration (yrs):** **D1:** 9 **D2:** 8.5 **D3:** 13 **D4:** 6 **D5:** 9 **D6:** 7 **TJC, mean:** **D1:** 13.3 **D2:** 12.6 **D3:** 12.6 **D4:** 10 **D5:** 10.6 **D6:** 10.9 **SJC, mean:** **D1:** 10.4 **D2:** 10.7 **D3:** 10.2 **D4:** 7.7 **D5:** 7.4 **D6:** 8.5 **DMARD use (#):** **D1:** 3.9 **D2:** 3.7 **D3:** 4.2 **D4:** 2.1 **D5:** 2.4 **D6:** 2.2 **Corticosteroid use, %:** NR **MTX naive, %:** NR	**Continuation rates** **D1** and **D2** similar **D3** significantly lower **Txt continuation at 1 yr, %** **D1**: 68.6 ETA+ MTX : 71.6 **D2**: 65.4 **D6**: 66.2 **D3**: 59 AKA vs. ETA; P = 0.004; ANA vs. INF; P = 0.03 **Txt discontinuation because of adverse events, %:** D2: 18.7 INF+MTX: 18.2 D1: 12.6% ETA+MTX 13.3 D3: 16.3 **Txt discontinuation because of lack of efficacy, %:** **D1:** 19.9 ETA + MTX :16.9; **D2:** 45 INF+MTX: 17.9 **D3:** 29.6	NR	**Overall Attrition Rate, %:** N/A **ITT Analysis:** N/A: registry **Quality Rating:** Good

Evidence Table 1. KQ 1. Rheumatoid arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005 (continued)			**Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.1 **D2:** 6 **D3:** 6.1 **D4:** 5.4 **D5:** 5.5 **D6:** 5.6 **MTX use:** **D1:** 91.2 **D2:** 92.1 **D3:** 78.6 **D4:** 68.7 **D5:** 94.2 **D6:** 90.7			

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Clark, 2004, International: Europe, U.S., Canada, Australia, Health Technology Assessment Programme (U.K.) **Study Design:** Systematic review and meta analysis **Aims of Review:** To review evidence on clinical benefits, hazards, and cost-effectiveness of AKA in adult RA pts **Number of Pts:** 2,905	**Studies included:** Efficacy Trials: • Bresnihan (1998) • Cohen (2001) • Cohen (2002) • Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 mos) Safety Trial: • Fleischmann (2001) **Characteristics of included studies:** • RCTs (except 1) of AKA or AKA + MTX in pts with highly active RA • Fleischmann control arm consisted of placebo + DMARD txt **Characteristics of included populations:** • Mean ages 50s • Duration 6 mos to 10 yrs • Majority had failed at least 1 DMARD and some were taking MTX up to trial start • Majority taking low-dose steroids and NSAIDs **Characteristics of interventions:** • AKA alone: • AKA from 2.5 mg/day to 150 mg/day • AKA + MTX: AKA 0.04 mg/kg per day to 2.0 mg/kg per day or fixed dose 100 mg/day	Adjusted indirect comparisons with anti TNF agents (ETA, INF) suggested that AKA may be significantly less effective at relieving clinical symptoms than anti-TNF agents (-0.21; 95% CI, -0.32 to -0.10) Adjusted indirect comparisons: • RD (95% CI) • TNF+MTX vs. MTX 0.37 (0.28 to 0.45) • AKA+MTX vs. MTX 0.16 (0.09 to 0.23) • AKA+MTX vs. TNF+MTX -0.21 (-0.32 to -0.10)	Withdrawals due to adverse events: • Control: 4.1% to 9% • AKA: 5% to 13% Specific adverse events: • SAEs: Control: 3.2% to 11.6% AKA: 4.4% to 12.8% • Malignancy: Control: 0% to 1.8% AKA: 0% to 1.1% • Injection Site Reactions: Control: 3% (low-dose study) to 33% AKA: 19.8% (low-dose study) to 73% • Any infection: Control: 13.3% (low-dose study) to 50% AKA: 13.5% (low-dose study) to 48.4% • Serious infections: Control: 0.4% to 1.4% AKA: 0.8% to 2.1% • Neutropenia: Control: 0% to 4% AKA: 0% to 9% • Antibodies to IL-1Ra: Control: 0% to 1.8% AKA: 0.9% to 5%	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good		

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Gartlehner et al., 2006 US **Study Design:** Metaanalysis (random effects model); systematic review **Aims of the Review:** To assess comparative efficacy and safety of biologic agents for RA **Number of Patients:** ADA: 2,354 ETA: 1,151 INF: 704 AKA:1,039 (#'s refer to 17 sudies used for adjusted indirect comparisons of efficacy)	**Studies included:** • 26 controlled trials • 18 additional studies assessed safety **Characteristics of included studies:** • Often limited to 1 year of follow-up • Reported on DAS-28 • Radiographic progression, functional capacity, and QOL **Characteristics of included populations:** • Narrowly defined populations • Mean age 53.4 • 76% female • 89% caucasion **Characteristics of interventions:** • All efficacy studies except 1 were funded by the pharmaceutical industry • All 12 weeks plus of duration (for observational studies it was 3 months or greater and 100 or more patients)	• Adjusted indirect comparison indicate no significant differences in efficacy between antiTNF drugs • Anti-TNF drugs appear to be more efficacious than AKA but do not differ among each other. Indirect comparisons of INF and of anti-TNF drugs as a class compared to AKA yielded a statistically significant greater efficacy on ACR 20 [RR 0.58 (95%CI 0.38-0.90) and RR 0.61 (95% CI 0.39-0.96), respectively], but not ACR 50 • Few studies assessed longterm radiographic outcomes. In general, rate of radiographic progression was significantly lower in patients treated with biologics than in placebo-treated patients, regardless of concomitant DMARD therapy. Similarly, QoL improved significantly for patients treated with biologics	• Because of lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about comparative safety of biologics • Higher rates of injection site reactions for AKA than ADA and ETA (56% vs. 19% vs. 25%)	**Publication Bias Assessed**: Yes **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes - briefly describe in box: Searched Medline, Embase, Cochrane and International Pharmaceutical Abstracts from 1980-2006. Also explored CDER database. **Quality Rating:** Good		

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Hochberg et al., 2003 Multinational NR **Study Design:** Systematic review and indirect comparisons **Aims of the Review:** Differences in efficacy of TNF alpha blocking agents, as measured by rate ratios for American College of Rheumatology (ACR) 20/50/70 responses, in patients with RA with an incomplete response to methotrexate. **Number of Patients:** 1053 380 placebo 673 active	**Studies included:** Maini et al. 1999 Lipsky et al. 2000 Weinblatt et al 1999 Weinblatt et al. 2003 **Characteristics of included studies:** Placebo controlled, double blind, randomised clinical trials of at least 24 weeks' **Characteristics of included populations:** NR- assuming that it is adults with active RA with lack of response to MTX **Characteristics of interventions:** the addition of TNF blocking agents (INF, ETA and ADA) to methotrexate in a "step-up" strategy	Indirect comparisons, Relative Risk (95% CI) • Etanercept vs. adalimumab ACR 20 1.10 (0.57 to 2.12) 2.60 (0.35 to 19.0) • Infliximab vs. adalimumab 1.07 (0.66 to 1.73) 1.35 (0.47 to 3.85) • Etanercept vs. infliximab 1.03 (0.49 to 2.18) 1.92 (0.22 to 17.0)	NR	**Publication Bias Assessed**: NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** Yes - briefly describe in box **Quality Rating:** Fair		

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of Review:** To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA Meta-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts **Number of Pts:** 1,144 LEF 312 to Placebo 680 to MTX 132 to SSZ Only 920 used in meta-analysis 2 yr extension: LEF:158 SSZ: 60 MTX 101	**Studies included:** 6 trials **Characteristics of included studies:** Randomized, double-blind, placebo and/or active controlled **Characteristics of included populations:** All with active RA **Characteristics of interventions:** 5, 10 or 25 mg/d vs placebo or MTX or SSZ	• LEF significantly better than placebo at 6,12 and 24 mos. • LEF vs. MTX • ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77) • No significant differences at 2 yrs but more responders with MTX than with LEF; OR 1.28 (0.98-1.67) • ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS	• Total withdrawals lower in LEF group (10% greater than Placebo [70/416 vs 18/311]); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos • AEs+ GI sympotms, elevated liver funcitn tests, alopecia, and infections	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good		

Evidence Table 2. KQ 1. Rheumatoid arthritis systematic reviews: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Wailoo et al., 2006 AHRQ **Study Design:** Decision analytic model and metaanalysis **Aims of the Review:** Cost effectiveness of ETA, ADA,, ANA and INF alone and in sequence **Number of Patients:** 17,000 in disease registry (National Databank for Rheumatic Diseases) and 6694 in RCTs	**Studies included:** Disease registry (National Databank for Rheumatic Diseases) and 6694 in 13 RCTs **Characteristics of included studies:** Treatment duration of at least 6 months **Characteristics of included populations:** Adult patients with RA **Characteristics of interventions:** Placebo and MTX controlled	• Odds ratio of ACR50 • INF/ETA 1.17 (0.68, 2.08) • ADA/ETA 1.02 (0.54, 1.97) • ADA/INF 0.87 (0.47, 1.57)	NR	**Publication Bias Assessed**: Yes **Heterogeneity Assessed:** NR **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** Yes **Quality Rating:** Fair		

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni et al., 2005; Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational, 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5 **Concomitant MTX, %:** **56**	• ACR50 Placebo 0/52 (0.0%) vs. INF 24/52 (46.2%) • ACR70 Placebo 0/52 (0.0%) vs. INF 15/52 (28.8%) • # of tender joints Placebo -23.6 vs. INF 55.2 • # of swollen joints Placebo -1.8 vs. INF 59.9 • DAS Placebo 2.8 vs. INF 45.5 $P < 0.001$ • HAQ Placebo -1.6 vs. INF 49.8 $P < 0.001$ • PsARC Placebo -12% vs. INF +86% $P < 0.001$ • ACR20 wk 16 Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) $P < 0.001$ • At 50 wks • Total modified vdH-S score, 85% and 84% in Placebo/INF and INF/INF groups had no worsening. • Change in erosion scores INF/INF 0.921, placebo/INF 0.536 ($P = 0.780$) • Change in JSN INF/INF -0.51, placebo/INF -0.47 ($P = 0.211$) • 16 wks-PsARC INF 75% vs. Placebo 21% ($P < 0.001$) • PASI75 INF 68% vs, placebo 0% ($P < 0.001$)	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni, 2005; Kavanaugh et al., 2006 IMPACT2 study **Country, Setting:** Multinational 36 sites in clinics **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:Overall 100** **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (P < 0.001) and wk 24 4 vs. 41 (P < 0.001) • ACR70 at wk 14 1 vs. 15 (P < 0.001) and wk 24 2 vs. 27 (P < 0.001) • PsARC at wk 14 27 vs. 77 (P < 0.001) and wk 24 32 vs. 70 (P < 0.001) • •HAQ improvement at wk 14 -18.4 vs. 48.6 (P < 0.001) and wk 24 -19.4 vs. 46 (P < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (P < 0.001) and wk 24 1.3 vs. 7.7 (P < 0.001) • Mental wk 14-1.2 vs. 3.8 (P = 0.001) and wk 24 0.4 vs. 3.9 (P = 0.047) • ACR20 at Wk 14 11 vs. 58 (P < 0.001) and Wk 24 16 vs. 54 (P < 0.001) • PASI 50: wk 14: 9 vs. 82 (P <0.01), wk 24: 8 vs. 75 (P <75 (P<0.01); PASI 75 wk 14: 2 vs. 64 (P < 0.01), wk 24: 1 vs. 50 (P < 0.01); • improvement wk 14: 0 vs. 41 (P < 0.01), wk 24: 0 vs. 39 (P < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (P < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (P = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational, multicenter (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX, %:** 0	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC ($P < 0.0001$) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 ($P = 0.0267$) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 $P = 0.0030$ • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 $P = 0.0173$ • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate (%):** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US, single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study the efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate (%):** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 (2nd yr outcomes) **Country, Setting:** US, 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts ($P < 0.0001$) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts ($P = 0.001$) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo ($P = 0.0001$) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group ($P < 0.0001$) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate (%):** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 3. KQ1. Psoriatic arthritis trials: treatment response, disease progression, and remission (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2005 ADEPT Study **Country, Setting:** Multinational, multi-clinic (50) **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **Concomitant MTX use, %:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% ($P < 0.001$) • ACR70 ADA, 23% vs. placebo, 1% ($P < 0.001$) • The PASI75 ADA 59% vs. placebo 1% ($P < 0.001$) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 ($P < 0.001$) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; $P < 0.001$). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo ($P < 0.001$) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) ($P < 0.001$ for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 ($P < 0.001$) • Change in baseline to wk 24; 1.4 vs 9.3 ($P < 0.001$) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (P NS) • Change in baseline to wk 12; 0.6 vs 1.8 (P NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate (%):** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study **Country, Setting:** US, clinics **Funding:** Immunex **Research Objective:** To compare ETA and MTX in pts with early RA **Study Design:** RCT **Overall N:** 632 (468 extension) **Study Duration:** 12 mos (1 year open label extension; 2 more years, total of 5 yrs)	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: < 3 yrs • Positive serum test for RF or at least 3 bone erosions evident on radiographs of hands, wrists, or feet • At least 10 swollen joints and at least 12 tender or painful joints • ESR ≥ 28 mm per hour • Serum CRP concentration of at least 2.0 mg per deciliter • Morning stiffness that lasted at least 45 minutes • Stable doses of NSAIDS and PRE allowed **Exclusion Criteria:** • Prior txt with MTX • No other important concurrent illnesses	**Interventions, dose:** **D1:** MTX (19 mg/wk) **D2:** ETA (10 mg twice wkly) **D3:** ETA (25 mg twice wkly) **N:** **D1:** 49 **D2:** 50 **D3:** 51 **Mean age, yrs:** **D1:** 49 **D2:** 50 **D3:** 51 **Sex, % female:** **D1:** 75 **D2:** 75 **D3:** 74 **Race, % white:** **D1:** 88 **D2:** 84 **D3:** 86	**Mean disease duration, yrs:** **D1:** 12 mos **D2:** 11 mos **D3:** 12 mos **TJC, mean:** **D1:** 30 (16.1) **D2:** 31 (15.5) **D3:** 31 (15.8) **SJC, mean:** **D1:** 24 (11.9) **D2:** 24 (11.7) **D3:** 24 (11.9) **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 41 **D2:** 42 **D3:** 39 **MTX naive, %:** **D1:** 100 **D2:** 100 **D3:** 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** **D1:** 100 **D2:** 100 **D3:** 100 **Baseline DAS, mean:** NR	**First 12 weeks** Mean changes in SF-36, HAQ, and ASHI significantly better in with ETA vs. MTX ($P < 0.0001$) **16 to 52 weeks** No significant difference in SF-36, HAQ, and ASHI scores between groups **At 6 months** Significantly more pts on ETA (25 mg) than on MTX achieved ACR50 and ACR70 responses (data NR, $P < 0.05$) **At 12 months** **ACR 20 response rates, %:** **D1**: 65 **D3**: 72 *(P* = 0.16) **Mean increase in Sharp score** **D1**: 1.00 **D3**: 1.59 *(P* = 0.11) **Erosion score change** **D1**: 1.03 **D3**: 0.47 *(P* = 0.002) Despite improvement, QoL measures remained below general population ($P < 0.0001$); at start QoL measures were significantly below that of general population ($P < 0.0001$) **24 month open-label extension**:	**At year 2** **SAEs:** 20.6 **Cardiovascular Events:** 1.8 MI **Malignancies:** 3% overall Total events: 18 Breast: 3 Prostate: 3 Colon: 3 Lung: 12 Malignant melanoma: l2 Leukemia: 1 Kidney: 1 Hodgkins: 1 Adenocarcinoma: 1 **URTI:** Pnuemonia 2 Overall SAE rate of 0.093 events per pt-year comparable to rate observed in first year of efficacy study, events per pt-year MTX: 0.109 ETA: 0.091	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon, 2000; Genovese 2002; Kosinski et al., 2002; Genovese, 2005 ERA study (continued)				**ACR20,%** **D1:** 59 **D3:** 72 (*P* = 0.005); **ACR50, %** **D1:** 49 **D3:** 42 **ACR 70,%** **D1:** 29 **D2:** 24 **HAQ improvement of at least 0.5 units, %:** **D1:** 55 **D2:** 37 (*P* < 0.001) **Total modified Sharp score change** **D1**: 1.3 **D3**: 3.2 *(P* = 0.001) **Erosion score change** **D1**: 0.7 **D3**: 1.9 *(P* = 0.001)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study **Country, Setting:** Netherlands and Belgium, multicenter **Funding:** Netherland **Research Objective:** Comparing efficacy and radiographic outcomes of combination of SSZ, MTX and PNL with SSZ alone **Study Design:** RCT **Overall N:** 155 (148) **Study Duration:** 56 wks; (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 69 • Diagnosed with RA according to ACR criteria • Duration of condition < 2 yrs • NSAID txt at least 3 mos, 6 or more active inflamed joints AND presence of 2 or more (9 or more tender joints, morning stiffness 45 min or more, EST of 28 or more in first hour **Exclusion Criteria:** • Pregnant or lactating: adequate contraception • Prior txt with: DMARDS except HCQ or steroids • Past TB • Impaired renal or hepatic system serious comorbidity surgery in past 3 mos • Unable to comply with protocol • Allergy to study med • Alcohol or substance abuse	**Interventions, dose:** **D1:** Combined txt (SSZ, MTX, PNL) **D2:** SSZ Only SSZ: 2g/d MTX: 7.5 mg/wk, weaned after 40 wks PNL: 60 mg/d wk 1 40 mg/d wk 2 25 mg/d wk 3 20 mg/d wk 4 15 mg/d wk 5 10 mg/d wk 6 then 7.5 mg/d until wk 28 then weaned off **N:** **D1:** 76 **D2:** 79 **Mean age, yrs:** NR **Sex, % female:** **D1:** 66% **D2:** 52% **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 4 mos **D2:** 4 mos **TJC, mean:** NR **SJC, mean:** NR **Antimalarial use (%):** **D1:** 21 **D2:** 24 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Erosions on hand or foot xrays, %:** **D1:** 74 **D2:** 79	**At week 28** **Mean pooled index** **D1:** - 1.4 (95% CI, 1.2-1.6) **D2:** - 0.8 (95% CI, 0.6-1.0) (*P* < 0.0001) **ACR20, %:** **D1:** 72 **D2:** 49 (*P* = 0.006) **ACR50, %:** **D1:** 49 **D2:** 27 (*P* = 0.007) **DAS median change:** **D1:** -2.1 (SD 1.2) **D2:** -1.3 (SD 1.2) (*P* < 0.0001) **HAQ mean change:** **D1:** -1.1 (SD 0.8) **D2:** -0.6 (SD 0.6) (*P* < 0.0001) **Sharp mean change**: **D1:** 1 **D2:** 4 (*P* < 0.001) **At week 56** **Mean pooled index:** **D1:** 1.1 (SD 0.8) **D2:** 0.9 (SD 0.8) (*P* =0.20) **DAS median change:** **D1:** 1.4 (SD 1.2) **D2:** 1.3 (SD 1.4) (*P* = 0.78) **HAQ mean change:** **D1:** 0.8 (SD 0.8) **D2:** 0.6 (SD 0.7) (*P* < 0.06)	**Overall:** **D1:** 72.3 **D2:** 62.0 **SAEs:** **D1:** 2.6 **D2:** 7.6 **Infections:** **D1:** 15.8 **D2:** 7.6 **Cardiovascular Events:** **D1:** 7.9 **D2:** 5.1 **Hepatotoxicity:** **D1:** 2.6 **D2:** 0	**Overall Attrition Rate, %:** 3.2 **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **At week 80** **Sharp mean change**: **D1:** 4 **D2:** 12 (*P* < 0.01) **Five yr follow up** **Sharp score mean change:** **D1:** 5.6 (95% CI, 4.3, 7.1) (*P* = 0.001) **D2:** 8.6 (95%CI, 6.2-11) (*P* = 0.001) **Time averaged DAS28, points/yr**: **D1:** -0.07 **D2:** **-0.17**		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study **Country, Setting:** Multinational (Europe, North America, Australia), multicenter (133) **Funding:** Abbott Laboratories **Research Objective:** To compare efficacy and safety of ADA + MTX vs. MTX or ADA in pts with early, aggressive RA (RA) who had not previously received MTX txt **Study Design:** RCT **Overall N:** 799 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: 3 yrs or less • MTX naive pts • > 8 swollen joints, > 10 tender joints, and an erythrocyte sedimentation rate of > 28 • Folic acid only other med allowed **Exclusion Criteria:** • Prior txt with: MTX, cyclophosphamide, cyclosporine, azathioprine	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ADA (40 mg/biwkly) **D3:** ADA (40 mg/biwkly) + MTX (20 mg/wk) **N:** **D1:** 257 **D2:** 274 **D3:** 268 **Mean age, yrs:** **D1:** 52 **D2:** 52.1 **D3:** 51.9 **Sex, % female:** **D1:** 73.9 **D2:** 77.4 **D3:** 72 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** .8 **D2:** .7 **D3:** .7 **TJC, mean:** **D1:** 32.3 **D2:** 31.8 **D3:** 30.7 **SJC, mean:** **D1:** 22.1 **D2:** 21.8 **D3:** 21.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 35.4 **D2:** 36.5 **D3:** 35.8 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.3 **D2:** 6.4 **D3:** 6.3 **HAQ:** **D1:** 1.5 **D2:** 1.6 **D3:** 1.5 **Erosion score:** **D1:** 13.6 **D2:** 11.3 **D3:** 11.0	**At 6 months** **Radiographic progression; change in Sharp scores:** **D1:** 3.5 **D2:** 2.1 (*P* < 0.001) **At 1 yr** **Radiographic progression; change in Sharp scores:** **D1:** 5.7 **D2:** 3.0 (*P* < 0.001) **HAQ DI improvement, mean units +/- sd:** **D1**: -0.8 +/- 0.7 **D2:** -0.8 +/- 0.6 **D3**: -1.1 +/- 0.6 **D2** vs. **D1**, *P* = NR **D3** vs. **D1**: *P* < 0.001 **D3** vs. **D2**: *P* = 0.002) **At 2 yrs** **ACR50 response, %:** **D1:** 43 **D2:** 37 **D3:** 59 **D3** vs. **D2** or **D1**: *P* < 0.001 **D1** vs. **D2**: *P*= NS **Clinical remission, %:** **D1:** 25 **D2:** 25 **D3:** 49 (both *P* < 0.001) **Radiographic progression; change in Sharp scores:** **D1:** 10.4 **D2:** 5.5 (*P* < 0.001)	**SAEs:** **D1:** 18.5 **D2:** 21.1 **D3:** 15.9 **Infections:** **D1:** 123 **D2:** 110 **D3:** 119 **Serious Infections:** **D1:** 2.9 **D2:** 0.7 **D3:** 1.6 **Malignancies:** **D1:** 0.4 **D2:** 0.9 **D3:** 0.9 **Withdrawal because of adverse events:** **D1:** 7% **D2:** 10% **D3:** 12%	**Overall Attrition Rate, %:** 32% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study	Inclusion and	Characteristics	Baseline Disease	Health Outcomes	Adverse	Analysis and

Characteristics	Exclusion Criteria	and Interventions	and Treatment Characteristics		Events, %	Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study				**Withdrawal because of lack of efficacy, %:** **D1:** 18 **D2:** 19 **D3:** 4.9 **HAQ DI improvement, mean units +/- sd:** **D1**: -0.9 +/- 0.6 **D2:** -0.9 +/- 0.7 **D3**: -1.0 +/- 0.7 **D2** vs. **D1**, *P* = NR **D3** vs. **D1;** *P* < 0.05 **D3** vs. **D2**; *P* = 0.058 **% with HAQ DI score of zero:** **D1**: 19 **D2:** 19 **D3**: 33 **D3** vs. **D2**, *P* < 0.001 **D3** vs. **D1**: *P* < 0.001 **% with HAQ DI improvement of ≥ 0.22 units from baseline:** **D1**: 63 **D2:** 58 **D3**: 72 **D3** vs. **D2**, *P* < 0.05 **D3** vs. **D1**: *P* < 0.05		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 **Country, Setting:** Scotland, 8 NHS sites **Funding:** Wyeth and Pharmacia - drugs Arthritis Research Campaign **Research Objective:** If a combination of SSZ and MTX is superior to either alone in RA pts with supoptimal response to 6 mos of SSZ **Study Design:** RCT **Overall N:** 165 **Study Duration:** Phase I: 6 mos; Phase 2: 12 additional mos for those with DAS > 2.4 after 6 mos	**Inclusion Criteria:** • Age: 18 to 80 • Duration of condition: < 10 yrs • Active disease defined by DAS > 2.4 after 6 mos SSZ txt were eligble for phase II • NSAIDs and other medications were continued • Intra-articular or intramuscular corticosteroid was permitted but not within 1 mo of 6, 12, & 18 mo assessments **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: MTX or SSZ • Impaired renal or hepatic system: creatinine > 150 mmol/dl, ALT, aspertate aminotransferase > 80 IU/l, alkaline phosphatase > 700 IU/l, gamma GT x3 • Other: abnormal white cell count (< 4 x 10*9/l)	**Interventions, dose:** **D1:** SSZ + MTX **D2:** SSZ + placebo **D3:** MTX + placebo Phase I MTX: 7.5 mg/w (3 x 2.5 mg) increasing by 2.5 mg/mo until max of 25 mg or toxicity SSZ: enteric coated 500 mg/d increased by 500 mg/wkly until 40 mg/kg per d to a max of 4g/d for initial 6 mos Placebo: Folic Acid 5 mg/wk given 3 days after MTX and MTX + placebo **N:** **D1:** 56 **D2:** 55 **D3:** 54 Overall: 687 **Mean age, yrs:** **D1:** 56 **D2:** 55 **D3:** 53 Overall: 55 **Sex, % female:** **D1:** 75 **D2:** 75 **D3:** 79 Overall: 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 1.9 **D2:** 1.6 **D3:** 1.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** All **Txt resistant, %:** All **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 3.63 **D2:** 3.67 **D3:** 3.5 **Sharp:** **D1:** 17.0 **D2:** 14.0 **D3:** 12.0	**Median change 18 mos:** **DAS:** **D1:** -0.67 **D2:** -0.30 **D3:** -0.26 (**D1** vs. **D2**; *P* = 0.039) (**D1** vs. **D3**; *P* = 0.023) (**D2** vs. **D3**; *P* = 0.79) **HAQ:** **D1:** -0.50 **D2:** -0.25 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.51) (**D1** vs. **D3**; *P* = 0.57) (**D2** vs. **D3**; *P* = 0.99) **SJC:** **D1:** -3.00 **D2:** -3.00 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.94) (**D1** vs. **D3**; *P* = 0.81) (**D2** vs. **D3**; *P* = 0.74) **ACR20, % :** **D1:** 29 **D2:** 18 (OR 1.25 (95% CI, 0.56-2.79) ; *P* = 0.68) **D3:** 15 (OR 2.01 (95% CI, 0.85-4.76), *P* = 0.14) **ACR50, %:** **D1:** 11 **D2:** 6 (OR 1.43 (95% CI, 0.43-4.81), *P* = 0.76) **D3:** 7 (OR 1.79 (95% CI, 0.49-6.49), *P* = 0.53)	NR	**Overall Attrition Rate, %:** 28.5 • 687 pts entered phase I (6 mos) • At 6 mos, 165 were not eliglbe to enter phase II (discontinued SSZ because of side effects: 19%, did not attend: 3.6%, died: 0.4%) • Another 191 were not randomized because DAS score was < 2.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **D2:** 2 (OR 1.50 (95% CI, 0.24-9.34), *P* = 1.00) **D3:** 2 (OR 3.00 (95% CI, 0.30-29.78), *P* = 0.62)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 **Country, Setting:** Europe, multicenter **Funding:** Wyeth **Research Objective:** To compare efficacy and safety of ETA and SSZ, alone and in combination, in pts with active RA despite SSZ txt **Study Design:** RCT **Overall N:** 260 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • Diagnosed according to ACR criteria; • Functional class of: I-III • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Duration of condition < 20 yrs • Stable doses of oral corticosteroids (10 mg/d of PRE or equivalent), one NSAID, simple analgesics with no anti-inflammatory action or daily doses of aspirin (300 mg) **Exclusion Criteria:** • Prior txt with: (1) ETA or other TNF antagonists or (2) received a DMARD other than SSZ within 3 mos. Or any biologic or cyclophosphamide within 6 mos, corticosteroids within 4 wks	**Interventions, dose:** **D1:** SSZ (2,2.5, or 3 g /d) + placebo **D2:** ETA (25 mg SC twice wkly) + placebo **D3:** ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) **N:** **D1:** 50 **D2:** 103 **D3:** 101 Overall: 254 **Mean age, yrs:** **D1:** 53.3 **D2:** 51.3 **D3:** 50.6 Overall: 51.4 **Sex, % female:** **D1:** 82.0 **D2:** 78.6 **D3:** 80.2 Overall: 79.9 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 5.6 (sd 4.4) **D2:** 7.1 (sd 5.2) **D3:** 6.5 (sd 5.1) **TJC, mean:** **D1:** 14.0 **D2:** 14.7 **D3:** 14.1 **SJC, mean:** **D1:** 11.1 **D2:** 10.1 **D3:** 10.4 **DMARD use, %:** **D1:** 58.0 **D2:** 69.9 **D3:** 58.4 **Corticosteroid use, %** **D1:** 40.0 **D2:** 59.2 **D3:** 44.6 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D1:** 28.0 **D2:** 73.8 **D3:** 74.0 ($P < 0.01$) **ACR50, %:** **D1:** 14.0 **D2:** 46.6 **D3:** 52.0 ($P < 0.01$) **ACR70, %:** **D1:** 2.0 **D2:** 21.4 **D3:** 25.0 ($P < 0.01$) In groups receiving ETA, significant differences in ACR core components were observed by wk 2 compared with those receiving SSZ alone ($P < 0.01$) **DAS improvement, %:** **D1:** 19.6 **D2:** 48.2 **D3:** 49.7 ($P < 0.01$) **Mean HAQ improvement, %:** **D1:** 9.2 **D2:** 35.3 **D3:** 40.2 ($P < 0.01$)	**Infections:** **D1:** 13 **D2:** 47 **D3:** 31 **Infusion or injection reaction:** **D1:** 3 **D2:** 38 **D3:** 21 **Abdominal Pain:** **D1:** 0 **D2:** 7 **D3:** 8 **Headache:** **D1:** 4 **D2:** 5 **D3:** 15 **Nausea:** **D1:** 3 **D2:** 3 **D3:** 12 **URTI:** **D1:** 5 **D2:** 10 **D3:** 11	**Overall Attrition Rate, %:** 13 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **Country, Setting:** Finland, France, Germany (France only for 5 yr), multicenter **Funding:** Pharmacia Upjohn **Research Objective:** Clinical benefit of MTX + SSZ compared to either drug alone early, active RA pts fulfilling some criteria of poor potential long term outcome **Study Design:** RCT **Overall N:** 209 (146) **Study Duration:** 52 wks (5 yrs)	**Inclusion Criteria:** • Diagnosed according to ACR criteria • Duration < 1 yr • Presence of active disease as defined by DAS ≥ 3 (calculation based on Ritchie articular index, 44 SJC, and ESR) and presence of RF and/or HLA DR 1/4 • Concommitant drugs allowed were analgesics and NSAIDS **Exclusion Criteria:** • Prior txt with steroids, DMARDS, or any drugs to treat RA other than analgesic or NSAIDS • Pts with contraindications to use of SSZ or MTX	**Interventions, dose:** **D1:** SSZ + placebo **D2:** MTX + placebo **D3:** SSZ + MTX MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate SSZ: increased to 2 grams daily by d #9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate Other?: combo MTX + SSZ **N:** **D1:** 68 **D2:** 69 **D3:** 68 **Mean age, yrs:** **D1:** 52 **D2:** 50 **D3:** 52 **Sex, % female:** **D1:** 71 **D2:** 74 **D3:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 2.9 mos since diagnosis, 10.8 since onset **D2:** 2.3 mos from diagnosis, 18.4 from onset **D3:** 3.4 mos from diagnosis, 10.6 from onset **TJC, mean:** NR **SJC, mean:** **D1:** 10.5 **D2:** 9.4 **D3:** 9.4 **DMARD use, %:** All groups: 0 **Corticosteroid use, %** All groups: 0 MTX naive, %: All groups: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** All groups: 100	**DAS change:** **D1:** -1.15 **D2:** -0.87 **D3:** -1.26 (*P* = 0.019 from inter-group comparisons using analysis of variance) **RAI changes:** **D1:** -7.1 **D2:** -4.2 **D3:** -9.4 (*P* = 0.001) **ACR response, %:** **D1:** 59 **D2:** 59 **D3:** 65 (*P* = NR) **At 5 years** Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared to monotherapy with either drug used alone **Mean DAS:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9)	**Overall:** **D1:** 75 **D2:** 75 **D3:** 91 **Abdominal Pain:** **D1:** 9 **D2:** 6 **D3:** 13 **Dizziness:** **D1:** 6 **D2:** 1 **D3:** 3 **Headache:** **D1:** 9 **D2:** 4 **D3:** 12 **Nausea:** **D1:** 32 **D2:** 23 **D3:** 49	**Overall Attrition Rate, %:** 27% (28.8) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 **Country, Setting:** Multinational, 117 centers **Funding:** NR **Research Objective:** To compare both short and long-term (up to 2 yr) clinical efficacy and safety of LEF and MTX for txt of RA **Study Design:** RCT **Overall N:** 999 **Study Duration:** 1 yr, optional second yr	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria: Active Disease • Previous use of DMARDs: only if discontinued 28 ds before trial • Duration of condition: for at least 4 mos, but no longer than 10 yrs • NSAIDs and steroids were allowed provided a stable dose of NSAIDs or steroid (≤ 10 mg/d) PNL for at least 28 ds prior to study entry • Women of childbearing age were required to use adequate contraception **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: Intra-articular corticosteriod injections w/in 6 wks of efficacy assessment	**Interventions, dose:** **D1:** LEF Yr 1 **D2:** MTX Yr 1 **D3:** LEF Yr 2 **D4:** MTX Yr 2 MTX: 7.5 to 15 mg/wk LEF: loading dose of 100 mg/d for 3 ds, followed by maintenance dose 20/ mg/d **N:** **D1:** 501 **D2:** 498 **D3:** 292 **D4:** 320 **Mean age, yrs:** **D1:** 58.3 **D2:** 57.8 **D3:** 57.7 **D4:** 57.0 **Sex, % female:** **D1:** 70.7 **D2:** 71.3 **D3:** 71.2 **D4:** 71.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.7 **D2:** 3.8 **D3:** 3.5 **D4:** 3.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 66.3 **D2:** 66.9 **D3:** 64.7 **D4:** 66.9 **Corticosteroid use, %** **D1:** 36.3 **D2:** 33.5 **D3:** 14.0 **D4:** 11.3 **MTX naive, %:** NR **DMARD Txt resistant, %:** **D1:** 1.1 **D2:** 1.1 **D3:** 1.0 **D4:** 1.1 **Pts with Early RA (≤ 3 yrs):** NR	**At year 1** **ACR20:** **D1:** 50.5% **D2:** 64.8% ($P < 0.001$) **HAQ improvement:** Minimal quantitative difference between groups, but statistically significant (shown in figure only; $P < 0.05$) **Radiograph change, Larsen Scores:** **D1** and **D2**: 0.03 increase (P =NS, NR) **Primary clinical efficacy endpoints**: **TJC:** **D1:** -8.3 **D2:** - 9.7 **SJC:** **D1:** -6.8 **D2:** -9.0 **Physician global assessment:** **D1:** -0.9 **D2:** -1.2 **Pt global assessment:** **D1:** -0.9 **D2:** -1.2 **At year 2** **ACR20, %:** **D1:** 64.3 **D2:** 71.7 (P = NS, NR)	**SAEs:** **D1:** 7% **D2:** 8% **Headache:** **D1:** 6.2 **D2:** 4.8 **Hepatotoxicity:** **D1:** 5.4 **D2:** 16.3 **D3:** 2.7 **D4:** 5.9 **Nausea:** **D1:** 11.2 **D2:** 15.7 **URTI:** **D1:** 5.2 **D2:** 5.0 **D3:** 4.5 **D4:** 5.6 **Deaths** MTX: 2	**Overall Attrition Rate, %:** • 26.3% (263/999) during yr 1 • Combined 2 yrs, attrition 50.3% (502/999) of those initially starting study at baseline • During yr 2, attrition 18.8% (115/612) of those agreeing to continue study for 2nd yr **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age > 18 yrs • RA according to ACR criteria • Duration of condition < 2 yrs • Active disease with at least 6 of 66 swollen joints • At least 6 of 68 tender joints • ESR > 28 mm/hr OR global health score greater than or equal to 20mm on 0 to 100 VAS • Concomittant NSAIDS and intraarticular steroids **Exclusion Criteria:** • Pregnant • Prior txt with: DMARDS other than antimalarials • Impaired renal or hepatic system	**Interventions, dose:** **D1:** sequential monotherapy **D2:** step-up combination therapy **D3:** initial combination with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 **Country, Setting:** Netherlands, 1 academic and 6 peripheral clinics **Funding:** Pharmachemie BV; Pharmacia AB **Research Objective:** Compare efficacy and safety of SSZ, MTX, and combination of both in pts with early RA **Study Design:** RCT **Overall N:** 105 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed with RA according to ACR criteria: ACR criteria • RF positive and/or HLA-DR4 positive and/or HLA DR1 positive • Functional class of: DAS ≥ 3.0 • Duration of condition: < 12 mos • Analgesica and NSAIDS allowed **Exclusion Criteria:** • Prior txt with: DMARDS other than analgesics and NSAIDS • Other: contraindications to SSZ or MTX	**Interventions, dose:** **D1:** SSZ (1 g/day; max 3 g/day) **D2:** MTX (7.5 mg/wk; max 15 mg/wk) **D3:** MTX (7.5 mg/wk; max 15 mg/wk) + SSZ (1 g/day; max 3 g/day) **N:** **D1:** 34 **D2:** 35 **D3:** 36 **Mean age, yrs:** **D1:** 56.8 **D2:** 54.9 **D3:** 57.0 **Sex, % female:** **D1:** 61.8 **D2:** 65.7 **D3:** 66.7 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.1 mos **D2:** 3.0 mos **D3:** 2.6 mos **TJC, mean:** **D1:** 20.8 **D2:** 20.6 **D3:** 24.8 **SJC, mean:** **D1:** 17.0 **D2:** 19.9 **D3:** 20.8 **DMARD use, %:** Overall: 0 **Corticosteroid use, %** Overall: 0 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.6 **D2:** 4.7 **D3:** 5.0	No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable **At 52 weeks** **DAS mean change:** **D1:** -1.6 (95% CI, -2.0 to -1.2) **D2:** -1.7 (95% CI, -2.0 to -1.4) **D3:** -1.9 (95% CI, -2.2 to -2.3) **Ritchie mean change:** **D1:** -8.6 (95% CI, -10.7 to -6.5) **D2:** -8.2 (95% CI, -10.1 to -6.4) **D3:** -9.4 (95% CI, -11.1 to -7.7) **Swollen joints mean change**: **D1:** SSZ -7.9 (95% CI, -10.1 to -5.7) **D2:** -10.2 (95% CI, -12.5 to -8.0) **D3:** -11.3 (95% CI, -13.5 to -9.2)	**Overall:** **D1:** 88.2 **D2:** 77.1 **D3:** 88.9 **SAEs:** **D1:** 8.8 **D2:** 0 **D3:** 0 **Abdominal Pain:** **D1:** 26.5 **D2:** 20 **D3:** 36 **Cardiovascular Events (Dyspnea):** **D1:** 5.9 **D2:** 0 **D3:** 5.6 **Dizziness:** **D1:** 17.6 **D2:** 8.6 **D3:** 27.8 **Headache:** **D1:** 17.6 **D2:** 11.4 **D3:** 11.1 **Nausea:** **D1:** 29.4 **D2:** 25.7 **D3:** 63.9 **URTI** **D1:** 17.6 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from baseline:** **D1:** -0.32 (95% CI, -0.53 to -0.10) **D2:** -0.46 (95% CI, -0.68 to -0.25) **D3:** -0.51 (95% CI, -0.76 to -0.26) **Number of pts with a response according to ACR criteria at end of study:** **D1:** 25 **D2:** 25 **D3:** 28 **Number of pts with good response according to EULAR definition:** **D1:** 14 **D2:** 15 **D3:** 14		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004; van der Heijde, 2006 TEMPO study **Country, Setting:** Multinational (Europe), multicenter **Funding:** Wyeth Research **Research Objective:** To compare safety and efficacy of combination of ETA and MTX with monotherapies in pts with RA who had failed previous DMARD txt **Study Design:** RCT **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**Inclusion Criteria:** • Age ≥ 18 • Diagnosed according to ACR criteria • Functional class I-III • Less than satisfactory response to at least 1 DMARD other than MTX • Duration 6 mos to 20 yrs • RA defined as > 10 swollen and > 12 painful joints and at least one of: ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs **Exclusion Criteria:** • TNF antagonist, any immuno-suppressive drugs w/in 6 mos • Any investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ETA (25 mg 2x wkly) **D3:** ETA (25 mg 2x wkly) + MTX (7.5 titrated to 20 mg/wk) **N:** **D1:** 228 (152) **D2:** 223 (163) **D3:** 231 (188) Overall (at 2yrs): 503 **Mean age, yrs:** **D1:** 53 **D2:** 53.2 **D3:** 52.5 Overall (at 2yrs): 52.1 **Sex, % female:** **D1:** 79 **D2:** 77 **D3:** 74 Overall (at 2yrs): 76 **Race, % white:** **D1:** 98 **D2:** 99 **D3:** 98 Overall (at 2yrs): 99	**Mean disease duration, yrs:** **D1:** 6.8 **D2:** 6.3 **D3:** 6.8 **TJC, mean:** **D1:** 33.1 **D2:** 35 **D3:** 34.2 **SJC, mean:** **D1:** 22.6 **D2:** 23 **D3:** 22.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 64 **D2:** 57 **D3:** 62 **MTX naive, %:** **D1:** 58 **D2:** 58 **D3:** 56 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**At 24 weeks** **AUC of ACR-N, %-yrs:** **D1:** 12.2 **D2:** 14.7 **D3:** 18.3 (*P* < 0.0001) **ACR20, %:** **D1:** 75 **D2:** 76 **D3:** 85 (*P* = 0.0151) **ACR50, %:** **D1:** 43 **D2:** 48 **D3:** 69 (*P* < 0.0001) **ACR70, %:** **D1:** 19 **D2:** 24 **D3:** 43 (*P* < 0.0001) **At 52 weeks** **DAS < 1.6 remission, %:** **D1:** 13 **D2:** 16 **D3:** 35 (**D3** vs. **D2:** *P* < 0.0001; **D2** vs. **D1:** *P* = 0.5031) **HAQ, decline:** **D1:** 0.65 **D2:** 0.7 **D3:** 1.0 (*P* < 0.05) **D3** therapy significantly more likely to attain HAQ DI similar to population norms (< 0.5) than monotherapy	**Overall:** **D1:** 81 (87) **D2:** 86 (92) **D3:** 81 (86) **Infections:** **D1:** 64 (75) **D2:** 59 (71) **D3:** 67 (76) **Serious Infections:** **D1:** 4 (7) **D2:** 4 (6) **D3:** 4 (6) **Infusion or injection reaction:** **D1:** 2 (2) **D2:** 21 (21) **D3:** 10 (11) **Abdominal Pain:** **D1:** 18 **D2:** 12 **D3:** 18 **Hypertension:** **D1:** 5 **D2:** 13 **D3:** 9 **Headache:** **D1:** 14 **D2:** 15 **D3:** 15 **Nausea:** **D1:** 32 (39) **D2:** 10 (13) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**Radiograhic outcomes** **Total Sharp Score change:** **D1:** 0.28 **D2:** 0.52 **D3**: -0.54; D3 vs D2; *P* = 0.0006 D2 vs D1; *P* =0.047 **Erosion score change:** **D1:** 1.68 **D2:** 0.21 **D3**: -0.30; D3 vs D2; *P* = 0.0001 D2 vs D1; *P* =0.008 **JSN score change:** **D2:** 0.32 **D3**: -0.23; *P* = 0.0007 **At 2 years** **Total Sharp score change:** **D1:** 1.12 **D2:** 1.10 **D3**: -0.56; *P* = 0.05 D3 vs D2; *P* = 0.05 D2 vs D1; *P* = NR **Erosion score change** **D2:** 0.36 **D3:** -0.76 P < 0.05 **JSN score change** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study **Country, Setting:** Finland, NR **Funding:** Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital **Research Objective:** Efficacy and tolerability of combo of DMARDs vs. a single DMARD **Study Design:** RCT **Overall N:** 199 randomized, 187 completed 2 yrs, 160 at 5 yrs **Study Duration:** 24 mos (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 65 • Diagnosed with RA according to ACR criteria: active disease, 1987 criteria • Duration of condition: < 2 yrs **Exclusion Criteria:** • Previous use of DMARDs • Underwent glucocorticoid glucocorticoid therapy within the previous • 2 weeks • serious comorbidity • suspected inabilty to • comply with the protocol • hypersensitivity to any study medication • history of cancer • pregnant women • women of childbearing age who were not using reliable methods of contraception	**Interventions, dose:** **D1:** Combo: MTX + HCQ + SSZ + PNL **D2:** Single DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 months **N:** **D1:** 97 **D2:** 98 **Mean age, yrs:** **D1:** 45 **D2:** 46 **Sex, % female:** **D1:** 58 **D2:** 66 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.3 mos **D2:** 8.6 mos **TJC, mean:** **D1:** 18 **D2:** 20 **SJC, mean:** **D1:** 14 **D2:** 14 **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Larsen Score:** **D1:** 0 **D2:** 2	**At 2 years** **Eroded joints, number:** **D1:** 2 **D2:** 3 (*P* = 0.006) btw groups Progression of radiological joint damage lower in combination versus monotherapy **Larsen Erosion Score improvement:** **D1:** 2 **D2:** 10 (*P* = 0.002) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **Clinical remission, %:** **D1:** 37.9 **D2:** 18.4 (*P* = 0.011) **ACR50, %:** **D1:** 71 **D2:** 58 (*P* = 0.058) Median work disability per pt-observation yr, days: **D1:** 12.4 **D2:** 32.2 (*P* = 0.008) **At 5 years** **Eroded joints, number:** **D1:** 3 **D2:** 6	**Overall:** **D1:** 70 **D2:** 71 **SAEs:** **D1:** 3 **D2:** 5 **Cardiovascular Events:** **D1:** 1 MI **D2:** 2 MIs **Malignancies:** 1 prostate cancer; 1 multiple myeloma **URTI:** 1 pneumonia	**Overall Attrition Rate, %:** 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **5 year Remiission** D1: 28 D2: 22 (*P* = NS) **Increase in Larsen score** D1: lower than (*P* =0.004)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial **Country, Setting:** Multinational, unversity hospitals **Funding:** Centocor **Research Objective:** To compare benefits of initiating txt with MTX and anti-TNFá with those of MTX txt alone in pts with RA of < 3 yrs duration **Study Design:** RCT **Overall N:** 1049 **Study Duration:** 54 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3 mos and < 3 yrs • > 10 swollen joints, and > 12 tender joints • 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS • 20 mg MTX (required) **Exclusion Criteria:** • Prior txt with: MTX, received other DMARDs within 4 wks of entry • Used ETA, INF, ADA or other anti-TNF-á agent • History of TB; HIV, hepatitis B or C virus, CHF, or lymphoma or other malignancy	**Interventions, dose:** **D1:** MTX (20 mg/wk) + placebo **D2:** MTX + INF (3 mg/kg/wk) **D3:** MTX + INF (6 mg/kg/wk) **N:** **D1:** 282 **D2:** 359 **D3:** 363 **Mean age, yrs:** **D1:** 50 **D2:** 51 **D3:** 50 **Sex, % female:** **D1:** 75 **D2:** 71 **D3:** 68 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 0.9 **D2:** 0.8 **D3:** 0.9 **TJC, mean:** **D1:** 34 **D2:** 32 **D3:** 33 **SJC, mean:** **D1:** 22 **D2:** 21 **D3:** 22 **DMARD use, %:** **D1:** 35 **D2:** 29 **D3:** 32 **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** NR **JSN:** **D1:** 3.0 **D2:** 2.9 **D3:** 2.9	**At weeks 30 to 54** **HAQ:** **D1:** 0.68 **D2:** 0.80 **D3:** 0.88; (**D2** vs. **D1**; *P* = 0.03) (**D3** vs. **D1**; *P* < 0.001) **At 54 weeks** **HAQ > 0.22, %:** **D1:** 65.2 **D2:** 76.0 **D3:** 75.5 (**D2** vs. **D1**; *P* = 0.003) (**D3** vs. **D1**; *P* < 0.004) **ACR20, %:** **D1:** 53.6 **D2:** 62.4 **D3:** 66.2 (**D2** vs. **D1**; *P* = 0.028) (**D3** vs. **D1**; *P* < 0.001) **ACR50, %:** **D1:** 32.1 **D2:** 45.6 **D3:** 50.4 (**D2** vs. **D1**; *P* = 0.001) (**D3** vs. **D1**; *P* < 0.001) **ACR70, %:** **D1:** 21.2 **D2:** 32.5 **D3:** 37.2 (**D2** vs. **D1**; *P* = 0.002) (**D3** vs. **D1**; *P* < 0.001)	**SAEs:** **D1:** 11 **D2:** 14 **D3:** 14 **Serious Infections:** **D1:** 2.1 **D2:** 5.6 **D3:** 5.0 **Infusion or injection reaction:** **D1:** 7 **D2:** 21 **D3:** 15 **TB:** **D1:** 0 **D2:** 0.8 **D3:** 0.3 **Nausea:** **D1:** 18 **D2:** 20 **D3:** 17 **URTI:** **D1:** 21 **D2:** 25 **D3:** 28	**Overall Attrition Rate, %:** 14.9 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **D3:** 46.7 (*P* < 0.001) **Modified Sharp:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 (*P* < 0.001) **Increase in radiographic score, %:** INF: 39 vs. MTX 61 (*P* < 0.001) **Employability:** INF+MTX (OR 2.4, *P* < 0.001) MTX (*P* = 0.56) Combo has higher probability of improvement than MTX alone **Net increase in employability:** MTX+INF: 8% MTX-only: 2% **Employability status changed from employable to unemployable, %:** INF: 8 MTX-only: 14 (*P* = 0.05) **SF-36 Physical component summary scores** **D1:** 11.7 **D2:** 13.2 **D3:** 10.1 **D3** vs. **D1**, *P* =0.10 **D3** vs. **D2**; *P* =0.003		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 *P* < 0.001 **Erosion Score change:** **D1:** 3.0 **D2:** 0.3 **D3:** 0.1 *P* < 0.001 **JSN Score change:** **D1:** 0.6 **D2:** 0.1 **D3:** 0.2 *P* < 0.001		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Smolen et al., 1999; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **Study Design:** RCT **Overall N:** 266 (358 including placebo arm) **Study Duration:** 24 wks (12 and 24 month followup)	**Inclusion Criteria:** • Age: ≥ 18 • Active RA defined by: ≥ 6 tender and swollen joints, based on a 28-joint count, physician and pt global assessments of RA activity of "fair, poor, or very poor", CRP > 2.0 mg/dL or ESR > 28 mm/h • Functional class I – III • Other DMARDs discontinued ≥ 4 wks • Stable doses of NSAIDS permitted -acetylsalicylic acid, oral steroids (prednisolone ≤ 10 mg/day), and up to 3 intra-articular steroid injections, not exceeding 60 mg triamcinolone • Intra-articular steroid injections not permitted during first 6 mos **Exclusion Criteria:** • Pregnant or lactating	**Interventions:** **D1:** LEF **D2:** SSZ **N:** **D1:** 133 **D2:** 133 **Mean age, yrs:** **D1:** 58.3 **D2:** 58.9 **Sex, % female:** **D1:** 75.9 **D2:** 69.2 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.6 **D2:** 7.4 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 60.2 **D2:** 48.9 **Corticosteroid use, %:** **D1:** 28.6 **D2:** 27.8 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF positive:** **D1:** 79% **D2:** 80%	**At 24 weeks** **ACR 20, %:** **D1:** 55 **D2:** 56 **ACR 50, %:** **D1:** 33 **D2:** 30 **Improving HAQ scores, change (%):** **D1:** -0.50 (45) **D2:** -0.29 (29) (*P* = 0.0086) **Change in Sharp; number, change (SD):** **D1:** 87 1.23 (2.85) **D2:** 84 2.32 (10.11) **Larsen score change:** **D1:** 0.01 **D2:** 0.01 (*P* = NS) **At 1 year** **Change in Sharp; number, change (SD):** **D1:** 60 0.97 (6.11) **D2:** 53 1.38 (2.88) **Larsen score change:** **D1:** 0.02 **D2:** 0.02 (*P* = NS) **At 2 years** **Larsen score change:** **D1:** -0.07 **D2:** -0.02 (*P* = NS) Similar ACR20 response rates D1: 48; D2: 44; *P*=NR	**SAEs:** **D1:** 5 **D2:** 7 **Headache:** **D1:** 7 **D2:** 11 **Nausea:** **D1:** 10 **D2:** 17 **URTI:** **D1:** 14 **D2:** 15 **Diarrhea:** **D1:** 17 **D2: 9** **Alopecia:** **D1:** 8 **D2: 5** **Rash:** **D1:** 10 **D2: 9** **Withdrawal due to AEs:** **D1:** 14 **D2: 19** 2 cases of reversible agranulocytosis in SSZ	**Overall Attrition Rate, %:** 33% at 24 wks **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 **Country, Setting:** US and Canada, multicenter (47 university & private rheumatology practices) **Funding:** Hoescht Marion Roussel **Research Objective:** Efficacy and safety of LEF with placebo and MTX in active RA **Study Design:** RCT **Overall N:** 482 (active arms-364) **Study Duration:** 12 mos (w/ 1 year followup)	**Inclusion Criteria:** • Age: 18 or older • Diagnosed according to ACR criteria; DMARDs discontinued at least 30 days prior • Duration of condition at least 6 mos • 10 mg stable prednisone (or equivalent) • NSAIDs if dosages stable at least 30 days prior to enrollment **Exclusion Criteria:** • Pregnant or lactating • Prior treatment with: MTX • Inflammatory joint disease not caused by RA, • History of clinically significant drug or alcohol abuse, or admitted to consumption of more than 1 alcoholic drink per day	**Interventions:** **D1:** LEF (20 mg/week) **D2:** MTX (7.5 to 15 mg/week) **N:** **D1:** 182 **D2:** 182 **Mean age, yrs:** **D1:** 54.1 **D2:** 53.3 **Sex, % female:** **D1:** 72.5 **D2:** 75.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.0 **D2:** 6.5 **TJC, mean:** **D1:** 15.5 **D2:** 15.8 **SJC, mean:** **D1:** 13.7 **D2:** 13.0 **DMARD use, %:** **D1:** 55.5 **D2:** 56.0 **Corticosteroid use, %:** **D1:** 53.8 **D2:** 52.7 **MTX naive, %:** Both groups 100 **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **NR** **RF positive:** **D1:** 64.8 **D2:** 59.4 **MHAQ:** **D1:** 0.8 **D2:** 0.8	**At 12 mos** **ACR 20, %** **D1:** 52 **D2:** 46 **ACR 50, %** **D1:** 34 **D2:** 23 **ACR 70, %** **D1:** 20 **D2:** 9 **MHAQ mean change** **D1:** -0.3 **D2:** -0.2 **Sharp score change** **D1:** 0.53 (n:131) **D2:** 0.88 (n= 138) (*P* = 0.05) **Mean change HAQ-DI** **D1:** -0.45 (n= 164) **D2:** -0,26 (n= 168) (*P* ≤ 0.01) **Mean change SF-36 physical component** **D1:** 7.6 (n= 157) **D2:** 4.6 (n=162) **Work productivity mean change** **D1:** 9.8 (n= 138) **D2:** 7.5 (n= 148) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**SAEs:** **D1:** 1.1 **D2:** 2.7 **Infections:** **D1:** 56.6 **D2:** 59.9 **Abdominal Pain:** **D1:** 13.7 **D2:** 15.4 **Nausea:** **D1:** 20.9 **D2:** 19.2 **Back pain:** **D1:** 8 **D2:** 2 **Diarrhea:** **D1:** 36.8 **D2:** 21.6 **Oral Ulcers:** **D1:** 6.8 **D2:** 10.5 **GI Events:** **D1:** 5.5 **D2:** 1.7 **Elevated Transaminases:** **D1:** 7.1 **D2:** 4.4 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al 2005 **Country, Setting** Sweden Multicenter **Funding:** Swedish Rheumatism Association and others **Research Objective** Efficacy of low-dose PNL on joint damage and disease activity in pts with early RA being treated concomitantly with DMARDs **Study Design:** RCT **Overall N:** 250 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age 18 to 80 yrs • Diagnosed according ARA 1987 revised criteria • Duration ≤ 1 yr: pt in BARFOT study • DAS28 score >3.0 • Started by treating rheumatologist on first DMARD • Concomitant NSAIDS txt permitted • Intraarticular steroid injections allowed except 2 wks prior to any clinical evaluation **Exclusion Criteria:** • Pregnant or lactating • Glucocorticoids, DMARDs • Contraindication for glucocorticoid therapy • Previous fragility fractures, pts < 65 years with T score < -2.5 on bone mineral densitometry	**Interventions, dose:** **D1:** DMARD (SSZ 2 g/day or MTX mean dose 10 mg/week, dosages NR) + PNL (7.5 mg/d) **D2:** DMARD only **N:** **D1:** 119 **D2:** 131 **Mean age, yrs:** **D1:** 51 **D2:** 59 **Sex, % female:** **D1:** 65 **D2:** 63 **Race, % white:** **D1:** NR **D2:** NR	**Mean disease duration, yrs:** **D1:** 6.5 mos **D2:** 5.8 mos **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** Overall: 100 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 5.28 **D2:** 5.42 **HAQ:** **D1:** 1.01 **D2:** 0.98 **SOFI:** **D1:** 8 **D2:** 9	**At 2 yrs:** **DAS < 2.6 disease remission, % achieved** **D1**: 55.5 **D2**: 32.8 (*P* = 0.0005) **DAS28, scores over time ± SD** **D1**: 5.3 ± 1.1 at baseline to 2.7 ± 1.5 after 1 yr and 2.7 ± 1.3 after 2 yrs **D2**: 5.4 ± 1.0, 3.3 ± 1.5, and 3.2 ± 1.4 **HAQ scores mean decrease over time :** **D1**: 1.0 at baseline to 0.4 at 1 year and 0.5 **D2**: 1.0, 0.6, and 0.7 (*P* value NR) **Improvement in mean SOFI index** **D1:** mean decreased from 8 at baseline to 4 at 1 year and 4 after 2 years **D2:** 9, 6, and 7 respectively (*P* value NR) **Total sharp score ,median IQR change** i D1: 1.8 (IQR 0.5-6.0) D2: 3.5 (IQR 0.5-10.0) (*P* = 0.019) **Newly eroded joints per pt, median** D1: 0.5 (IQR 0-2) D2: 1.25 (IQR 0-3.25) (*P* = 0.007)	NR	**Overall Attrition Rate, %:** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al 2005 (continued)	• 65 or older with Z score ≤ 1			**Radiographic progression beyond smallest detectable difference, %** **D1:** 25.9 **D2:** 39.3 (*P* = 0.033) **Joint space narrowing score, median change** **D1:** 1 **D2:** 2 (*P* = 0.08)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 **Country, Setting:** US, rheumatology practices (509) **Funding:** Immunex Corporation **Research Objective:** To evaluate effectiveness of select biologics, MTX (MTX), and other DMARDs in management of adult RA in routine clinical practice **Study Design:** Prospective cohort study **Overall N:** 5,397 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18 or older • Diagnosed with RA according to ACR criteria: 1987 ACR • Pts requiring a change in RA txt **Exclusion Criteria:** • Pregnant or lactating • Active infection, • Concurrent enrollment in a clinical trial	**Interventions, dose:** **D1:** MTX (10 to 15 mg/wk) **D2:** ETA (50 mg/wk) **D3:** ETA (50 mg/wk) +MTX **D4:** INF (3.8 mg/8wks) **D5:** INF (3.8 mg/8wks) + MTX (15 mg/wk) **D6:** LEF (20 mg/d) **D7:** LEF (20 mg/d) +MTX (15 mg/wk) **D8:** MTX (15 mg/wk) +HCQ (400 mg/d) **D9:** MTX (15 mg/wk) +HCQ (400 mg/d) +SSZ (2000 mg/d) **N:** **D1:** 941 **D2:** 1251 **D3:** 1783 **D4:** 120 **D5:** 540 **D6:** 204 **D7:** 191 **D8:** 325 **D9:** 42 **Mean age, yrs:** **D1:** 56.8 **D2:** 53.2 **D3:** 52.6 **D4:** 60.2 **D5:** 58.5 **D6:** 57.7 **D7:** 55.5 **D8:** 53.8 **D9:** 47.8	**Mean disease duration, yrs:** **D1:** 3.5 **D2:** 9.2 **D3:** 7.7 **D4:** 10.6 **D5:** 9.5 **D6:** 10.1 **D7:** 7.4 **D8:** 4.6 **D9:** 7.2 **TJC, mean:** **D1:** 13 **D2:** 13.4 **D3:** 13.3 **D4:** 14.8 **D5:** 3.9 **D6:** 12.8 **D7:** 12.2 **D8:** 11.8 **D9:** 10.1 **SJC, mean:** **D1:** 11.3 **D2:** 11.1 **D3:** 11.5 **D4:** 13.9 **D5:** 12.0 **D6:** 11.8 **D7:** 11.4 **D8:** 9.2 **D9:** 10.2	**mACR20, %:** **D1:** 37 **D2:** 41 **D3:** 43 **D4**: 26 **D5:** 35 **Adjusting for baseline covariates** **D3:** vs. **D1**(OR 1.29, 95% CI, 1.09-1.52; *P* < 0.01) **D2** vs. **D1** (OR 1.23, 95% CI, 1.02-1.47; *P* < 0.05) **D1** vs. **D5** (OR 0.96 CI 0.76-1.21 p = 0.72) **D1** vs. **D4** (OR 0.66, 95% CI, 0.43-1.02; *P* = 0.06) **Mean change HAQ improvement, %** **D1:** 7 **D2:** 17 (*P* < 0.001) **D3:** 17 (*P* < 0.001) **mACR20 response** **D5** vs. **D1**: (OR 0.68, 95% CI, 0.48-0.96; *P* < 0.05) **D6** vs. **D1** (OR 0.76, 95% CI, 0.54-1.06; *P* = 0.11) **D8** vs, **D1**: (OR 0.94, 95% CI, 0.72-1.23; *P* = 0.64) **D9** vs. **D1**: (OR 0.57, 95% CI, 0.27-1.18; *P* = 0.13) **SJC % improvement** **D1** vs **D1**: 34 (N/A) **D2** vs. **D1**: 53 (*P* < 0.0001) **D4** vs. **D1**: 29 (*P* = NS) **D3** vs. **D1**: 55 (*P* < 0.0001) **D5** vs **D1**:48 (*P* < 0.01)	NR	**Overall Attrition Rate, %:** 33.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)		**Sex (% female** **D1:** 75 **D2:** 75 **D3:** 79 **D4:** 71 **D5:** 77 **D6:** 76 **D7:** 78 **D8:** 80 **D9:** 79 **Race, % white:** **D1:** 77 **D2:** 81 **D3:** 81 **D4:** 78 **D5:** 81 **D6:** 78 **D7:** 82 **D8:** 83 **D9:** 79	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **D7:** 95 **D8:** 78 **D9:** 88 **Corticosteroid use, %** **D1:** 53 **D2:** 48 **D3:** 51 **D4:** 63 **D5:** 57 **D6:** 48 **D7:** 56 **D8:** 50 **D9:** 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**TJC % improvement** D1: 34(N/A) D2 vs. D1: 53% (*P* < 0.001) D4 vs D1: 29% (*P* = NS) D3 vs D1: 55% (*P* < 0.0001) D5 vs D1: 48% (*P* = NS) **HAQ % improvement amongst pts < 65 yrs** **D2:** 22 **D4:** 4 (*P* = NR)		

Evidence Table 5. KQ2. Rheumatoid arthritis trials: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 6. KQ 2. Rheumatoid arthritis systematic reviews: functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of Review:** To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA Meta-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts **Number of Pts:** 1,144 LEF 312 to Placebo 680 to MTX 132 to SSZ Only 920 used in meta-analysis 2 yr extension: LEF:158 SSZ: 60 MTX 101	**Studies included:** 6 trials **Characteristics of included studies:** Randomized, double-blind, placebo and/or active controlled **Characteristics of included populations:** All with active RA **Characteristics of interventions:** 5, 10 or 25 mg/d vs placebo or MTX or SSZ	• LEF significantly better than placebo at 6,12 and 24 mos. • LEF vs. MTX • ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77) • No significant differences at 2 yrs but more responders with MTX than with LEF; OR 1.28 (0.98-1.67) • ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS	• Total withdrawals lower in LEF group (10% greater than Placebo [70/416 vs 18/311]); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos • AEs+ GI sympotms, elevated liver funcitn tests, alopecia, and infections	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good		

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni et al., 2005 and Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5	• ACR50 Placebo 0/52 (0.0%) vs. INF 24/52 (46.2%) • ACR70 Placebo 0/52 (0.0%) vs. INF 15/52 (28.8%) • # of tender joints Placebo -23.6 vs. INF 55.2 • # of swollen joints Placebo -1.8 vs. INF 59.9 • DAS Placebo 2.8 vs. INF 45.5 $P < 0.001$ • HAQ Placebo -1.6 vs. INF 49.8 $P < 0.001$ • PsARC Placebo -12% vs. INF +86% $P < 0.001$ • ACR20 wk 16 Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) $P < 0.001$ • At 50 wks • Total modified vdH-S score, 85% and 84% in Placebo/INF and INF/INF groups had no worsening. • Change in erosion scores INF/INF 0.921, placebo/INF 0.536 ($P = 0.780$) • Change in JSN INF/INF -0.51, placebo/INF -0.47 ($P = 0.211$) • 16 wks-PsARC INF 75% vs. Placebo 21% ($P < 0.001$) • PASI75 INF 68% vs, placebo 0% ($P < 0.001$)	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Antoni, 2005 And Kavanaugh et al., 2006 **Country, Setting:** Multinational 36 sites in clinics IMPACT2 Study **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (*P* < 0.001) and wk 24 4 vs. 41 (*P* < 0.001) • ACR70 at wk 14 1 vs. 15 (*P* < 0.001) and wk 24 2 vs. 27 (*P* < 0.001) • PsARC at wk 14 27 vs. 77 (*P* < 0.001) and wk 24 32 vs. 70 (*P* < 0.001) • •HAQ improvement at wk 14 - 18.4 vs. 48.6 (*P* < 0.001) and wk 24 -19.4 vs. 46 (*P* < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (*P* < 0.001) and wk 24 1.3 vs. 7.7 (*P* < 0.001) • Mental wk 14-1.2 vs. 3.8 (*P* = 0.001) and wk 24 0.4 vs. 3.9 (*P* = 0.047) • ACR20 at Wk 14 11 vs. 58 (*P* < 0.001) and Wk 24 16 vs. 54 (*P* < 0.001) • PASI 50: wk 14: 9 vs. 82 (*P* <0.01), wk 24: 8 vs. 75 (*P* <75 (*P*<0.01); PASI 75 wk 14: 2 vs. 64 (*P* < 0.01), wk 24: 1 vs. 50 (*P* < 0.01); • improvement wk 14: 0 vs. 41 (*P* < 0.01), wk 24: 0 vs. 39 (*P* < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (*P* < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (*P* = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational Multi-center (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC ($P < 0.0001$) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 ($P = 0.0267$) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 $P = 0.0030$ • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 $P = 0.0173$ • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate, %:** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US Single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study the efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate, %:** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 (2nd yr outcomes) **Country, Setting:** US, 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts (P < 0.0001) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts (P = 0.001) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo (P = 0.0001) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group (P < 0.0001) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate, %:** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 7. KQ2. Psoriatic arthritis trials: Functional capacity and quality of life (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Mease et al., 2005 **Country, Setting:** Multinational, multi-clinic (50) ADEPT Study **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **MTX use:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% ($P < 0.001$) • ACR70 ADA, 23% vs. placebo, 1% ($P < 0.001$) • The PASI75 ADA 59% vs. placebo 1% ($P < 0.001$) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 ($P < 0.001$) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; $P < 0.001$). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo ($P < 0.001$) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) ($P < 0.001$ for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 ($P < 0.001$) • Change in baseline to wk 24; 1.4 vs 9.3 ($P < 0.001$) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (P NS) • Change in baseline to wk 12; 0.6 vs 1.8 (P NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate, %:** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 **Country, Setting:** Sweden; registries **Funding:** Swedish Cancer Society; AFA Insurance Company; Wyeth-Ayerst; Schering-Plough; Abbott Immunology; Bristol-Myers Squibb; King Gustav V; Österlund and Kock Foundations; Reumatikerför-bundet **Research Objective:** The risk of TB pts with RA **Study Design:** Retrospective cohort study **Overall N:** 36,115 w/ RA **Study Duration:** 467,770 PY	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria • RA inpatient btwn 1964 to 2001 **Exclusion Criteria:** • Psoriatic arthritis, SLE, or AS diagnosis	**Interventions, dose:** **D1:** RA inpatient **D2:** Early RA **D3:** TNF treated RA **N:** **D1:** 31,185 **D2:** 2430 **D3:** 2500 **Mean age, yrs:** **D1:** 0-39: 19.08%;40-59: 40.80%;60-79: 35.90%;80+: 4.22% **D2:** 0-39: 15.80%;40-59: 38.40%;60-79: 41.60%;80+: 4.20% **D3:** 0-39: 18.40%;40-59: 49.44%;60-79: 30.52%;80+: 1.64% **Sex, % female:** **D1:** 73.4 **D2:** 70.2 **D3:** 73.4 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** NA **D2:** 3.6 **D3:** 5.8 **HAQ:** **D1:** NA **D2:** 0.8 **D3:** 1.84 TB cases: **D1:** 27 **D2:** 2	1987 to 2001 • RA inpatient vs. General RR 3.9 (95% CI,3.1-5.0) • RA inpatient vs. General inpatient RR 1.6 (95% CI,1.3-1.9) 1999 to 2001 • RA inpatient vs. General were at increased risk of TB RR 2.0, (95% CI,1.2-3.4) • TNF treated RA had a 4-fold increased risk of TB RR 4.0, (95% CI,1.3-12) vs. RA inpatient	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 **Country, Setting:** Sweden, **Multicenter Funding:** Swedish Cancer Society; insurance company AFA; Wyeth Ayerst, Schering-Plough, Abbott, Bristol Myer Squibb; Swedish National Board of Health and Welfare **Research Objective:** Cancer pattern of contemporary pts with RA and risk of solid cancer after TNF **Study Design:** Retrospective cohort study **Overall N:** 60,930 **Study Duration:** NR	**Inclusion Criteria:** • Inpatient Register RA cohort: inpts > 16 yrs or age ever discharged with an RA diagnosis between January 1990 and December 31 2003 • Early RA cohort: pts diagnosed within 1 yr with RA from 1995 through 2003. • TNF antagonist cohort: pts with RA treated with ETA, INF, or ADA from a Swedish registry of pts treated with anti-TNF medications **Exclusion Criteria:** • Pregnant or lactating • Inpatient Register RA cohort • Pts discharged with SLE, AS, or PsA Observed and expected cancers during the 1st yr of follow up	**Interventions, dose:** **D1:** Inpatient RA Cohort **D2:** Early Arthritis RA Cohort **D3:** TNF antagonist cohort **N:** NR **Mean age, yrs:** NR **Sex, % female:** **D1:** 71.4 **D2:** 69.9 **D3:** 74.8 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** NR **D2:** 3.5 **D3:** 5.5 **% age 45-74 yrs:** **D1:** 56.3 **D2:** 65.4 **D3:** 71.8	**Inpatient RA cohort:** Based on 3379 observed solid cancers, this cohort had minimally increased overall risk of solid cancer (SIR = 1.05, 95% CI,1.01 to 1.08) **Overall RR was 1.19 (95% CI,1.13 to 1.26, N:1311) among men and 0.97 (95% CI,0.93 to 1.02, N:2068) among women** GI cancer risk (SIR = 0.85, 95% CI,0.78 to 0.93); Lung cancers (SIR = 1.48, 95% CI,1.33 to 1.65); (SIR = 1.66, 95% CI,1.50 to 1.84); **Early Arthritis cohort:** 138 solid cancers (SIR = 1.1, 95% CI,0.9 to 1.3), women (SIR = 0.87, 95% CI,0.67 to 1.11, n =64) Men (SIR = 1.42, 95% CI,1.12 to 1.79, n =74) **TNF cohort** • 67 solid cancers observed (SIR = 0.9, 95% CI,0.7 to 1.2) **Women (SIR = 0.87, 95% CI,0.63 to 1.16, N:45) Men 1.06 (95% CI,0.67 to 1.61, N:22)** Risk of colorectal cancer (SIR = 1.2 lung cancer (SIR = 1.8), breast cancer (SIR = 0.4), NMSC (SIR = 3.6)	NA	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA: retrospective cohort **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling, 2005 **Country, Setting:** Sweden, Registry data **Funding:** AFA Insurance Company, Pharmas: Swedish National Board of Health and Welfare; Swedish Cancer Society **Research Objective:** Risks of hemapoetic malignancies, especially those with associtaed with TNF **Study Design:** Retrospective cohort study **Overall N:** Prevalent Cohort (inpatient): 53,067 **Study Duration:** 4 yrs	**Inclusion Criteria:** • Age: Prevalence: 16+ • Diagnosed with RA according to ACR criteria • Prevalence: 1987 **Exclusion Criteria:** • Prevalence: discharged with systemic lupus, AS, or PsA	**Interventions, dose:** **D1:** Prevalence **D2:** Incidence **D3:** TNF Antagonist **N:** **D1:** 53,067 **D2:** 3,703 **D3:** 4,160 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	See AEs	**Haematopoetic malignancnies:** **D1:** SIR: 1.7 (1.5-1.8) **D2:** SIR: 1.6 (0.9-2.6) **D3:** 2.1 (1.1-3.8)	**Overall Attrition Rate, %:** **ITT Analysis:** NA **Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Baecklund et al 2006 **Country, Setting:** Sweden, inpatient **Funding:** Swedish Rheumatism Society; Lions Cancer Research Foundation of Uppsala; AFA InsuranceSwedish Cancer Society **Research Objective:** To investigate which RA pts are at highest risk of lymphoma, and whether antirheumatic txt is hazardous or protective **Study Design:** Observational **Overall N:** 756 **Study Duration:** 1964 to 1995	**Inclusion Criteria:** • Age: ≥ 16 • RA and lymphoma • All pts receiving inpatient care in Sweden discharged with a diagnosis of RA (ICD) • Randomly selected as potential controls 3 individuals from underlying RA cohort • From potential controls, we included first of 3 whose medical record could be identified and who fulfilled ACR criteria for RA **Exclusion Criteria:** NR	**Interventions, dose:** NR MTX SSZ Other?: steroids **N:** 756 378 cases 378 controls **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Risk of developing lymphoma is increased in subset of RA with severe disease.(Cases vs. controls) Inflammatory activity • Low inflammatory activity: 94 (25%) vs. 278 (74%) OR 1 (referent) • Medium: 196 (52%) vs. 94 (25%) OR 7.7 (95% CI,4.8-12.3) • High: 86 (23%) vs. 4 (1%) OR 71.3 (95% CI,24.1-211.4) Functional class • I 34 (9) vs. 138 (37) OR 1 (referent) • II 185 (49) vs. 204 (54) OR 3.9 (95% CI,2.4-6.3) • III 105 (28) vs. 31 (8) OR 13.8 (95% CI,7.2-26.2) • IV 52 (14) vs. 3 (1) OR 67.5 (95% CI,18.9-239.8) • DMARD OR 0.9 (95% CI,0.6-1.2) • MTX crude OR 0.8 (95% CI,0.4-1.4); adjusted OR 0.7 (95% CI,0.3-1.6) • SSZ; crude OR 0.6 (95% CI,0.4-1.0); adjusted OR 0.6 (95% CI,0.3-1.1) • Oral steroids (adjusted OR 0.6 [95% CI,0.4-0.9]) and intraarticular steroids (adjusted OR 0.4 [95% CI,0.2-0.6]), calculated with adjustment for disease activity and DMARD use	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: Case contol study **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bergstrom, 2004 **Country, Setting:** US, 5 practices **Funding:** NR **Research Objective:** To assess if pts who were treated with TNF antagonists have a higher risk of developing coccidioido-mycosis **Study Design:** Retrospective cohort study **Overall N:** 985 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Pts with RA, reactive arthritis, PsA, JRA • Other meds were allowed **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** INF **D2:** Other Anti-TNF alpha **D3:** control **N:** **D1:** 7 **D2:** 4 **D3:** 974 **Mean age, yrs:** **D1:** 64.8 **D2:** 64 **D3:** 57.8 **Sex, % female:** **D1:** 71 **D2:** 75 **D3:** 77 **Race, % white:** **D1:** 86 **D2:** 75 **D3:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 100 **D2:** 50 **D3:** 50	Pts treated with INF are at higher risk for developing symptomatic coccidioidomycosis 7 of 247 pts receiving INF and 4 of 738 pts receiving other therapies developed symptomatic coccidioidomycosis (relative risk 5.23, 95% confidence interval 1.54-17.71; *P* < 0.01)	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study **Country, Setting:** Netherlands and Belgium, multicenter **Funding:** Netherland **Research Objective:** Comparing efficacy and radiographic outcomes of combination of SSZ, MTX and PNL with SSZ alone **Study Design:** RCT **Overall N:** 155 (148) **Study Duration:** 56 wks; (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 69 • Diagnosed with RA according to ACR criteria • Duration of condition < 2 yrs • NSAID txt at least 3 mos, 6 or more active inflamed joints AND presence of 2 or more (9 or more tender joints, morning stiffness 45 min or more, EST of 28 or more in first hour **Exclusion Criteria:** • Pregnant or lactating: adequate contraception • Prior txt with: DMARDS except HCQ or steroids • Past TB • Impaired renal or hepatic system serious comorbidity surgery in past 3 mos • Unable to comply with protocol • Allergy to study med • Alcohol or substance abuse	**Interventions, dose:** **D1:** Combined txt (SSZ, MTX, PNL) **D2:** SSZ Only SSZ: 2g/d MTX: 7.5 mg/wk, weaned after 40 wks PNL: 60 mg/d wk 1 40 mg/d wk 2 25 mg/d wk 3 20 mg/d wk 4 15 mg/d wk 5 10 mg/d wk 6 then 7.5 mg/d until wk 28 then weaned off **N:** **D1:** 76 **D2:** 79 **Mean age, yrs:** NR **Sex, % female:** **D1:** 66% **D2:** 52% **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 4 mos **D2:** 4 mos **TJC, mean:** NR **SJC, mean:** NR **Antimalarial use (%):** **D1:** 21 **D2:** 24 **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Erosions on hand or foot xrays, %:** **D1:** 74 **D2:** 79	**At week 28** **Mean pooled index** **D1:** - 1.4 (95% CI, 1.2-1.6) **D2:** - 0.8 (95% CI, 0.6-1.0) (*P* < 0.0001) **ACR20, %:** **D1:** 72 **D2:** 49 (*P* = 0.006) **ACR50, %:** **D1:** 49 **D2:** 27 (*P* = 0.007) **DAS median change:** **D1:** -2.1 (SD 1.2) **D2:** -1.3 (SD 1.2) (*P* < 0.0001) **HAQ mean change:** **D1:** -1.1 (SD 0.8) **D2:** -0.6 (SD 0.6) (*P* < 0.0001) **Sharp mean change**: **D1:** 1 **D2:** 4 (*P* < 0.001) **At week 56** **Mean pooled index:** **D1:** 1.1 (SD 0.8) **D2:** 0.9 (SD 0.8) (*P* =0.20) **DAS median change:** **D1:** 1.4 (SD 1.2) **D2:** 1.3 (SD 1.4) (*P* = 0.78) **HAQ mean change:** **D1:** 0.8 (SD 0.8) **D2:** 0.6 (SD 0.7) (*P* < 0.06)	**Overall:** **D1:** 72.3 **D2:** 62.0 **SAEs:** **D1:** 2.6 **D2:** 7.6 **Infections:** **D1:** 15.8 **D2:** 7.6 **Cardiovascular Events:** **D1:** 7.9 **D2:** 5.1 **Hepatotoxicity:** **D1:** 2.6 **D2:** 0	**Overall Attrition Rate, %:** 3.2 **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997; Landewe et al., 2002 COBRA study (continued)				**Sharp mean change:** **D1:** 2 **D2:** 6 (*P* < 0.004) **At week 80** **Sharp mean change**: **D1:** 4 **D2:** 12 (*P* < 0.01) **Five yr follow up** **Sharp score mean change:** **D1:** 5.6 (95% CI, 4.3, 7.1) (*P* = 0.001) **D2:** 8.6 (95%CI, 6.2-11) (*P* = 0.001) **Time averaged DAS28, points/yr**: **D1:** -0.07 **D2:** **-0.17**		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Brown, 2002 **Country, Setting:** US, NA **Funding:** Authors are from FDA and National Cancer Institute **Research Objective:** Occurrence of lympho-proliferative disorders in pts treated with ETA and INF **Study Design:** Database analysis; AERS system **Overall N:** 26 cases **Study Duration:** NA	**Inclusion Criteria:** MedWatch reports submitted to FDA for biologic products ETA and INF. All reports citing neoplasms, benign or malignant, were reviewed. Any report with a keyword of lymphoma or mentioned lymphoma in text was investigated further. Cases reported to MedWatch through December 2000 comprise basis for current summary **Exclusion Criteria:** NA	**Interventions, dose:** **D1:** ETA (various) **D2:** INF (various) **N:** **D1:** 18 **D2:** 8 **Mean age, yrs:** **D1:** 64 **D2:** 62 **Sex, % female:** **D1:** 61.1 **D2:** 25.0 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 72.2 **D2:** 25	**ETA** 19 cases per 100,000 treated persons **INF** • 6.6 cases per 100,000 treated persons • In general, diffuse large B cell lymphoma (non-Hodgkin's) were most common form • (21 of 26 were non-Hodgkin's lymphomas) • Treated person rates of lymphomas in ETA and INF users is probably an underestimate based on underreporting, according to authors (Age adjusted rate of lymphomas in US from 1992-1998 18.3 per 100,000 people) • Median time to lymphoma diagnosis was 8 wks (range 2-52 wks) for ETA and 6 wks (range 2-44 wks) for INF	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Cannon et al., 2004 **Country, Setting:** US, claims database **Funding:** Aventis Pharmaceuticals; Veterans Affairs **Research Objective:** The incidence of serious adverse events during txt of RA with DMARDs, focusing on LEF **Study Design:** Retrospective cohort study **Overall N:** 40594 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18 and older • Diagnosed with RA according to ACR criteria: ICD 9 code (rx for LEF-surrogate marker), 90 d observation period prior to entry **Exclusion Criteria:** • Impaired renal or hepatic system: if on DMARD other than LEF-hepatic event 90 ds prior to entering cohort • unable to determine sex or date of birth	**Interventions, dose: NR** HCT MTX LEF SSZ ETA INF **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Rates of AE in LEF group, alone and combined with MTX, were lower than or comparable to AE rates seen with MTX and other agents. LEF monotherapy had lowest rate of hepatic events in DMARD monotherapy groups All AE rates: LEF monotherapy (94 events/1000 PY, 95%CI, 84.4-104.8), MTX monotherapy (145 events/1000 PY, 95%CI,136.3-154.3), other DMARD (143 events/1000 PY, 95%CI,137.4-150.3), no DMARD (383 events/1000 PY, 95%CI,365.8-399.6) (*P* < 0.001). LEF + MTX (42.8/1000 PY, 95%CI, 32.8-55.9), LEF + other DMARD (58.7/1000 PY, 95%CI, 52.0-66.2), DMARD + MTX (69.5/1000 PY, 95%CI, 65.0-74.3; *P* = 0.002)	**Overall (rate per 1000 PY adjusted for age, sex, and comorbidities):** **D1:** 94.1 **D2:** 145.0 **D3:** 143.7 **D4:** 42.8 **Hepatotoxicity (adjusted rate per 1000 PY):** **D1:** 4.1 **D2:** 6.9 **D3:** 4.2 **D4:** 4.6	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chakravarty, 2005 **Country, Setting:** US, multicenter **Funding:** Bristol-Myers-Squibb **Research Objective:** Rates of NMSC (non-melanoma skin camcer) in a large cohort of pts with RA or OA and to evaluate the role of immunosuppressive medications on the development of NMSC **Study Design:** Retrospective cohort study **Overall N:** 15,789 (RA); 3,639 (OA) **Study Duration:** NR	**Inclusion Criteria:** • Participants in National Data Bank for Rheumatic Diseases (NDB) • Recruited from 908 US rheumatologists; pts who returned at least 2 questionnaires between January 1999 and January 2003 **Exclusion Criteria:** NR	**Interventions, dose:** **D1:** pts with RA **D2: pts with OA** PRE MTX LEF **TNF inhibitors** **N:** **D1:** 15789 **D2:** 3639 **Mean age, yrs:** **D1:** 62 **D2:** 67 **Sex, % female:** **D1:** 77 **D2:** 83 **Race, % white:** **D1:** 91 **D2:** 94	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Skin cancer before NDB:** **D1:** 3.8 **D2:** 5.8 **History of smoking:** **D1:** 56 **D2:** 46	A total of 738 pts with RA reported new cases of NMSC during followup within the NDB; crude incidence rate = 18.1 / 1000 PY (95% CI, 16.8 -19.4 / 1000 PY) After excluding prevalent cases of NMSC, incidence rate was 15.2 / 1000 PY (95% CI, 14.1 -16.5) Based on multivariate Cox proportional hazard analysis restricted to pts with RA Use of PNL was associated with an increased hazard ratio (HR) (HR = 1.28, *P* = 0.014) for development of NMSC No association found with use of LEF or MTX alone Use of any anti-TNF (ETA, INF, and ADA) alone showed a slightly increased risk An approximately 2-fold HR for development of NMSC was found among pts with RA using both MTX and any TNF inhibitor (HR 1.97, *P* = 0.001)	NA	**Overall Attrition Rate, %:** After initial assessment, ~ 8% of pts decline to participate each yr **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chung, 2003 **Country, Setting:** US, University clinics (32 centers) **Funding:** Centocor **Research Objective:** To assess effectiveness and safety of INF in pts with moderate to severe congestive heart failure **Study Design:** RCT **Overall N:** 150 **Study Duration:** 28 wks	**Inclusion Criteria:** • Age: 18+ • Stable New York Heart Association (NYHA) class III or IV heart failure **Exclusion Criteria:** • Prior txt with txt within 3 mos of INF or other therapeutic agents that could interfere with actions of TNF (eg, ETA, pentoxifylline, thalidomide, or **D2**E7) • History of TB: had latent TB or had had TB within 3 yrs • NSAID other than aspirin; experienced a serious infection within 2 mos • Documented HIV infection	**Interventions, dose:** **D1:** placebo **D2:** INF 5mg/kg **D3:** INF 10mg/kg **N:** **D1:** 49 **D2:** 50 **D3:** 51 **Mean age, yrs:** **D1:** 60 **D2:** 62 **D3:** 62 **Sex, % female:** **D1:** 24 **D2:** 14 **D3:** 16 **Race, % white:** **D1:** 88 **D2:** 88 **D3:** 84	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% confidence interval 1.01 to 7.97; nominal *P* = 0.043 using log-rank test);Pts in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than pts in the placebo or 5 mg/kg INF groups	**Overall:** **D1:** 83.3 **D2:** 92.2 **D3:** 84 **SAEs:** **D1:** 29.2 **D2:** 23.5 **D3:** 44 **Serious Infections:** **D1:** 2.1 **D2:** 5.9 **D3:** 8 **Dizziness:** **D1:** 4.2 **D2:** 31.4 **D3:** 20	**Overall Attrition Rate, %:** NR **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: De Bandt et al., 2005 **Country, Setting:** France, clinical reports **Funding:** NR **Research Objective:** To report cases and incidence of anti-TNF-induced SLE from a French national survey **Study Design:** Case series **Overall N:** 10,700 (22 cases) **Study Duration:** varied	**Inclusion Criteria:** • Pts in France given INF or ETA; cases of SLE-like illness during anti-TNF txt were sought; retrospective survey of French rheumatologists and internists between June and October 2003 • All French hospital centres prescribing anti-TNF txts (ETA and INF at that time) were surveyed **Exclusion Criteria:** • Improper diagnosis of lupus	**Interventions, dose:** **D1:** Limited skin lupus **D2: Complete lupus** ETA: varied **INF: varied** **N:** **D1:** 10 **D2: 12** **Mean age, yrs:** **D1:** of RA onset 39 **D2: 36** **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **INF/ETA:** **D1:** 6 / 4 **D2:** 9 / 3	Incidence 15/7700 = 0.19% with INF and 7/3800 = 0.18% with ETA 32 initially reported, 10 were ruled out leaving 22 cases 10 pts only had anti-DNA antibodies and skin manifestations 1 could classify as 'limited skin lupus' or 'toxidermia' in a context of autoimmunity, and 12 pts had more complete drug-induced lupus with systemic manifestations	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dixon et al., 2006 **Country, Setting:** Britain Multicenter **Funding:** Schering Plouogh, Wyeth, Abbott, and Amgen all fund The British Society for Rheumatology Biologics Register (BSRBR) **Research Objective:** The rate of serious infection anti-TNF-pts compared with RA pts treated with traditional DMARDs **Study Design:** Prospective cohort study **Overall N:** 8,973 **Study Duration:** 11,220 PY	**Inclusion Criteria:** • ANTI-TNF cohort: diagnosed by physician w/ RA • Treated with ETA, INF, or ADA as first anti-TNF drug, at least 6 mos of followup by September 2005 • Comparison cohort: physician diagnosis of RA, active disease (guideline DAS28 >4.2), current txt with a DMARD, and no previous use of biologic drugs. • Comparison pts also completed at least 6 mos of followup by September 2005. **Exclusion Criteria:** • Anti-TNF cohort: pts who had been registered >6 mos after start of biologic therapy	**Interventions, dose:** **D1:** DMARD **D2:** All anti-TNF **D3:** ETA **D4:** INF **D5: ADA** **N:** **D1:** 1354 **D2:** 7664 **D3:** 3596 **D4:** 2878 **D5:** 1190 **Mean age, yrs:** **D1:** 60 **D2:** 56 **D3:** 56 **D4:** 56 **D5:** 57 **Sex, % female:** **D1:** 71 **D2:** 76 **D3:** 77 **D4:** 76 **D5:** 74 **Race, % white:** NR	**Median disease duration, yrs:** **D1:** 6 **D2:** 12 **D3:** 12 **D4:** 12 **D5:** 11 **TJC (median):** **D1:** 6 **D2:** 16 **D3:** 16 **D4:** 16 **D5:** 15 **SJC (median):** **D1:** 5 **D2:** 11 **D3:** 11 **D4:** 12 **D5:** 12 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 22 **D2:** 47 **D3:** 47 **D4:** 48 **D5:** 44 **MTX naive, %:** NR **Txt resistant %:** NR	:In pts with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD txt, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues	**Serious Infections**: • **D1:** N:56 (41 events/1000 PY) • **D2:** N:525 (53 events/1000 PY) **UTI:** • **D1:** N:3 (2.2 events/1000 PY) • **D2:** N:45 (4.6 events/1000 PY)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dixon et al., 2006 (continued)			**Pts with Early RA (≤3 yrs):** NR **Baseline DAS mean:** **D1:** 5.1 **D2:** 6.6 **D3:** 6.6 **D4:** 6.6 **D5:** 6.6 **Diabetes %:** **D1:** 5.5 **D2:** 5.4 **D3:** 6.0 **D4:** 4.6 **D5:** 5.5 **COPD/asthma %:** **D1:** 20 **D2:** 13 **D3:** 14 **D4:** 12 **D5:** 13			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study **Country, Setting:** Multinational (Europe, North America, Australia), multicenter (133) **Funding:** Abbott Laboratories **Research Objective:** To compare efficacy and safety of ADA + MTX vs. MTX or ADA in pts with early, aggressive RA (RA) who had not previously received MTX txt **Study Design:** RCT **Overall N:** 799 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria • Duration of condition: 3 yrs or less • MTX naive pts • > 8 swollen joints, > 10 tender joints, and an erythrocyte sedimentation rate of > 28 • Folic acid only other med allowed **Exclusion Criteria:** • Prior txt with: MTX, cyclophosphamide, cyclosporine, azathioprine	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ADA (40 mg/biwkly) **D3:** ADA (40 mg/biwkly) + MTX (20 mg/wk) **N:** **D1:** 257 **D2:** 274 **D3:** 268 **Mean age, yrs:** **D1:** 52 **D2:** 52.1 **D3:** 51.9 **Sex, % female:** **D1:** 73.9 **D2:** 77.4 **D3:** 72 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** .8 **D2:** .7 **D3:** .7 **TJC, mean:** **D1:** 32.3 **D2:** 31.8 **D3:** 30.7 **SJC, mean:** **D1:** 22.1 **D2:** 21.8 **D3:** 21.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 35.4 **D2:** 36.5 **D3:** 35.8 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.3 **D2:** 6.4 **D3:** 6.3 **HAQ:** **D1:** 1.5 **D2:** 1.6 **D3:** 1.5 **Erosion score:** **D1:** 13.6 **D2:** 11.3 **D3:** 11.0	**At 6 months** **Radiographic progression; change in Sharp scores:** **D1:** 3.5 **D2:** 2.1 (*P* < 0.001) **At 1 yr** **Radiographic progression; change in Sharp scores:** **D1:** 5.7 **D2:** 3.0 (*P* < 0.001) **HAQ DI improvement, mean units +/- sd:** **D1**: -0.8 +/- 0.7 **D2:** -0.8 +/- 0.6 **D3**: -1.1 +/- 0.6 **D2** vs. **D1**, *P* = NR **D3** vs. **D1**: *P* < 0.001 **D3** vs. **D2**: *P* = 0.002) **At 2 yrs** **ACR50 response, %:** **D1:** 43 **D2:** 37 **D3:** 59 **D3** vs. **D2** or **D1**: *P* < 0.001 **D1** vs. **D2**: *P*= NS **Clinical remission, %:** **D1:** 25 **D2:** 25 **D3:** 49 (both *P* < 0.001) **Radiographic progression; change in Sharp scores:** **D1:** 10.4 **D2:** 5.5 (*P* < 0.001)	**SAEs:** **D1:** 18.5 **D2:** 21.1 **D3:** 15.9 **Infections:** **D1:** 123 **D2:** 110 **D3:** 119 **Serious Infections:** **D1:** 2.9 **D2:** 0.7 **D3:** 1.6 **Malignancies:** **D1:** 0.4 **D2:** 0.9 **D3:** 0.9 **Withdrawal because of adverse events:** **D1:** 7% **D2:** 10% **D3:** 12%	**Overall Attrition Rate, %:** 32% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006 PREMIER study				**Withdrawal because of lack of efficacy, %:** **D1:** 18 **D2:** 19 **D3:** 4.9 **HAQ DI improvement, mean units +/- sd:** **D1**: -0.9 +/- 0.6 **D2:** -0.9 +/- 0.7 **D3**: -1.0 +/- 0.7 **D2** vs. **D1**, *P* = NR **D3** vs. **D1;** *P* < 0.05 **D3** vs. **D2**; *P* = 0.058 **% with HAQ DI score of zero:** **D1**: 19 **D2:** 19 **D3**: 33 **D3** vs. **D2**, *P* < 0.001 **D3** vs. **D1**: *P* < 0.001 **% with HAQ DI improvement of ≥ 0.22 units from baseline:** **D1**: 63 **D2:** 58 **D3**: 72 **D3** vs. **D2**, *P* < 0.05 **D3** vs. **D1**: *P* < 0.05		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 **Country, Setting:** Scotland, 8 NHS sites **Funding:** Wyeth and Pharmacia - drugs Arthritis Research Campaign **Research Objective:** If a combination of SSZ and MTX is superior to either alone in RA pts with supoptimal response to 6 mos of SSZ **Study Design:** RCT **Overall N:** 165 **Study Duration:** Phase I: 6 mos; Phase 2: 12 additional mos for those with DAS > 2.4 after 6 mos	**Inclusion Criteria:** • Age: 18 to 80 • Duration of condition: < 10 yrs • Active disease defined by DAS > 2.4 after 6 mos SSZ txt were eligble for phase II • NSAIDs and other medications were continued • Intra-articular or intramuscular corticosteroid was permitted but not within 1 mo of 6, 12, & 18 mo assessments **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: MTX or SSZ • Impaired renal or hepatic system: creatinine > 150 mmol/dl, ALT, aspertate aminotransferase > 80 IU/l, alkaline phosphatase > 700 IU/l, gamma GT x3 • Other: abnormal white cell count (< 4 x 10*9/l)	**Interventions, dose:** **D1:** SSZ + MTX **D2:** SSZ + placebo **D3:** MTX + placebo Phase I MTX: 7.5 mg/w (3 x 2.5 mg) increasing by 2.5 mg/mo until max of 25 mg or toxicity SSZ: enteric coated 500 mg/d increased by 500 mg/wkly until 40 mg/kg per d to a max of 4g/d for initial 6 mos Placebo: Folic Acid 5 mg/wk given 3 days after MTX and MTX + placebo **N:** **D1:** 56 **D2:** 55 **D3:** 54 Overall: 687 **Mean age, yrs:** **D1:** 56 **D2:** 55 **D3:** 53 Overall: 55 **Sex, % female:** **D1:** 75 **D2:** 75 **D3:** 79 Overall: 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 1.9 **D2:** 1.6 **D3:** 1.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** All **Txt resistant, %:** All **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 3.63 **D2:** 3.67 **D3:** 3.5 **Sharp:** **D1:** 17.0 **D2:** 14.0 **D3:** 12.0	**Median change 18 mos:** **DAS:** **D1:** -0.67 **D2:** -0.30 **D3:** -0.26 (**D1** vs. **D2**; *P* = 0.039) (**D1** vs. **D3**; *P* = 0.023) (**D2** vs. **D3**; *P* = 0.79) **HAQ:** **D1:** -0.50 **D2:** -0.25 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.51) (**D1** vs. **D3**; *P* = 0.57) (**D2** vs. **D3**; *P* = 0.99) **SJC:** **D1:** -3.00 **D2:** -3.00 **D3:** -2.00 (**D1** vs. **D2**; *P* = 0.94) (**D1** vs. **D3**; *P* = 0.81) (**D2** vs. **D3**; *P* = 0.74) **ACR20, % :** **D1:** 29 **D2:** 18 (OR 1.25 (95% CI, 0.56-2.79) ; *P* = 0.68) **D3:** 15 (OR 2.01 (95% CI, 0.85-4.76), *P* = 0.14) **ACR50, %:** **D1:** 11 **D2:** 6 (OR 1.43 (95% CI, 0.43-4.81), *P* = 0.76) **D3:** 7 (OR 1.79 (95% CI, 0.49-6.49), *P* = 0.53)	NR	**Overall Attrition Rate, %:** 28.5 • 687 pts entered phase I (6 mos) • At 6 mos, 165 were not eliglbe to enter phase II (discontinued SSZ because of side effects: 19%, did not attend: 3.6%, died: 0.4%) • Another 191 were not randomized because DAS score was < 2.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 (continued)	• Pre-existing pulmonary fibrosis • Use of oral steroids > 7.5 mg/d • Known SSZ allergies			**ACR70, %:** **D1:** 4 **D2:** 2 (OR 1.50 (95% CI, 0.24-9.34), *P* = 1.00) **D3:** 2 (OR 3.00 (95% CI, 0.30-29.78), *P* = 0.62)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 **Country, Setting:** Europe, multicenter **Funding:** Wyeth **Research Objective:** To compare efficacy and safety of ETA and SSZ, alone and in combination, in pts with active RA despite SSZ txt **Study Design:** RCT **Overall N:** 260 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • Diagnosed according to ACR criteria; • Functional class of: I-III • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Duration of condition < 20 yrs • Stable doses of oral corticosteroids (10 mg/d of PRE or equivalent), one NSAID, simple analgesics with no anti-inflammatory action or daily doses of aspirin (300 mg) **Exclusion Criteria:** • Prior txt with: (1) ETA or other TNF antagonists or (2) received a DMARD other than SSZ within 3 mos. Or any biologic or cyclophosphamide within 6 mos, corticosteroids within 4 wks	**Interventions, dose:** **D1:** SSZ (2,2.5, or 3 g /d) + placebo **D2:** ETA (25 mg SC twice wkly) + placebo **D3:** ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) **N:** **D1:** 50 **D2:** 103 **D3:** 101 Overall: 254 **Mean age, yrs:** **D1:** 53.3 **D2:** 51.3 **D3:** 50.6 Overall: 51.4 **Sex, % female:** **D1:** 82.0 **D2:** 78.6 **D3:** 80.2 Overall: 79.9 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 5.6 (sd 4.4) **D2:** 7.1 (sd 5.2) **D3:** 6.5 (sd 5.1) **TJC, mean:** **D1:** 14.0 **D2:** 14.7 **D3:** 14.1 **SJC, mean:** **D1:** 11.1 **D2:** 10.1 **D3:** 10.4 **DMARD use, %:** **D1:** 58.0 **D2:** 69.9 **D3:** 58.4 **Corticosteroid use, %** **D1:** 40.0 **D2:** 59.2 **D3:** 44.6 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D1:** 28.0 **D2:** 73.8 **D3:** 74.0 ($P < 0.01$) **ACR50, %:** **D1:** 14.0 **D2:** 46.6 **D3:** 52.0 ($P < 0.01$) **ACR70, %:** **D1:** 2.0 **D2:** 21.4 **D3:** 25.0 ($P < 0.01$) In groups receiving ETA, significant differences in ACR core components were observed by wk 2 compared with those receiving SSZ alone ($P < 0.01$) **DAS improvement, %:** **D1:** 19.6 **D2:** 48.2 **D3:** 49.7 ($P < 0.01$) **Mean HAQ improvement, %:** **D1:** 9.2 **D2:** 35.3 **D3:** 40.2 ($P < 0.01$)	**Infections:** **D1:** 13 **D2:** 47 **D3:** 31 **Infusion or injection reaction:** **D1:** 3 **D2:** 38 **D3:** 21 **Abdominal Pain:** **D1:** 0 **D2:** 7 **D3:** 8 **Headache:** **D1:** 4 **D2:** 5 **D3:** 15 **Nausea:** **D1:** 3 **D2:** 3 **D3:** 12 **URTI:** **D1:** 5 **D2:** 10 **D3:** 11	**Overall Attrition Rate, %:** 13 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Combe et al., 2006 (continued)	• Presence of relevant comorbidity, including active infections		**Baseline DAS, mean:** **D1:** 5.0 **D2:** 5.1 **D3:** 5.2	**Mean % improvement EuroQOL VAS** D2: 64.6 D3: 67.6 (*P* = NS, NR) No meaningful clinical advantage to use of ETA in combination with SSZ		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Doran et al., 2002 **Country, Setting:** US, Minnessota cohort **Funding:** Immunnex; NIH **Research Objective:** Identify predictors of serious infections amnong pts with RA **Study Design:** Retrospective Cohort **Overall N:** 609 **Study Duration:** 39 yrs	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria **Exclusion Criteria:** • NR	**Interventions, dose: DMARDS** **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Age, /10-yr increment OR 1.49 95% CI,1.33-1.67 *P* < 0.001 • Alcoholism OR 2.00 95%CI,1.27-3.16 *P* = 0.003 • Leukopenia OR 2.17 95%CI,1.58-2.98 *P* < 0.001 • Organic brain disease OR 2.94 95%CI,2.08-4.16 *P* < 0.001 • DM OR 2.45 95%CI,1.84-3.27 *P* < 0.001 • Chronic lung disease OR 2.83 95%CI,2.15-3.72 *P* < 0.001 • Extraarticular RA OR 3.22 95%CI,2.17-4.77 *P* < 0.001 • RF OR 1.65 95%CI,1.24-2.20 *P* < 0.001 • RA nodules OR 1.76 95%CI,1.32-2.33 *P* < 0.001 • Functional capacity OR 1.87 95%CI,1.49-2.35 *P* < 0.001 • ESR OR 1.63 95%CI,1.25-2.13 *P* < 0.001 • Chemo OR 5.02 95%CI,2.44-10.3 *P* < 0.001 • Cyclophosphamide OR 6.14 95%CI,3.12-11.8 *P* < 0.001 • Cyclosporine OR 1.99 95%CI,1.25-3.16 p = 0.004 • Corticosteroids OR 1.90 95%CI,1.47-2.47 *P* < 0.001	NA	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., 2003 **Country, Setting:** Finland, France, Germany (France only for 5 yr), multicenter **Funding:** Pharmacia Upjohn **Research Objective:** Clinical benefit of MTX + SSZ compared to either drug alone early, active RA pts fulfilling some criteria of poor potential long term outcome **Study Design:** RCT **Overall N:** 209 (146) **Study Duration:** 52 wks (5 yrs)	**Inclusion Criteria:** • Diagnosed according to ACR criteria • Duration < 1 yr • Presence of active disease as defined by DAS ≥ 3 (calculation based on Ritchie articular index, 44 SJC, and ESR) and presence of RF and/or HLA DR 1/4 • Concommitant drugs allowed were analgesics and NSAIDS **Exclusion Criteria:** • Prior txt with steroids, DMARDS, or any drugs to treat RA other than analgesic or NSAIDS • Pts with contraindications to use of SSZ or MTX	**Interventions, dose:** **D1:** SSZ + placebo **D2:** MTX + placebo **D3:** SSZ + MTX MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate SSZ: increased to 2 grams daily by d #9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate Other?: combo MTX + SSZ **N:** **D1:** 68 **D2:** 69 **D3:** 68 **Mean age, yrs:** **D1:** 52 **D2:** 50 **D3:** 52 **Sex, % female:** **D1:** 71 **D2:** 74 **D3:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 2.9 mos since diagnosis, 10.8 since onset **D2:** 2.3 mos from diagnosis, 18.4 from onset **D3:** 3.4 mos from diagnosis, 10.6 from onset **TJC, mean:** NR **SJC, mean:** **D1:** 10.5 **D2:** 9.4 **D3:** 9.4 **DMARD use, %:** All groups: 0 **Corticosteroid use, %** All groups: 0 MTX naive, %: All groups: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** All groups: 100	**DAS change:** **D1:** -1.15 **D2:** -0.87 **D3:** -1.26 (*P* = 0.019 from inter-group comparisons using analysis of variance) **RAI changes:** **D1:** -7.1 **D2:** -4.2 **D3:** -9.4 (*P* = 0.001) **ACR response, %:** **D1:** 59 **D2:** 59 **D3:** 65 (*P* = NR) **At 5 years** Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared to monotherapy with either drug used alone **Mean DAS:** **D1:** 2.2 (sd 1) **D2:** 2.2 (sd 1) **D3:** 2.2 (sd 1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9)	**Overall:** **D1:** 75 **D2:** 75 **D3:** 91 **Abdominal Pain:** **D1:** 9 **D2:** 6 **D3:** 13 **Dizziness:** **D1:** 6 **D2:** 1 **D3:** 3 **Headache:** **D1:** 9 **D2:** 4 **D3:** 12 **Nausea:** **D1:** 32 **D2:** 23 **D3:** 49	**Overall Attrition Rate, %:** 27% (28.8) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 and Maillefert et al., [1] 2003 (continued)			**Baseline DAS, mean:** **D1:** 4.23 **D2:** 4.13 **D3: 4.24** **RF positive, %:** **D1:** 75 **D2:** 62 **D3:** 71 **RAI:** **D1:** 17.6 **D2:** 16.5 **D3:** 18.9	**Median radiologic score** D2: 7.5 D3: 8.5: (*P* = 0.7)**D3:** 2.2 (sd 1.1)(*P* = 0.9) **HAQ:** **D1:** 0.6 (0.7) **D2:** 0.6 (0.7) **D3:** 0.6 (0.6) (*P* = 0.9) **Median radiologic score** D2: 7.5 D3: 8.5 (*P* = 0.7) Similar results with 3 groups (**D3** vs. **D2** vs. **D1**) instead of 2 groups (**D3** vs. **D2** or **D1**) when compared, but data not shown **Attrition rate**: 21%		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 **Country, Setting:** Multinational, multicenter (26 rheumatology centers) **Funding:** Roche **Research Objective:** To confirm role of B cells in RA by evaluating effect of RIT in pts with active RA according to ACR and EULAR criteria **Study Design:** RCT **Overall N:** 161 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 21 • Diagnosed according to 1987 ACR criteria • Failed previous MTX treatment • > MTX 10 mg/wk and active disease • RF-positive • NSAIDS at stable doses or Css at doses < 12.5 mg per d of PNL • All received 17-d txt with Css and a 10 mg dose of leucovorin **Exclusion Criteria:** • Autoimmune disorder other than RA (except Srjogen's) • Functional class IV • Active rheumatoid vasculitis • Systemic diseases associated with arthritis • CFS • Serious, uncontrolled diseases • Active infection	**Interventions, dose:** **D1:** MTX (≥10 mg/wk) **D2:** RIT (1000 mg on ds 1 and 15) **D3:** RIT (1000 mg on ds 1 and 15) + CYP (750 mg d 3,17) **D4:** RIT (1000 mg on ds 1 and 15) + MTX (≥10 mg/wk) **N:** **D1:** 40 **D2:** 40 **D3:** 41 **D4:** 40 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 53 **D4:** 54 **Sex, % female:** **D1:** 80 **D2:** 73 **D3:** 83 **D4:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 9 **D3:** 10 **D4:** 12 **TJC, mean:** **D1:** 32 **D2:** 34 **D3:** 33 **D4:** 32 **SJC, mean:** **D1:** 19 **D2:** 21 **D3:** 19 **D4:** 23 **DMARD use (#):** **D1:** 2.6+/- 1.3 **D2:** 2.5+/-1.6 **D3:** 2.6+/-1.4 **D4:** 2.5+/-1.4 **Corticosteroid use, %** NR **MTX naive, %:** 0 **Txt resistant, %:** 100 **Pts with Early RA (≤3 yrs):** NR	**At 24 weeks** **ACR20, %:** **D2:** 65 **D4:** 73 (*P* = NR) **ACR50, %:** **D2:** 33 **D4:** 43 (*P* = NR) **ACR70, %:** **D2:** 15 **D4:** 23 (*P* = NR) **Rates of moderate or good EULAR responses, %:** **D2:** 85 **D4:** 83 (*P* = NR) **DAS:** **D2:** -2.2 **D4:** -2.6 **At 48 weeks** **ACR20, %:** **D2:** 33 **D4:** 65 (*P* = NR) **ACR50, %:** **D2:** 15 **D4:** 35 (*P* = NR) **ACR70, %:** **D2:** 10% **D4:** 15% (*P* = NR)	**Overall:** **D1:** 80 **D2:** 80 **D3:** 73 **D4:** 85 **SAEs:** **D1:** 8.0 **D2:** 5.0 **D3:** 4.9 **D4:** 8.0 **Infusion or injection reaction:** **D1:** 30 **D2:** 45 **D3:** 32 **D4:** 33 **Nausea:** **D1:** 3 **D2:** 5 **D3:** 10 **D4:** 0 **URTI:** **D1:** 15 **D2:** 10 **D3:** 5 **D4:** 10	**Overall Attrition Rate, %:** at 24 wks 6.2% at 48 wks 37.8% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Edwards, 2004 (continued)	• History of recurrent infection or recurrent bacterial infections with encapsulated organisms • Primary of secondary immunodeficiency • History of cancer		**Baseline DAS, mean:** **D1:** 6.9 **D2:** 6.8 **D3:** 6.9 **D4:** 6.8			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 **Country, Setting:** Multinational, 117 centers **Funding:** NR **Research Objective:** To compare both short and long-term (up to 2 yr) clinical efficacy and safety of LEF and MTX for txt of RA **Study Design:** RCT **Overall N:** 999 **Study Duration:** 1 yr, optional second yr	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA according to ACR criteria: Active Disease • Previous use of DMARDs: only if discontinued 28 ds before trial • Duration of condition: for at least 4 mos, but no longer than 10 yrs • NSAIDs and steroids were allowed provided a stable dose of NSAIDs or steroid (≤ 10 mg/d) PNL for at least 28 ds prior to study entry • Women of childbearing age were required to use adequate contraception **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: Intra-articular corticosteriod injections w/in 6 wks of efficacy assessment	**Interventions, dose:** **D1:** LEF Yr 1 **D2:** MTX Yr 1 **D3:** LEF Yr 2 **D4:** MTX Yr 2 MTX: 7.5 to 15 mg/wk LEF: loading dose of 100 mg/d for 3 ds, followed by maintenance dose 20/ mg/d **N:** **D1:** 501 **D2:** 498 **D3:** 292 **D4:** 320 **Mean age, yrs:** **D1:** 58.3 **D2:** 57.8 **D3:** 57.7 **D4:** 57.0 **Sex, % female:** **D1:** 70.7 **D2:** 71.3 **D3:** 71.2 **D4:** 71.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.7 **D2:** 3.8 **D3:** 3.5 **D4:** 3.8 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 66.3 **D2:** 66.9 **D3:** 64.7 **D4:** 66.9 **Corticosteroid use, %** **D1:** 36.3 **D2:** 33.5 **D3:** 14.0 **D4:** 11.3 **MTX naive, %:** NR **DMARD Txt resistant, %:** **D1:** 1.1 **D2:** 1.1 **D3:** 1.0 **D4:** 1.1 **Pts with Early RA (≤ 3 yrs):** NR	**At year 1** **ACR20:** **D1:** 50.5% **D2:** 64.8% ($P < 0.001$) **HAQ improvement:** Minimal quantitative difference between groups, but statistically significant (shown in figure only; $P < 0.05$) **Radiograph change, Larsen Scores:** **D1** and **D2**: 0.03 increase (P =NS, NR) **Primary clinical efficacy endpoints**: **TJC:** **D1:** -8.3 **D2:** - 9.7 **SJC:** **D1:** -6.8 **D2:** -9.0 **Physician global assessment:** **D1:** -0.9 **D2:** -1.2 **Pt global assessment:** **D1:** -0.9 **D2:** -1.2 **At year 2** **ACR20, %:** **D1:** 64.3 **D2:** 71.7 (P = NS, NR)	**SAEs:** **D1:** 7% **D2:** 8% **Headache:** **D1:** 6.2 **D2:** 4.8 **Hepatotoxicity:** **D1:** 5.4 **D2:** 16.3 **D3:** 2.7 **D4:** 5.9 **Nausea:** **D1:** 11.2 **D2:** 15.7 **URTI:** **D1:** 5.2 **D2:** 5.0 **D3:** 4.5 **D4:** 5.6 **Deaths** MTX: 2	**Overall Attrition Rate, %:** • 26.3% (263/999) during yr 1 • Combined 2 yrs, attrition 50.3% (502/999) of those initially starting study at baseline • During yr 2, attrition 18.8% (115/612) of those agreeing to continue study for 2nd yr **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 (continued)			**Baseline DAS, mean:** NR **NSAIDS, %:** **D1:** 80 **D2:** 84.7 **D3:** 37.3 **D4:** 42.5 **Larsen score:** **D1:** 1.25 **D2:** 1.29 **D3:** 1.27 **D4:** 1.31	**HAQ improvement:** difference between groups in change from baseline HAQ, NS **Radiograph change, Larsen Scores:** No further increase in joint damage in pts txted with LEF and small improvement in MTX pts; small net result, but statistically significant difference with MTX better than LEF (overall scores and significance NR)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Feltelius, 2005 **Country, Setting:** Sweden, Swedish Society of Rheumatology database **Funding:** Wyeth Research **Research Objective:** To describe a nationwide system for postmarketing follow up of new antirheumatic drugs; to analyze safety and effectiveness in an ETA-treated cohort **Study Design:** Case series **Overall N:** 1,073 **Study Duration:** >2 yrs	**Inclusion Criteria:** • Previous use of DMARDs: previous treatment with > 1 DMARD in addition to MTX • Active RA as evaluated by the attending physician **Exclusion Criteria:** • NR **Interventions:** **D1: ETA** **Etanercept:** 25mg twice weekly **N:** **D1:** 1073 **Mean age (yrs):** **D1:** 52 **Sex, % female:** **D1:** 76.6 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 56.3 **Corticosteroid use, %:** **D1:** 95.2 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.9 **D1:** MTX use: 40.1	In 294 pts (27%) , at least 1 adverse drug reaction (ADR) was reported (421 reports; mean 1.5 report per patient; median 1; rand 1 to 6) 80 ADR reports (19%) were serious and 331 (79%)were non-serious 76 pts (7%) experienced at least one serious event and 114 (11%) had events exclusively classified as nonserious Incidence of adverse events remained constant over time	**Overall:** **D1:** 27 (% of pts) **Serious AEs:** **D1:** 7 (% of pts) **Infections:** **D1:** 22 (% of all AE diagnoses) **Serious Infections:** **D1:** 5.4 (% of all AE diagnoses) **Infusion or injection reaction:** NR **Abdominal Pain:** NR **Cardiovascular Events:** **D1:** 4.8 (% of all AE diagnoses) **Dizziness:** NR **Headache:** NR **Hepatotoxicity:** **D1:** liver/biliary 0.6% (of all AE diagnoses) **Malignancies:** NR **Nausea:** NR **URTI:** NR **UTI:** NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** Not applicable (Why not?) **Quality Rating:** Fair	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Fleischmann 2003; 1478 and 1081 and 2008 **Country, Setting:** Multinational, multicenter **Funding:** Amgen **Research Objective:** Long term safety of AKA in a large population of pts with RA **Study Design:** RCT **Overall N:** 1414 (1399) enrolled (open label 1103) **Study Duration:** 6 mos (up to 30 mos open label for a total of 3 yrs)	**Inclusion Criteria:** • Age: 18+ • Diagnosed according to ACR criteria; duration 3+ mos • Stable doses of NSAIDs and Cs for one mo; and stable doses of DMARDs for 2 mos • NSAIDS, Cs, and DMARDs (except TNF inhibitors) **Exclusion Criteria:** • Pregnant or lactating • Uncontrolled medical condition • Malignancy other than basal cell carcinoma of skin or in situ carcinoma of cervix • Felty's syndrome • HIV • Leukopenia • Neutropenia • Tthrombocy-topenia	**Interventions, dose:** **D1:** AKA (100mg/d) **D2:** placebo **N:** **D1:** 1116 **D2:** 283 **Mean age, yrs:** **D1:** 54.6 **D2:** 55.7 **Sex, % female:** **D1:** 74.7 **D2:** 74.6 **Race, % white:** **D1:** 87.8 **D2:** 90.1	**Mean disease duration, yrs:** **D1:** 10.2 (9.6) **D2:** 10.7 (9.5) **TJC, mean:** **D1:** 22.6 (14.7) **D2:** 22.6 (14.5) **SJC, mean:** **D1:** 18.8 (11.9) **D2:** 18.3 (11.7) **DMARD use excluding MTX, and TNF inhibitors %:** **D1:** 47.7 **D2:** 47.7 **Corticosteroid use, %:** **D1:** 57 **D2:** 60.8 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 51.9 **D2:** 59.4	• 6 mos-injection site reactions, AKA vs. placebo. (72.6% v. 32.9%) *P*-value NR • 13.4% AKA withdrew due to AE vs, 9.2% placebo (*P* = 0.057); overall discontinuation rates (21.6% vs. 18.7%) • Serious infections AKA vs. placebo (2.1% v. 0.4%), may be clinically significant. (*P* = 0.068) • Comorbid conditions, serious infectious events (2.5% vs. 0.0%; *P* = NR). • Trend towards increased risk of serious infectious events with AKA in pts with pulmonary comorbidities vs. placebo (3.4% v. 1.6%), *P* = NS • From 0-3 yrs rates per 100 yrs of patient exposure • ISRs (122.26 events), • Rheumatoid arthritis progression (67.80 events) • URTIs(26.09 events)	**Overall:** **D1:** 92 **D2:** 92.2 **D3:** 96 **SAEs:** **D1:** 7.7 **D2:** 7.8 **D3:** 27 **Infections:** **D1:** 41.2 **D2:** 43.5 **Serious Infections:** **D1:** 2.1 **D2:** 0.4 **D3:** 8 **Infusion or injection reaction:** **D1:** 72.6 **D2:** 32.9 **URTI:** **D1:** 13.3 **D2:** 18.4 **UTI:** **D1:** 4.6 **D2: 5.3**	**Overall Attrition Rate, %:** 21 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Fleischmann 2003 Abstracted with 1478 and 1081 and 2008 (continued)	• Abnormal liver function test result • Hepatitis B or C			• Concomitant use of corticosteroids vs. not serious infection (7.13 events/100 PY v 2.87 events/100 PY). pneumonia (1.5 events/100 PY v 0.96 events/100 PY) • Cellulitis (1.2 events/100 PY v 0.21 events/100 PY)	**Adherence:** AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8; <70% adherent: 0.8% vs. 1.7%>40% missed no injections and >90% received at least 90% of intended doses	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Flendrie et al., 2003 **Country, Setting:** Netherlands. University medical centre (Nijmegen) **Funding:** Not reported **Research Objective:** To determine the drug survival during treatment of RA pts with TNF blocking agents **Study Design:** Retrospective cohort study **Overall N:** 230 **Study Duration:** About 6 yrs. (maximum follow up times for 3 groups were 69, 35, and 30 mos)	**Inclusion Criteria:** • Age: adult • Diagnosed with RA according to ACR criteria1) started treatment with ADA, INF, or ETA prior to January 1 2003 at department of rheumatology of University Medical Centre Nijmegen. 2) pts receiving ADA had been treated in phase 1, 2, and 3 clinical trials. ADA was given in different dosages subcutaneously or intravenously. The pts then entered an open label extension study. 3) INF and ETA pts were treated in daily clinical practice and fulfilled the Dutch criteria for TNF blocking therapy; had moderate to high disease activity, and high dosage MTX and at least one other DMARD had failed **Exclusion Criteria:** NR	**Interventions:** **D1:** ADA **D2:** INF **D3:** ETA **N:** **D1:** 94 **D2:** 120 **D3:** 16 **Mean age (yrs):** **D1:** 55.2 **D2:** 56.4 **D3:** 50.6 : 55.5 **Sex, % female:** **D1:** 63 **D2:** 72 **D3:** 63 **Race, % white:** NR **Mean disease duration, yrs:** **D1:** 11.4 **D2:** 11.9 **D3:** 10.1 **TJC, mean:** NR **SJC, mean:** NR	About 70% of pts were still receiving TNF blocking agents after the first yr. One yr. drug survival percentages (percentage of pts still taking the drug) were 73% for ADA, 66% for INF, and 74% for ETA group. No significant differences between groups	**Overall:** **D1:** 12 **D2:** 30 **D3: 7** **Serious AEs:** NR **Infections:** **D1:** 2 **D2:** 6 **D3:** 0 **Serious Infections:** **D1:** 6.4 **D2:** 7.2 **D3:** 0 **Infusion or injection reaction:** **D1:** 3 **D2:** 14 **D3:** 0 **Malignancies:** **D1:** 2 **D2:** 0 **D3:** 0	**Overall Attrition Rate, %:** 17 **ITT Analysis:** NA **Quality Rating:** Fair	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Flendrie et al., 2003 (continued)		**DMARD use, %:** **D1:** previous DMARD use, mean 4.5 **D2:** 4.1 **D3:** 3.3 **Corticosteroid use, %:** **D1:** 51 **D2:** 24 **D3:** 19 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.4 **D2:** 5.9 **D3:** 5.8 **RF positive:** **D1:** 93% **D2:** 82% **D3:** 88%				

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Flendrie et al., 2005 **Country, Setting:** Netherlands, Hospital rheumatology clinic **Funding:** NR **Research Objective:** Whether dermatological conditions after TNF-alpha-blocking therapy are a significant and clinically important problem in RA pts receiving TNF-alpha -blocking therapy. **Study Design:** Prospective cohort study with historic control **Overall N:** 578 **Study Duration:** 911PY	**Inclusion Criteria:** • Previous use of DMARDs: failure or intolerability of at least 2 DMARDS, including MTX, in adequate dosage regimens • Control pts selected from Nijmegen inception cohort • Pts required to meet Dutch guidelines for biological therapies: a moderate to high DAS score (DAS28 > 3.2) • Besides therapy with registrated TNF-alpha-blocking agents -INF, ETA, and ADA -some pts were treated in clinical trials with lenercept **Exclusion Criteria:** NR	**Interventions, dose:** **D1:** TNF-apha blockers **D2:** Control **N:** NR **Mean age at diagnosis, yrs:** **D1:** 44.5 **D2:** 54.6 **Sex, % female:** **D1:** 69 **D2:** 62 **Race, % white:** NR	**Median disease duration, yrs:** **D1:** 9.2 **D2:** 6.2 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **PNL at baseline (%)** **D1:** 39 **D2:** 7 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.9 **D2:** 3.6	• Dermatological events recorded in 72/289 (25%) of RA pts receiving TNF-alpha-blocking therapy and in 37 (13%) of control group • OR of TNF-alpha-blocking therapy for dermatological referral was 2.26 (95% CI,1.46 to 3.50, *P* < 0.0005) • 128 dermatological events were recorded during follow-up in RA pts on TNF-alpha-blocking therapy (0.14 event per PY)	**Overall:** **D1:** 25 **D2:** 13 **Infections (skin):** **D1:** 9.3	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Furst, 2003 STAR Trial **Country, Setting:** US and Canada, multicenter (69 sites) **Funding:** Abbott Laboratories, Abbott Park II **Research Objective:** To evaluate the safety and efficacy of ADA when given with standard anti-rheumatic therapy in pts with active RA not adequately responding to standard therapies **Study Design:** RCT **Overall N:** 636 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age: 18+ • Diagnosed with RA (ACR criteria) • Continued txt with standard anti-rheumatic therapy which included traditional DMARD, Cs, NSAID, or analgesics **Exclusion Criteria:** • Prior txt with Anti-CD4 therapy or biologic DMARD • Participated in other trials biolgic DMARD in RA • History of active: inflammatory arthritide other than RA or active listeriosis or mycobacterial infection • Major infection requiring hospitalization • Txt with IV antibiotics within 30 ds • Oral antibiotics within 14 ds • Any uncontrolled medical condition	**Interventions, dose:** **D1:** ADA (40mg s.c. eavery other week) **D2:** placebo **N:** **D1:** 318 **D2:** 318 **Mean age, yrs:** **D1:** 55 **D2:** 55.8 **Sex, % female:** **D1:** 79.6 **D2:** 79.2 **Race, % white:** **D1:** 89 **D2:** 85.8	**Mean disease duration, yrs:** **D1:** 9.3 **D2:** 11.5 **TJC, mean:** **D1:** 27.3 **D2:** 27.6 **SJC, mean:** **D1:** 20.9 **D2:** 21.3 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 50.9 **D2:** 54.4 **MTX naive, %:** **D1:** 20.9 (11) **D2:** 21.3 (11.2) **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** **D1:** 50.9 **D2:** 54.4 **Baseline patient DAS (mean):** **D1:** 53.9 **D2:** 52.9 **Baseline physician DAS (mean):** **D1:** 59.9 **D2:** 59.6	**Health Outcome Measures:** • At endpoint, significantly more ADA (28.9%) pts achieved an ACR50 response than placebo pts (11.3%) ($P < 0.001$) • At endpoint, significantly more ADA (14.8%) pts achieved an ACR70 response than placebo pts (3.5%) ($P < 0.001$) **Intermediate Outcome Measures:** • At endpoint, significantly more ADA (52.8%) pts achieved an ACR20 response than placebo pts (34.9%) ($P < 0.001$)	**Overall:** **D1:** 86.5 **D2:** 82.7 **SAEs:** **D1:** 5.3 **D2:** 6.9 **Infections:** **D1:** 52.2 **D2:** 49.4 **Serious Infections:** **D1:** 1.3 **D2:** 1.9 **Rash:** **D1:** 10.7 **D2:** 6.0 **Infusion or injection reaction:** **D1:** 19.5 **D2:** 11.6 **URTI:** **D1:** 19.8 **D2:** 15.1 **UTI:** **D1:** 9.1 **D2:** 5.7 **Back pain:** **D1:** 5.3 **D2:** 1.6	**Overall Attrition Rate, %:** 9.1 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek et al., 2005 **Country, Setting:** Sweden, rheumatology centers **Funding:** Österlund and Kock Foundations, King Gustav V, and Reumatiker-förbundet **Research Objective:** To determine whether TNF blockers increase tumour risk in pts with RA **Study Design:** Retrospective cohort study **Overall N:** 1557 **Study Duration:** Median duration of anti-TNF txt was 1.7 yrs (5,571 PY)	**Inclusion Criteria:** • ACR criteria were fulfilled by 98% of cohort • Pts with RA treated with ETA or INF from South Swedish Arthritis Txt Group (SSATG), which includes pts from 8 rheumatologic centers • For comparison group, pts with RA not treated with anti-TNF drugs from a community based cohort in Malmo, a city from the SSATG catchment area. • Controls recruited from Malmo University outpatient rheumatology clinic and from 4 rheumatologists in private practice **Exclusion Criteria:** • Tumor diagnosis prior to study	**Interventions, dose:** **D1:** Anti-TNF txt **D2: Comparison** ETA: varied **INF: varied** **N:** **D1:** 757 **D2:** 800 **Median age, yrs:** **D1:** 56 **D2:** 64 **Sex, % female:** **D1:** 76 **D2:** 73 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 12 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **% with HAQ quartile > = 3:** **D1:** 61 **D2:** 41 **Median number of previous DMARDS:** **D1:** 3 **D2:** 1	**Anti-TNF vs. Control:** • All tumors: SIR 1.1 (95% CI, 0.6-1.8) vs. 1.4 (95% CI, 1.1-1.8) • Lymphomas: SIR 11.5 (95% CI,3.7 to 26.9) vs. 1.3 (95% CI,0.2 to 4.5) • All tumors excluding lymphomas: SIR 0.79 (95% CI, 0.4-1.42) vs. 1.39 (95% CI, 1.08-1.76) • Hazard ratio indicates a higher risk of lymphoma for anti-TNF drugs than for controls (RR: 4.9; 95% CI, 0.9-26.1)	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese et al., 2002 **Country, Setting:** US, NR **Funding:** Immunex **Research Objective:** To compare the clinical and radiographic outcomes in pts with RAwho received monotherapy with either ETA or MTX (MTX) for 2 yrs and to assess the safety of this therapy. After 2 yrs all pts received 25 mg of ETA for 3 additional yrs **Study Design:** Open-label extension of RCT **Overall N:** 632 (512) **Study Duration:** 2 yrs	**Inclusion Criteria:** • Age ≥ 18; duration of condition: no more than 3 yrs • At least 3 bone erosions of hands, wrists, feet • At least 10 swolllen joints • At least 12 tender or painful joints • ESR 28 or higher • CRP more than 2 • Morning stiffness at least 45 minutes **Exclusion Criteria:** • Prior txt with: MTX	**Interventions, dose:** **D1:** MTX (ext) **D2:** ETA 10mg (ext) **D3: ETA 25mg (ext)** **N:** **D1:** 217(169) **D2:** 208(166) **D3:** 207(177) **Mean age, yrs:** **D1:** 49(49) **D2:** 50(50) **D3:** 51(50) **Sex, % female:** **D1:** 75(75) **D2:** 75(75) **D3:** 74(74) **Race, % white:** **D1:** 88(88) **D2:** 84(86) **D3:** 86(86)	**Mean disease duration, yrs:** **D1:** 12 mos (12) **D2:** 11 mos (11) **D3:** 12 mos (12) **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 41 (46) **D2:** 42 (37) **D3:** 39 (36) **MTX naive, %:** NR **Txt resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Erosion (mean):** **D1:** 7.5 (6.9) **D2:** 6.1 (5.7) **D3:** 6.4 (5.7) **Sharp (mean):** **D1:** 12.9 (11.3) **D2:** 11.2 (9.7) **D3:** 12.4 (10.8)	• Radiographic mean outcome changes at 2 yrs- • Mean changes in total Sharp score ETA25 1.3 vs. MTX 3.2 *P* = 0.001 • Erosion score ETA25 0.66 units vs. MTX 1.86 units *P* = 0.001 • No increase in total Sharp score ETA25 63% vrsus MTX 51% (*P* = 0.017) • No increase in erosions ETA25 70% vs. MTX 58% (*P* = 0.012) • Incidence of adverse events remained constant over time	**SAEs:** **D1:** (16.1) **D2:** (21.2) **D3:** (20.6) **Serious Infections:** **D1:** 4.1 (4.9) **D2:** 2.4 (6.3) **D3:** 3.4 (8.7) **Infusion or injection reaction:** **D1:** 9 **D2:** 32 **D3:** 39 **Abdominal Pain:** **D1:** 15 **D2:** 13 **D3:** 13 **Dizziness:** **D1:** 12 **D2:** 7 **D3:** 15 **Headache:** **D1:** 28 **D2:** 27 **D3:** 25 **Malignancies:** **D1:** (per p-y 0.003) **D2:** (per p-y 0.008) **D3:** (per p-y 0.014) **Nausea:** **D1:** 31 **D2:** 14 **D3:** 20	**Overall Attrition Rate, %:** 34.5% at two yrs and 54.7% at 5 yrs **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese et al., 2002 (continued)			**JSN (mean):** **D1:** 5.4 (4.4) **D2:** 5.0 (4.0) **D3:** 6.0 (5.1)			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Gomez-Reino, 2003 **Country, Setting:** Spain 71 Centers **Funding:** Agencia Española del Medicamento (Ministerio de Sanidad y Consumo) **Research Objective:** Long-term safety of INF and ETA, in rheumatic diseases based on a national active-surveillance **Study Design:** Retrospective cohort study **Overall N:** 1,540 (1578 txts) **Study Duration:** Mean 1.1 yrs	**Inclusion Criteria:** • Pts with rheumatic diseases being treated with biologic response modifiers registered in BIOBADASER **Exclusion Criteria:** NA	**Interventions, dose:** **D1: INF/ETA** ETA: varies **INF: varies** **N:** **D1:** 1540 (1578 txts) **Mean age, yrs:** **D1:** 51 **Sex, % female:** **D1:** 72 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **PsA:** **D1:** 5.8 **AS:** **D1:** 4.9	• Background TB incidence in Spain in 2000 was 21/100,000 • 1,893 cases of TB per 100,000 pts in yr 2000 and 1,113 cases per 100,000 pts in yr 2001 in pts treated with TNF • RR of TNF pts compared general population 90.1 (95% CI,58.8-146.0) in yr 2000 and 53.0 (95% CI,34.5-89.0) in yr 2001 • Estimated annual incidence of TB among RA pts not exposed to TNF inhibitors was 95/100,000 • RR in RA pts who did not receive TNF of TB (adjusted for age and sex) was 4.13 (95% CI,2.59-6.83) relative to background rate • RR of TB in INF-treated RA pts vs. RA pts not exposed to this therapy was 19.9 (95% CI,16.2-24.8) in yr 2000 and 11.7 (95% CI,9.5-14.6) in yr 2001 • 15 pts with TB were diagnosed as having RA, and 2 additional pts with TB had PsA; all pts with active TB were being treated with INF; 59% were diagnosed with TB within 3 mos of txt initiation	**Infections:** **D1:** 7.7 **Infusion or injection reaction:** **D1:** 2 (INF) **URTI:** **D1:** 9 **UTI:** **D1:** 11	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Harley, 2003 **Country, Setting:** US, Health Plan Data **Funding:** Centocor **Research Objective:** To examine txt compliance and dosage administration with MTX, ETC and INF therapy for RA **Study Design:** Observational-retrospective data analysis **Overall N:** 2662 **Study Duration:** 30 mos	**Inclusion Criteria:** • Commercial or Medicare enrollees **Exclusion Criteria:** • MTX, ETA or INF within 182 days of index date	**Interventions:** **D1:** INF **D2:** ETA **D3:** INF **N:** **D1:** 141 **D2:** 853 **D3:** 1668 **Mean age (yrs):** **D1:** 56.3 **D2:** 47.4 **D3:** 53.3 **Sex, % female:** **D1:** 27 **D2:** 26.3 **D3:** 26.9 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 34 **D2:** 41 **D3:** 37.9 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	Compliance with at least 80% of expected dosages: • ETA: 68.4; OR 0.462; 95 CI, 0.290-0736 • MTX: 63.7; OR 0.385; 95 CI, 0.245-0604 • INF: 80.9 • OR =Reference • $P < 0.05$ Dosage Increases: • MTX: 61.6% • INF: 37.4% • ETA: 7.4%	NR	**Overall Attrition Rate, %: NA** **ITT Analysis:** Not applicable **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004 **Country, Setting:** US, multicenter, specialty clinic **Funding:** Amgen, Inc., Thousand Oaks, CA **Research Objective:** To determine potential for additive or synergistic effects of combination therapy with selective anti-TNF-alpha agent ETA and anti-IL1 agent AKA **Study Design:** RCT **Overall N:** 242 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age > 18 • RA according to ACR criteria • Duration of condition: > 6 mos • 6+ swollen joints • 9+ tender/painful joints • At least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of > 1.5 mg/dl, or ESR > 28 mm/hr; and, MTX > 16 wks, stable dose of 10-25 mg/wk > 8 wks; continued txt with stable doses of MTX and other stable medications, such as corticosteroids **Exclusion Criteria:** • Any DMARD other than MTX within past 4 wks • Txt with AKA or any protein-based TNF-alpha inhibitor	**Interventions, dose:** **D1:** ETA (25 mg twice wkly) **D2:** ETA (12.5 mg once wkly) + AKA (100 mg/d) **D3:** ETA (25 mg twice wkly) + AKA (100 mg/d) **N:** **D1:** 80 **D2:** 81 **D3:** 81 **Mean age, yrs:** **D1:** 54.4 **D2:** 53.8 **D3:** 55.7 **Sex, % female:** **D1:** 82.5 **D2:** 71.6 **D3:** 77.8 **Race, % white:** **D1:** 86.3 **D2:** 77.8 **D3:** 75.3	**Mean disease duration, yrs:** **D1:** 9.7 **D2:** 9.5 **D3:** 10.6 **TJC, mean:** **D1:** 31 **D2:** 31 **D3:** 35.9 **SJC, mean:** **D1:** 21.4 **D2:** 19.8 **D3:** 23.4 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 48.8 **D2:** 54.3 **D3:** 44.4 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**At week 24** **ACR20, %:** **D1:** 68 **D2:** 51 **D3:** 62 **D1** vs. **D2** (*P* = 0.037) All others NS **ACR50, %:** **D1:** 41 **D2:** 39 **D3:** 31(*P* = 0.914) OR (ETA + AKA vs. ETA alone) 0.64 (90% CI, 0.37-1.09); sensitivity analysis yielded similar results **ACR70, %:** **D1:** 21 **D2:** 24 **D3:** 14 (*P* = NR) **Sustained ACR20 response:** Between 43% and 54% of subjects in each group (specifics NR) **EULAR response, %:** **D1:** 79 **D2:** 66 **D3:** 73 (*P* = NR) **Mean % reduction in DAS:** **D1:** 39 **D2:** 41 **D3:** 40 (*P* = NR)	**Overall:** **D1:** 90 **D2:** 95.1 **D3:** 93.8 **SAEs:** **D1:** 2.5 **D2:** 4.9 **D3:** 14.8 **Infections:** **D1:** 40 **D2:** 37 **D3:** 46.9 **Serious Infections:** **D1:** 0 **D2:** 3.7 **D3:** 7.4 **Infusion or injection reaction:** **D1:** 40 **D2:** 67.9 **D3:** 70.4 **URTI:** **D1:** 20 **D2:** 11.1 **D3:** 13.6	**Overall Attrition Rate, %:** 15.7 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004 (continued)	• Received any intraarticular or systemic corticosteroid injections within past 4 wks • Recent history of significant infection or other important concurrent illness		**MTX use, %:** Overall: 100 **HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.6			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 BeST Study **Country, Setting:** The Netherlands, 18 peripheral and 2 university hospitals **Funding:** Schering-Plough BV and Centocor Inc Dutch College of Health Insurances **Research Objective:** To compare clinical and radiographic outcomes of 4 different txt strategies in pts with early RA **Study Design:** RCT **Overall N:** 508 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age > 18 yrs • RA according to ACR criteria • Duration of condition < 2 yrs • Active disease with at least 6 of 66 swollen joints • At least 6 of 68 tender joints • ESR > 28 mm/hr OR global health score greater than or equal to 20mm on 0 to 100 VAS • Concomittant NSAIDS and intraarticular steroids **Exclusion Criteria:** • Pregnant • Prior txt with: DMARDS other than antimalarials • Impaired renal or hepatic system	**Interventions, dose:** **D1:** sequential monotherapy **D2:** step-up combination therapy **D3:** initial combination with PRE **D4:** initial combination with INF **D5:** NR Overall: Totals **N:** **D1:** 126 **D2:** 121 **D3:** 133 **D4:** 128 Overall: 508 **Mean age, yrs:** **D1:** 54 **D2:** 54 **D3:** 55 **D4:** 54 Overall: 54 **Sex, % female:** **D1:** 86 **D2:** 86 **D3:** 86 **D4:** 85 Overall: 86 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 23 wks **D2:** 26 wks **D3:** 23 wks **D4:** 23 wks **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.5 +/- 0.9 **D2:** 4.5 +/- 0.8 **D3:** 4.4 +/- 0.9 **D4:** 4.3 +/- 0.9	**At 12 months** **Mean D-HAQ scores:** **D1:** 0.7 +/- 0.7 **D2:** 0.7 +/- 0.6 **D3:** 0.5 +/- 0.5 **D4:** 0.5 +/- 0.5 (**D1** vs. **D3**; *P* < 0.05) (**D3** vs. **D4**; *P* = NS) All others NR **Median total SHS increases (0 to 448 scale) from baseline:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (**D1** vs. **D3**; *P* = 0.003) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.007) (**D2** vs. **D4**; *P* < 0.001) **Progression of total SHS, %:** **D1:** 67 **D2:** 73 **D3:** 87 **D4:** 93 (**D1** vs. **D3** and **D4**; *P* = 0.001) (**D1** vs. **D4**; *P* < 0.001) (**D2** vs. **D3**; *P* = 0.010) (**D2** vs. **D4**; *P* < 0.001)	**Overall:** **D1:** 43 **D2:** 47 **D3:** 37 **D4:** 39 **SAEs:** **D1:** 6.3 **D2:** 7.4 **D3:** 12.8 **D4:** 4.7 **Infections:** **D1:** 4 **D2:** 7 **D3:** 8 **D4:** 8 **Serious Infections:** **D1:** 2.4 (pneumonia, HSV encephalitis, and fever) **D2:** 0.8 (diffuse peritonitis) **D3:** 0.8 (oral HSV) **D4:** 2.3 (pneumonia, pneumonitis, and septic arthritis) **Infusion or injection reaction:** **D4:** (10/128) = 7.8%	**Overall Attrition Rate, %:** 3.3% (17/508) **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Goekoop-Ruiterman et al., 2005 (continued)	• concomittant txt with an experimental drug • bone marrow hypoplasia • diabetes • alcohol or drug abuse • wish to conceive • inadequate contraception		**D-HAQ (0 to 3 scale):** **D1:** 1.4 +/-0.7 **D2:** 1.4 +/-0.6 **D3:** 1.4 +/-0.7 **D4:** 1.4 +/-0.7	**Sharp van der Heijde median increase:** **D1:** 2.0 **D2:** 2.5 **D3:** 1.0 **D4:** 0.5 (*P* < 0.001) **Sustain DAS44 ≤ 2.4, %:** **D1:** 53 **D2:** 64 **D3:** 71 **D4:** 74 (**D1** vs. **D3**; *P* = 0.004) (**D1** vs. **D4**; *P* < 0.001) (*P* = NS and NR for others) **Patients who progressed to erosive from nonerosive disease at baseline, %** **D1:** 29 (9/31) **D2:** 53 (18/34) **D3:** 38 (14/37) **D4:** 15 (5/34) D1 vs D2, *P* = 0.050 D2 vs D4, *P* = 0.028 D3 vs D4, *P* =NS, NR	**Cardiovascular Events:** **D1:** 2 (hypertension, TIA, PE) **D2:** 2 (peripheral bypass, pacemaker implantation) **D3:** 6 (3 MIs, heart failure **D4:** 2 (TIA, PE, peripheral vascular disease) **Malignancies:** **D2:** N:1 bladder **D3:** N:2 breast, lymphoma **Adherence** 24 (5%) non-adherent	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 **Country, Setting:** Netherlands, 1 academic and 6 peripheral clinics **Funding:** Pharmachemie BV; Pharmacia AB **Research Objective:** Compare efficacy and safety of SSZ, MTX, and combination of both in pts with early RA **Study Design:** RCT **Overall N:** 105 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed with RA according to ACR criteria: ACR criteria • RF positive and/or HLA-DR4 positive and/or HLA DR1 positive • Functional class of: DAS ≥ 3.0 • Duration of condition: < 12 mos • Analgesica and NSAIDS allowed **Exclusion Criteria:** • Prior txt with: DMARDS other than analgesics and NSAIDS • Other: contraindications to SSZ or MTX	**Interventions, dose:** **D1:** SSZ (1 g/day; max 3 g/day) **D2:** MTX (7.5 mg/wk; max 15 mg/wk) **D3:** MTX (7.5 mg/wk; max 15 mg/wk) + SSZ (1 g/day; max 3 g/day) **N:** **D1:** 34 **D2:** 35 **D3:** 36 **Mean age, yrs:** **D1:** 56.8 **D2:** 54.9 **D3:** 57.0 **Sex, % female:** **D1:** 61.8 **D2:** 65.7 **D3:** 66.7 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 3.1 mos **D2:** 3.0 mos **D3:** 2.6 mos **TJC, mean:** **D1:** 20.8 **D2:** 20.6 **D3:** 24.8 **SJC, mean:** **D1:** 17.0 **D2:** 19.9 **D3:** 20.8 **DMARD use, %:** Overall: 0 **Corticosteroid use, %** Overall: 0 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** **D1:** 4.6 **D2:** 4.7 **D3:** 5.0	No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable **At 52 weeks** **DAS mean change:** **D1:** -1.6 (95% CI, -2.0 to -1.2) **D2:** -1.7 (95% CI, -2.0 to -1.4) **D3:** -1.9 (95% CI, -2.2 to -2.3) **Ritchie mean change:** **D1:** -8.6 (95% CI, -10.7 to -6.5) **D2:** -8.2 (95% CI, -10.1 to -6.4) **D3:** -9.4 (95% CI, -11.1 to -7.7) **Swollen joints mean change**: **D1:** SSZ -7.9 (95% CI, -10.1 to -5.7) **D2:** -10.2 (95% CI, -12.5 to -8.0) **D3:** -11.3 (95% CI, -13.5 to -9.2)	**Overall:** **D1:** 88.2 **D2:** 77.1 **D3:** 88.9 **SAEs:** **D1:** 8.8 **D2:** 0 **D3:** 0 **Abdominal Pain:** **D1:** 26.5 **D2:** 20 **D3:** 36 **Cardiovascular Events (Dyspnea):** **D1:** 5.9 **D2:** 0 **D3:** 5.6 **Dizziness:** **D1:** 17.6 **D2:** 8.6 **D3:** 27.8 **Headache:** **D1:** 17.6 **D2:** 11.4 **D3:** 11.1 **Nausea:** **D1:** 29.4 **D2:** 25.7 **D3:** 63.9 **URTI** **D1:** 17.6 **D2:** 20.0 **D3:** 27.8	**Overall Attrition Rate, %:** 19 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Haagsma, 1997 (continued)			**HAQ:** **D1:** 0.97 **D2:** 0.92 **D3:** 1.20	**HAQ change from baseline:** **D1:** -0.32 (95% CI, -0.53 to -0.10) **D2:** -0.46 (95% CI, -0.68 to -0.25) **D3:** -0.51 (95% CI, -0.76 to -0.26) **Number of pts with a response according to ACR criteria at end of study:** **D1:** 25 **D2:** 25 **D3:** 28 **Number of pts with good response according to EULAR definition:** **D1:** 14 **D2:** 15 **D3:** 14		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Hyrich et al., 2006 **Country, Setting:** Great Britain, multiclinic **Funding:** Schering Plough, Wyeth, Abbott, A mgen British Society for Rheumatology Biologics Register **Research Objective:** Compare outcome at 6 mos in unselected real-world RA pts treated with ETA or INF alone or with MTX or another DMARD **Study Design:** Prospective cohort study	**Inclusion Criteria:** • Age > 16 yrs • Diagnosed with RA according to 1987 ACR criteria; starting either ETA or INF as first biologic drug • Other meds were allowed **Exclusion Criteria:** NR	**Interventions, dose:** **D1:** ETA (25 mg 2x wk) **D2:** ETA + DMARD **D3:** ETA + MTX **D4:** INF (3 mg/kg wks 0,2,6 then every 8wks) **D5:** INF + DMARD **D6:** INF + MTX Some doses NR **N:** **D1:** 763 **D2:** 245 **D3:** 250 **D4:** 128 **D5:** 121 **D6:** 1204 **Mean age, yrs:** **D1:** 58 **D2:** 55 **D3:** 54 **D4:** 59 **D5:** 58 **D6:** 55 **Sex, % female:** **D1:** 80 **D2:** 79 **D3:** 76 **D4:** 79 **D5:** 74 **D6:** 77 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 16 **D2:** 15 **D3:** 13 **D4:** 16 **D5:** 14 **D6:** 14 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 54 **D2:** 51 **D3:** 44 **D4:** 69 **D5:** 59 **D6:** 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR	**At 6 months** **EULAR response:** **D3** vs. **D1:** (OR 1.98, 95% CI, 1.45-2.71) **D2** vs. **D1** (OR 1.20, 95% CI, 0.89-1.61) **D3** vs **D2** (OR 1.66, 95% CI, 1.14-2.42) A better EULAR response in both MTX (OR 1.35 [95% CI, 0.92-2.00]) and DMARD (OR 1.26 [95% CI, 0.75-2.13]) subgroups as compared with INF monotherapy **DAS28**: **D1:** 4.8 +/-.4 **D2:** 4.6 +/- 1.5 **D3:** 4.3 +/- 1.5 **D4:** 5.0 +/- 1.6 **D5:** 4.9 +/- 1.6 **D6:** 4.6 +/- 1.6	**Adherence:** Drug survival at 6 mos: ETA 20% INF 21% ETA subgroups (22% mono, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy , vs. 22% DMARD co-therapy)	**Overall Attrition Rate, %:** 21 **ITT Analysis:** N/A **Quality; Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Hyrich et al., 2006 (continued) **Overall N:** 2711 **Study Duration:** 6 mos			**Baseline DAS, mean:** **D1:** 6.8 **D2:** 6.6 **D3:** 6.6 **D4:** 6.8 **D5:** 6.8 **D6:** 6.7			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004 with van der Heijde, 2006 TEMPO study **Country, Setting:** Multinational (Europe), multicenter **Funding:** Wyeth Research **Research Objective:** To compare safety and efficacy of combination of ETA and MTX with monotherapies in pts with RA who had failed previous DMARD txt **Study Design:** RCT **Overall N:** 686 (2 yr results: 503) **Study Duration:** 52 wks (2 yrs, 100 wks)	**Inclusion Criteria:** • Age ≥ 18 • Diagnosed according to ACR criteria • Functional class I-III • Less than satisfactory response to at least 1 DMARD other than MTX • Duration 6 mos to 20 yrs • RA defined as > 10 swollen and > 12 painful joints and at least one of: ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs **Exclusion Criteria:** • TNF antagonist, any immuno-suppressive drugs w/in 6 mos • Any investigational drug or biologic agent w/in 3 mos DMARD or css injection w/in 4 mos	**Interventions, dose:** **D1:** MTX (20 mg/wk) **D2:** ETA (25 mg 2x wkly) **D3:** ETA (25 mg 2x wkly) + MTX (7.5 titrated to 20 mg/wk) **N:** **D1:** 228 (152) **D2:** 223 (163) **D3:** 231 (188) Overall (at 2yrs): 503 **Mean age, yrs:** **D1:** 53 **D2:** 53.2 **D3:** 52.5 Overall (at 2yrs): 52.1 **Sex, % female:** **D1:** 79 **D2:** 77 **D3:** 74 Overall (at 2yrs): 76 **Race, % white:** **D1:** 98 **D2:** 99 **D3:** 98 Overall (at 2yrs): 99	**Mean disease duration, yrs:** **D1:** 6.8 **D2:** 6.3 **D3:** 6.8 **TJC, mean:** **D1:** 33.1 **D2:** 35 **D3:** 34.2 **SJC, mean:** **D1:** 22.6 **D2:** 23 **D3:** 22.1 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 64 **D2:** 57 **D3:** 62 **MTX naive, %:** **D1:** 58 **D2:** 58 **D3:** 56 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.5 **D2:** 5.7 **D3:** 5.5	**At 24 weeks** **AUC of ACR-N, %-yrs:** **D1:** 12.2 **D2:** 14.7 **D3:** 18.3 (*P* < 0.0001) **ACR20, %:** **D1:** 75 **D2:** 76 **D3:** 85 (*P* = 0.0151) **ACR50, %:** **D1:** 43 **D2:** 48 **D3:** 69 (*P* < 0.0001) **ACR70, %:** **D1:** 19 **D2:** 24 **D3:** 43 (*P* < 0.0001) **At 52 weeks** **DAS < 1.6 remission, %:** **D1:** 13 **D2:** 16 **D3:** 35 (**D3** vs. **D2:** *P* < 0.0001; **D2** vs. **D1:** *P* = 0.5031) **HAQ, decline:** **D1:** 0.65 **D2:** 0.7 **D3:** 1.0 (*P* < 0.05) **D3** therapy significantly more likely to attain HAQ DI similar to population norms (< 0.5) than monotherapy	**Overall:** **D1:** 81 (87) **D2:** 86 (92) **D3:** 81 (86) **Infections:** **D1:** 64 (75) **D2:** 59 (71) **D3:** 67 (76) **Serious Infections:** **D1:** 4 (7) **D2:** 4 (6) **D3:** 4 (6) **Infusion or injection reaction:** **D1:** 2 (2) **D2:** 21 (21) **D3:** 10 (11) **Abdominal Pain:** **D1:** 18 **D2:** 12 **D3:** 18 **Hypertension:** **D1:** 5 **D2:** 13 **D3:** 9 **Headache:** **D1:** 14 **D2:** 15 **D3:** 15 **Nausea:** **D1:** 32 (39) **D2:** 10 (13) **D3:** 24 (29)	**Overall Attrition Rate, %:** 52 wks: 23.5 2 Yrs: 38.4 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004 (continued)	• Previous txt with MTX if pt experienced clinically toxic side effects or had no response		**Sharp:** **D1:** 26.8 **D2:** 21.8 **D3:** 21.8 **JSN:** **D1:** 13.3 **D2:** 11.5 **D3:** 10.3	**Radiograhic outcomes** **Total Sharp Score change:** **D1:** 0.28 **D2:** 0.52 **D3**: -0.54; D3 vs D2; *P* = 0.0006 D2 vs D1; *P* =0.047 **Erosion score change:** **D1:** 1.68 **D2:** 0.21 **D3**: -0.30; D3 vs D2; *P* = 0.0001 D2 vs D1; *P* =0.008 **JSN score change:** **D2:** 0.32 **D3**: -0.23; *P* = 0.0007 **At 2 years** **Total Sharp score change:** **D1:** 1.12 **D2:** 1.10 **D3**: -0.56; *P* = 0.05 D3 vs D2; *P* = 0.05 D2 vs D1; *P* = NR **Erosion score change** **D2:** 0.36 **D3:** -0.76 P < 0.05 **JSN score change** **D2:** 0.74 **D3**: 0.20; *P* = NS, NR		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Jacobsson et al., 2005 **Country, Setting:** Sweden, population-based (2 Swedish registers) **Funding:** NR **Research Objective:** Risk of cardiovascular disease (CVD) in pts with RA treated with TNF inhibitors, compared to a standard RA population **Study Design:** Retrospective cohort study **Overall N:** 983 (combined cohort) **Study Duration:** NR	**Inclusion Criteria:** • Age-: 20 -79 yrs • Diagnosed according to 1987 ACR criteria • Case cohort • South Swedish Arthritis Txt Group (SSATG): pts with RA treated with anti-TNF agents and included in SSATG register between 2/1/99 and 12/31/01 **Exclusion Criteria:** • Previous hospital discharge due to CVD	**Interventions, dose:** **D1:** Anti-TNF exposed **D2:** Not Anti-TNF exposed **N:** **D1:** 531 **D2:** 452 **Median age, yrs:** **D1:** 55 **D2:** 61 **Sex, % female:** **D1:** 78 **D2:** 75 **Race, % white:** NR	**Median disease duration, yrs:** **D1:** 12 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **Median # of previous DMARDs used (IQR):** **D1:** 4 (2-5) **D2:** 2 (1-4) **PNL use, %:** **D1:** 75 **D2:** 22 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Median HAQ:** **D1:** 1.50 **D2:** 1.13 **VAS patient global assessment median:** **D1:** 69 **D2:** 48	• Decreased incidence and RR for the development of first-time CVD event when controlling for disease severity in pts with RA treated with TNF blocking therapy • Controlling for disability (HAQ), age-sex adjusted rate ratio was 0.46 (95% CI,0.25 -0.85; *P* = 0.013) in anti-TNF treated vs. not treated • Anti-TNF group, 13 CVD events (in 656 PY at risk); age-adjusted incidence rate = 14 events/1000 PY • Unexposed comparison group, 85 CVD events (in 2056 PY at risk); age-adjusted incidence rate = 35.4 events/1000 PY • Relative risk = 0.62 (95% CI, 0.34 to 1.12; *P* = 0.111) • SMR revealed increased risk of new onset CVD in those not treated with TNF blockers in relation to background population of Malmo (SMR = 228, 95% CI,179 to 277) TNF blockers, risk of new onset CVD was lower, with CIs enclosing unity with background population (SMR = 157, 95% CI,72 -242)	**Cardiovascular Events:** **D1:** n =13 (6 MI, 4 cerebrovascular disease, and 3 other) **D2:** n =85 (33 MIs, 15 cerebrovascular disease, 12 CHF, 2 ruptured aortic aneurysm, and 23 other)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Keane, 2001 **Country, Setting:** Multinational, NA NA **Funding:** National Heart, Lung and Blood Institute; Massachusetts Thoracic Society; American Lung Association of Massachusetts **Research Objective:** To explore relationship between INF and tuberculosis based on data from MedWatch **Study Design:** Database analysis; AERS **Overall N:** 70 cases 47 Crohn's: 18 other: 5 **Study Duration:** 1-52 wks	**Inclusion Criteria:** • If during or after txt with INF, patient received diagnosis of TB on basis of clinical, radiologic, and laboratory findings **Exclusion Criteria:** NR	**Interventions, dose:** **D1: TB pts** **INF: varies** **N:** **D1:** 57 Median age, yrs: **D1:** 57 **Sex, % female:** **D1:** 64 **Race, % white:** **D1:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 20 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Estimated incidence for pts with RA who have been treated with INF during previous is 24.4 cases per 100.000 per yr (95% CI,0.6 to 34.0); background incidence in US for pts with RA not exposed to TIM therapy: 6.2 cases per 100,000 per yr • Median interval from start of INF txt until development of TB = 12 wks; 68.6% developed TB after 3 or fewer INF infusions; reported frequency of TB in association with INF was much higher than reported frequency of other opportunistic infections associated with this drug	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kremer, 2002 **Country, Setting:** US and Canada, multicenter (20 outpatient practice centers) **Funding:** Aventis Pharmaceuticals **Research Objective:** To evaluate efficacy and safety of LEF vs. Placebo when added to ongoing stable dose MTX therapy in pts with persistently active RA **Study Design:** RCT **Overall N:** 263 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age: 18 or 75 • Diagnosed with RA according to ACR criteria: Active:>9 tender joints, >6 sollen joints, >45 mornign stiffness • Previous use of DMARDs: Failed in 11 pts • Other (Please include concomitant drugs that are allowed)? MTX (15-20mg/wk or 10-15mg/wk if max tolerated dose) for at least 6 mos, AND stable dosing for at least 8 wks **Exclusion Criteria:** • Pregnant or lactating • Prior txt with: prohibited DMARDs in past 30 ds • Impaired renal or hepatic system: Hep B or C, 3 or more elevations of AST or ALT, elevated SrCR • Psoriatic Arthritis or other acute inflammatory joint disease not RA	**Interventions, dose:** **D1:** MTX + LEF **D2:** MTX + Placebo Methotrexate: 15 - 20 mg/wk or 10 - 15 mg/wk if toleration problems Leflunomide: 100 mg 2 ds then 10mg/d or 10mg/every other d if adverse effects Placebo: Folate 1 mg/d for ALL **N:** **D1:** 130 **D2:** 133 **Mean age, yrs:** **D1:** 55.6 **D2:** 56.6 **Sex, % female:** **D1:** 76.2 **D2:** 80.5 **Race, % white:** **D1:** 90.8 **D2:** 87.2	**Mean disease duration, yrs:** **D1:** 10.5 **D2:** 12.7 **TJC, mean:** **D1:** 26.9 **D2:** 26.4 **SJC, mean:** **D1:** 17.3 **D2:** 18.7 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **HAQDI:** **D1:** 1.6 **D2:** 1.5	**ACR20:** • LEF 46.2%; Placebo 19.5% *P* <0.001 **HAQ:** • LEF -0.42 • Placebo -0.09 *P* < 0.001 • SF-36: LEf + 6.8 Placebo + 0.3 *P* < 0.001	**Overall:** **D1:** 89.2 **D2:** 89.5 **Infections:** **D1:** 40.8 **D2:** 51.9 Dizziness: **D1:** 7.7 **D2:** 5.3 **Headache:** **D1:** 10 **D2:** 8.3 **Nausea:** **D1:** 16.2 **D2:** 11.3 **URTI:** **D1:** 22.3 **D2: 24.1** **Adherence:** Overall, 98% adherent Mean adherence **Adherence:** • Rates 80 120% • Lef 87.7% • Placebo 90.2%	**Overall Attrition Rate, %:** Discontinuation Rates: LEF 23.1 Placebo 24.8% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006 **Country, Setting:** Sweden, multicenter **Funding:** Osterlund and Kock Foundations, 80-yr Fund of King Gustav V, and Reumatikerfor-bundet **Research Objective:** LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA pts treated in clinical practice **Study Design:** Prospective cohort study **Overall N:** 949 **Study Duration:** Varied (results reported for 3 yrs)	**Inclusion Criteria:** • Unsuccessful txt with 2 DMARDS including MTX • Pts diagnosed with RA according to clinical judgment of treating physician • Treated at 8 centers in Southern Sweden during March 1999 through January 2004 • Meds allowed, NR **Exclusion Criteria:** • Prior txt with biologic therapy	**Interventions, dose:** **D1:** ETA (25 mg s.c. twice wkly) **D2:** INF (≥3 mg/kg at 0, 2, 6, and 12 wks and then every 8 wks) **N:** **D1:** 309 **D2:** 640 **Mean age, yrs:** **D1:** 55.1 **D2:** 56.2 **Sex, % female:** **D1:** 82 **D2:** 75 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 14.7 **D2:** 12.7 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.9 **D2:** 5.6 **MTX use, %:** **D1:** 31 **D2:** 73 **HAQ:** **D1:** 1.6 **D2:** 1.4	**At 3 months** **D1:** 63 **D2:** 45 ($P < 0.001$) **At 6 months** **D1:** 61 **D2:** 47 (P = NS) **At 12 months** **LUNDEX values** (index of drug efficacy in clinical practice)**:** **D1:** ~ 55% (~ 4 0% at 3 yrs) **D2:** ~ 45% (~ 30% at 3 yrs) **ACR20, %:** **D1:** 69 **D2:** 53 (P = 0.001) **At 24 months** **ACR20, %:** **D1:** 65 **D2:** 56 (P = NS) **At 36 months** **ACR20, %:** **D1:** 63 **D2:** 61 (P = NS) **ACR50, %:** **D1:** 39 **D2:** 39 (P = NS) **ACR 70, %:** **D1:** 16 **D2:** 18 (P = NS)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006 (continued)				**EULAR (moderate), %:** **D1:** 46 **D2:** 29 (*P* = NS) **EULAR (good), %:** **D1:** 36 **D2:** 45 (*P* = NS) **Intermediate Outcome Measures:** INF had significantly lower adherence compared to ETA (*P* < 0.001)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kwon, 2003 **Country, Setting:** USA, Multicenter (FDA's MedWatch program) **Funding:** US Food and Drug Administration **Research Objective:** To describe adverse event reports of heart failure after TNF antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 47 cases **Study Duration:** long-term therapy	**Inclusion Criteria:** • Pts who reported heart failure as an adverse event while taking ETA or INF therapy in US since licensure of drugs until February 2002 • New onset failure and exacerbation of preexisting heart failure included **Exclusion Criteria:** • Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded	**Interventions, dose:** **D1:** New Onset Heart Failure without risk factors **D2:** New Onset Heart Failure with risk factors **D3:** Heart failure exacerbation ETA: any INF: any **N:** NR **Mean age, yrs:** **D1:** 59 **D2:** 67 **D3: 70** **Sex, % female:** **D1:** 74 **D2:** 42 **D3: 44** **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 8 **D2:** 10 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **%ETA:** **D1:** 12 **D2:** 14 **D3:** 3 **%INF:** **D1:** 7 **D2:** 5 **D3:** 6	• 38 pts (81%) developed new-onset heart failure • 9 (19%) experienced heart failure exacerbation of which: 19 pts had no documented risk factors, 10 pts were under age 50 • Of pts under 50, after cessation of TNF antagonist therapy 3 pts experienced complete resolution of heart failure, 6 pts showed improvement, and 1 patient died	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Langer, 2003 **Country, Setting:** Germany, multiple sites, daily clinical practice **Funding:** Amgen **Research Objective:** To assess the response rate, time to response, efficacy and safety of anakinra during 52 wks of therapy after launch in daily clinical practice in Germany and to gain knowledge of the routine application of anakinra in RA pts under special conditions (RA pts who failed TNF-blocking drugs) **Study Design:** Case series; postmarketing surveillance **Overall N:** 454 **Study Duration:** 52 wks	**Inclusion Criteria:** • Age: adult • Patients who fell within approved indication for anakinra • Pts with RA who had been ineffectively treated with at least 2 DMARDs including MTX **Exclusion Criteria:** NR	**Interventions:** **D1:** AKA, all pts **D2:** AKA, TNF-blocker naive **D3:** AKA, TNF-blocker pretreated Anakinra **N:** **D1:** 166 **D2:** 105 **D3: 61** **Mean age (yrs):** **D1:** 53.7 **D2:** 54.7 **D3: 51.9** **Sex, % female:** **D1:** 78.9 **D2:** 78.1 **D3: 80.3** **Race, % white:** NR **Mean disease duration, yrs:** **D1:** 12.3 **D2:** 12.0 **D3: 12.8** **TJC, mean:** **D1:** 12.8 **D2:** 12.4 **D3:** 13.4 **SJC, mean:** **D1:** 10.5 **D2:** 10.4 **D3:** 10.8	• Pts responded well to AKA therapy; 67.5% had good (21.0%) or moderate (46.5%) EULAR response after 6 mos. of therapy • DAS decreased by 44% for all pts • Tender joint count decreased by 53%, swollen joint count by 49%, pain by 31%, and global health by 28% • Response to AKA was rapid, within 1 mo; shown in figures • Data suggest AKA is effective in pts who have failed anti-TNF therapy with comparable results to anti-TNF naive pts • 69.4% of TNF-blocker pretreated pts had a good or moderate EULAR response at 6 mos. compared to 66.3% of TNF-blocker naive pts • Disease activity decreased by 39% and 47% respectively • Pain decreased by 35% and 29% respectively • Tender joint count by 49% vs. 55%	See adverse events	**Overall:** **D1:** 41.2 **Serious AEs:** **D1:** 4.2 **Infections:** **D1:** 6.6 **Serious Infections:** **D1:** 1.5 **Infusion or injection reaction:** **D1:** 20.7 **Abdominal Pain:** NR **Cardiovascular Events:** NR **Dizziness:** NR **Headache:** **D1: 2** **Hepatotoxicity:** NR **Malignancies:** NR **Nausea:** NR **URTI:** NR **UTI:** **NR**	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** **Fair**

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Langer, 2003 (continued)		**DMARD use, %:** **D1:** on MTX: 66.3 **D2:** 72.4 **D3:** 55.7 **Corticosteroid use, %:** **D1:** 84.9 **D2:** 81.9 **D3:** 90.1 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.8 **D2:** 5.6 **D3:** 6.1 **D1:** morning stiffness (minutes) 112.5 **D2:** 104.1 **D3:** 126.6 **D1: #** of previous DMARDs: 3.6 **D2:** 3.0 **D3:** 4.4	• Swollen joint count 44% vs. 52% • Global health by 33% vs. 26%			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lebwohl, 2005 **Country, Setting:** US, clinical trial participants receiving ETA from private and institutional practices **Funding:** Amgen Inc. **Research Objective:** Incidence of cutaneous SCC in pts with rheumatoid arthritis receiving ETA for up to 5 yrs **Study Design:** Postmarketing database review **Overall N:** 1,442 (4257 PY) **Study Duration:** Mean 3.7 yrs	**Inclusion Criteria:** • Participant in 1 of various studies* of ETA in pts with rheumatoid arthritis • Pts had active RA; and, received 10 to 50 mg ETA subcutaneously twice weekly for majority of time they received study drug. Specific inclusion criteria varied by included study **Exclusion Criteria:** NR	**Interventions, dose:** **D1: ETA** **N:** **D1:** 1442 **Mean age, yrs:** **D1:** 49.9 **Sex, % female:** **D1:** 76.5 **Race, % white:** **D1:** 87.4	**Mean disease duration, yrs:** **D1:** 7.1 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**Health Outcome Measures:** • Total # of cases of SCC reported from post-marketing database population: 4 cases **Age and sex-matched expected incident cases based on:** • From Arizona general population-based incidence study: 13.1 cases • From Minnesota general population-based incidence study: 5.9 cases • Number of cases of SCC per PY of exposure to ETA **In clinical trial population: 0.9/1000 PY** • From post-marketing surveillance data: .01/1000 PY **Summary Statement:** The incidence of SCC among pts taking ETA is likely no different from that of the general population.	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair:

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lee, 2002 **Country, Setting:** US, clinics **Funding:** NR **Research Objective:** To identify post-licensure cases of opportunistic histoplasmosis in pts treated with INF and ETA **Study Design:** Database analysis; AERS **Overall N:** 10 cases (from FDA passive surveillance database for monitoring postlicensure AEs) **Study Duration:** varied	**Inclusion Criteria:** • Any report of histoplasmosis in a patient receiving ETA or INF had been received by AERS by July 2001 **Exclusion Criteria:** NR	**Interventions, dose:** **D1:** ETA **D2:** INF **D3:** Overall ETA: varied INF: varied **N:** **D1:** 9 **D2:** 1 **D3:** 10 **Mean age, yrs:** **D1:** 11-78 (range) **D3:** median: 43.5 **Sex, % female:** **D1:** 4/9 (44.4%) **D2:** 0/1 (0%) **D3:** 40 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Concomitant immunosuppressive:** **D1:** 100 **D2:** 100	**Cases of histoplasmosis reported to the AERS by July 2001** • 9 cases among pts receiving INF • 1 case among pts receiving ETA **Through August 2001, number of pts treated** • With INF: ~150,000 • With ETA: ~96,500 **Histoplasmosis case rates per 100,000 pts receiving drug** • INF: ~6/100,000 • ETA: ~1/100,000 **Deaths due to histoplasmosis** • INF: 1/10 • ETA 0/1 **Summary:** More cases of histoplasmosis were reported to AERS by July 2001 among pts receiving INF than those receiving ETA. When accounting for actual number of pts taking each of drug, histoplasmosis case rate was ~6 times higher among pts receiving INF than among those receiving ETA	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2005 **Country, Setting:** Germany, population-based **Funding:** Joint grant from Essex, Wyeth, Amgen, and Abbott **Research Objective:** Incidence rates of serious and non-serious infections in pts with RA who start txt with a biologic agent, and to compare these rates with those in pts with RA who receive conventional txt **Study Design:** Prospective cohort study **Overall N:** 1529 **Study Duration:** Up to 12 mos	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to ACR criteria new txt with ETA, INF, or AKA • Controls: pts started on DMARD therapy after failure of > 1 other DMARD, or with additional DMARD added to existing DMARD **Exclusion Criteria:** • NR	**Interventions, dose:** **D1:** ETA **D2:** INF **D3:** AKA **D4:** DMARDS (control) **N:** **D1:** 512 **D2:** 346 **D3:** 70 **D4:** 601 **Mean age, yrs:** **D1:** 53.7 **D2:** 53.6 **D3:** 54.3 **D4:** 56.5 **Sex, % female:** **D1:** 78.1 **D2:** 70.8 **D3:** 77.1 **D4:** 82.7 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 9 **D2:** 8 **D3:** 13 **D4:** 6 **TJC, mean:** **D1:** 13.3 **D2:** 12.7 **D3:** 12.6 **D4:** 10 **SJC, mean:** **D1:** 10.5 **D2:** 10.8 **D3:** 10.2 **D4:** 7.7 **DMARD use, %:** **D1:** 51.6 **D2:** 89.6 **D3:** 71.4 **D4:** 0 **Glucocorticoids use, %:** **D1:** 87.4 **D2:** 85.2 **D3:** 87 **D4:** 77.2 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR	See AEs	**Overall:** **D1:** 22.6 per 100 PY **D2:** 28.3 per 100 PY **D3:** 17.5 per 100 PY (95% CI,8.8-31.2) **D4:** 6.8 per 100 PY **SAEs:** **D1:** 6.4 per 100 PY **D2:** 6.2 per 100 PY **D3:** 3.2 per 100 PY (95% CI,0.4-11.5) **D4:** 2.3 per 100 PY **Infections:** **D1:** 15 **D2:** 21 **D4:** 6 **Serious Infections:** **D1:** 6.4 per 100 PY **D2:** 6.2 per 100 PY Drug 3**D4:** 2.3 per 100 PY **URTI:** **D1:** 7.0 **D2:** 11.4 **D3:** 1.8	**Overall Attrition Rate, %:** 11.1 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2005 (continued)			**Baseline DAS, mean:** **D1:** 6.1 **D2:** 6.0 **D3:** 6.1 **D4:** 5.4 **MTX use:** **D1:** 33 **D2:** 64.5 **D3:** 61.4 **D4:** 20.1			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Maini et al. 2004 **Country, Setting:** Multinational Multicenter **Funding:** Centocor **Research Objective:** Efficacy and safety of repeated administration of infliximab plus MTX over a 2-yr period in pts with RA **Study Design:** RCT plus extension **Overall N:** 428 (259 in extension) **Study Duration:** 54 wks plus additional yr of follow-up	**Inclusion Criteria:** • Age 18-75 • Active RA despite MTX **Exclusion Criteria:** • NR	**Interventions, dose:** **D1:** INF **D2:** Placebo **Mean age, yrs:** **Overall: 54** **Sex, % female:** Overall: 78 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** **TJC, mean:** **Overall: 31** **SJC, mean:** **Overall: 20** **DMARD use, %: NR** **Corticosteroid use, %: NR** **MTX naïve, %:** NR **DMARD Txt resistant, %:** NR **Patients with Early RA (≤ 3 yrs):** NR	The incidence of serious adverse events remained constant over time	• Serious adverse events were reported by similar proportions of pts who received MTX only (33%) and infliximab plus MTX (29%) • Number of observed cancer cases vs. number expected Placebo 0 vs. 1.02 INF 5 vs. 5.15	**Overall Attrition Rate, %:** • At 52 wks 27% • At 2 yrs 17% of those that continued into extension **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al, 2001 **Country, Setting:** US, NA Medwatch, AERS **Funding:** NR **Research Objective:** To review occurrence of neurologic events suggestive of demylenation during anti TNF alpha therapy for inflammatory arthritides **Study Design:** Database analysis; AERS **Overall N:** 20 cases **Study Duration:** 4 mos	**Inclusion Criteria:** • Pts with refractory RA who developed confusion and difficulty walking • Other meds allowed: MTX, prednisone, amlodipine, estradiol, zolpidem, dexamethasone, a;prasolam, hydrocodone, naproxen sodium, acyclovir, metronidazole, ceftriaxone, ranitidine, atenolol, fluoxetine, piroxicam **Exclusion Criteria:** NA	**Interventions, dose:** NR **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR NR	In addition to 1 case reported of suspected demyelination, 17 cases of demyelination after ETA and 2 cases after INF txt were detected in MedWatch	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al., 2004 **Country, Setting:** Multinational, population-based **Funding:** NR **Research Objective:** To summarize all cases of TB following use of ETA reported to AERS from November 1998 through March 2002 **Study Design:** Database analysis; AERS **Overall N:** 25 cases **Study Duration:** NA	**Inclusion Criteria:** • All pts receiving ETA and reported to have active TB **Exclusion Criteria:** NR	**Interventions, dose:** **D1: ETA** **N:** **D1:** 25 cases **Mean age at diagnosis, yrs:** **D1:** 59 **Sex, % female:** **D1:** 72 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• As of April 2002, a total of 25 reports of TB associated with ETA therapy reported to FDA from 11/1998 through 3/2002 • 17 cases (68%) were reported from US, 7 (28%) from Europe, and 1 (4%) from India • 46% of 24 pts with a reported clinical manifestation had pulmonary TB • 2 deaths occurred among 25 pts • 17 US cases of TB have been reported to the FDA • According to ETA manufacturer, 113,238 pts treated with ETA in US between 11/1998 and 5/2002, with estimated 172,212 PY of exposure; thus reporting rate of TB among pts in US receiving ETA is ~10 cases / 100,000 PY of exposure	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Moreland et al., 2006 **Country, Setting:** Multinational, pooled retrospective analysis **Funding:** NR **Research Objective:** To evaluate safety and efficacy of long-term etanercept treatment in pts with DMARD refractory RA **Study Design:** RCT **Overall N:** 714 safety and 581 efficacy **Study Duration:** Up to 7 yrs	**Inclusion Criteria:** • Adult pts with DMARD-refractory RA involved in included Initial clinical trials and extension (7 trials, 3 of placebo-controlled, randomized, double-blind phase 2 or 3 trials; 2 were phase 1 randomized dose-finding trials, and 2 were open-label) **Exclusion Criteria:** NR	**Interventions:** **D1:** All pts **D2:** Patients in extension **N:** **D1:** 714 **D2:** 581 **Mean age yrs:** **D1:** 53 **D2:** 52 **Sex, % female:** **D1:** 79 **D2:** 80 **Race, % white:** **D1:** 90 **D2:** 90	**Mean disease duration, yrs:** **D1:** 12 **D2: 12** **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 65 **D2: 65** **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Overall rate of SAEs was 14.8/100 patient-yrs compared to initial trial rates 8 pts out of 152 reported SAE in placebo group (20.0 events/100 PY; 40 PY), and 17 pts out of 349 reported SAE in etanercept group (15.0 events/100 patient yrs; 117 PY). Incidence rates stayed the same over time • Serious adverse events overall rate = 14.8 events/100 PY • Serious infections overall rate = 4.2 events/100 PY); cancer (overall rate = 1.0 events/100 PY); deaths (overall rate = 0.7 events/100 PY) • Overall 13.7% withdrew because of AEs	See health outcomes	**Overall Attrition Rate, %:** 52% **ITT Analysis:** Not applicable **Quality Rating:** Fair for AEs

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study **Country, Setting:** Finland, NR **Funding:** Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital **Research Objective:** Efficacy and tolerability of combo of DMARDs vs. a single DMARD **Study Design:** RCT **Overall N:** 199 randomized, 187 completed 2 yrs, 160 at 5 yrs **Study Duration:** 24 mos (5 yr followup)	**Inclusion Criteria:** • Age: 18 to 65 • Diagnosed with RA according to ACR criteria: active disease, 1987 criteria • Duration of condition: < 2 yrs **Exclusion Criteria:** • Previous use of DMARDs • Underwent glucocorticoid glucocorticoid therapy within the previous • 2 weeks • serious comorbidity • suspected inabilty to • comply with the protocol • hypersensitivity to any study medication • history of cancer • pregnant women • women of childbearing age who were not using reliable methods of contraception	**Interventions, dose:** **D1:** Combo: MTX + HCQ + SSZ + PNL **D2:** Single DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 months **N:** **D1:** 97 **D2:** 98 **Mean age, yrs:** **D1:** 45 **D2:** 46 **Sex, % female:** **D1:** 58 **D2:** 66 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.3 mos **D2:** 8.6 mos **TJC, mean:** **D1:** 18 **D2:** 20 **SJC, mean:** **D1:** 14 **D2:** 14 **DMARD use, %:** NR **Corticosteroid use, %** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Larsen Score:** **D1:** 0 **D2:** 2	**At 2 years** **Eroded joints, number:** **D1:** 2 **D2:** 3 (*P* = 0.006) btw groups Progression of radiological joint damage lower in combination versus monotherapy **Larsen Erosion Score improvement:** **D1:** 2 **D2:** 10 (*P* = 0.002) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **Clinical remission, %:** **D1:** 37.9 **D2:** 18.4 (*P* = 0.011) **ACR50, %:** **D1:** 71 **D2:** 58 (*P* = 0.058) Median work disability per pt-observation yr, days: **D1:** 12.4 **D2:** 32.2 (*P* = 0.008) **At 5 years** **Eroded joints, number:** **D1:** 3 **D2:** 6	**Overall:** **D1:** 70 **D2:** 71 **SAEs:** **D1:** 3 **D2:** 5 **Cardiovascular Events:** **D1:** 1 MI **D2:** 2 MIs **Malignancies:** 1 prostate cancer; 1 multiple myeloma **URTI:** 1 pneumonia	**Overall Attrition Rate, %:** 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999; Korpela, 2004; Puolakka, 2004 FIN-RACo Study (continued)				**Larsen Erosion Score:** **D1:** 11 **D2:** 24 (*P* = 0.001) **Median increase in Larsen Score:** **D1:** 1.5 **D2:** 2.0 (*P* < 0.001) **5 year Remiission** D1: 28 D2: 22 (*P* = NS) **Increase in Larsen score** D1: lower than (*P* =0.004)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Nuki et al. 2002 **Country, Setting:** Multinational multicenter **Funding:** Amgen **Research Objective:** Long-term efficacy of anakinra, in pts with RA **Study Design:** RCT plus extension **Overall N:** 472 (309 enrolled in 54 wk extension) **Study Duration:** 76 wks	**Inclusion Criteria:** • ACR criteria • Disease duration of ≥ 12 mos < 8.5 yrs **Exclusion Criteria:** NR is this article	**Interventions, dose:** **D1:** Anakinra **D2:** Placebo **N:** **D1:** 351 **D2:** 121 **Mean age, yrs:** **D1:** 53.4 **D2:** 52.2 **Sex, % female:** **D1:** 76.6 **D2: 70.2** **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 4.1 **D2:** 3.7 **TJC, mean:** **D1:** 34.8 **D2:** 32.8 **SJC, mean:** **D1:** 26.3 **D2:** 25.6 **DMARD use, %:** **D1:** 73.5 **D2:** 80.0 **Corticosteroid use, %** **D1:** 43.6 **D2:** 39.7 **MTX naïve, %:** NR **DMARD Txt resistant, %:** NR **Patients with Early RA (≤ 3 yrs):** NR	See AEs	Number of occurrences per subject-yr of exposure n for safety = **D1:** 427 **D2:** 121 **ISRs:** **D1:** 2.00 **D2: 0.82** Frequency of injection site reactions (ISRs) was 0.82 per patient-yr of exposure in placebo group (first 24 wks) and 1.01, 2.43, and 3.73 for 30-mg, 75-mg, and 150-mg doses over 72 wks	**Overall Attrition Rate, %:** **At 24 wks 27%** At 76 wks 32% of those that continued into extension **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al 2006 **Country, Setting:** US, multicenter **Funding:** NR **Research Objective:** Determine safety and efficacy of ETA in combination with SSZ, hydroxychloro-quine, IM Gold over 48 wks **Study Design:** Observational **Overall N:** 119 **Study Duration:** 48 wks	**Inclusion Criteria:** • Age: 19-75 • Diagnosed according to ACR criteria; stable SSZ or HCQ doses; 10mg or less/d steroids > 4wks • Active disease with 6 or more swollen and tender joints **Exclusion Criteria:** • Pregnant or lactating • ETA • Biologics in past 4 wks • Impaired renal or hepatic system • Antibody to TNFalpha • Anti C**D4** antibody • Diphterial interleukin 2 fusion protein • Active or chronic infections	**Interventions, dose:** **D1:** ETA (25mg sc twice weekly) + SSZ **D2:** ETA (25mg sc twice weekly) + HCQ **D3:** (Gold + ETA) **N:** **D1:** 50 **D2:** 50 **D3:** 19 **Mean age, yrs:** **D1:** 47 **D2:** 49.7 **Sex, % female:** **D1:** 78 **D2:** 76 **Race, % white:** **D1:** 88 **D2:** 92	**Mean disease duration, yrs:** **D1:** 8.1 **D2:** 8.7 **TJC, mean:** **D1:** 16.5 **D2:** 16.4 **SJC, mean:** **D1:** 17.7 **D2:** 17.1 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 58 **D2:** 68 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR HAQ: **D1:** 1.32 **D2:** 1.33	• Pts in each ETA combination showed significant improvement at 24 and 48 wks • No significant differences for ACR20/50 BETWEEN combination groups at 24 or 48 wks (NR). At 24 and 48 wks, ETA/SSZ combo showed highest ACR70 response (NR) • At 24 wks change in HAQ SSZ -0.56+/-0.77 HCQ -0.71+/-0.65 *P* = NR	NR	**Overall Attrition Rate, %:** 30% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Saag et al., 1994 **Country, Setting:** US, multicenter **Funding:** General Clinical Research Program, NIH and Halifax Clinical Research Center **Research Objective:** To determine whether low dose steroids in txt of RA independently cause an increased incidence of steroid-associated SAEs **Study Design:** Observational **Overall N:** 224 **Study Duration:** At least one yr (4.9 +/-3.9 yrs of txt).	**Inclusion Criteria:** • Age > 16 • Diagnosed according to ACR criteria • On low-dose steroids ≥ 1 yr; matched for age, sex, race, and duration of disease prior to study inception; allowed occasional intraarticular or parenteral steroids or oral steroid pulses to certain defined limits. • SAARDs were allowed **Exclusion Criteria:** • CXT, chlorambucil, nitrogen mustard, or experimental antirheumatic drugs • Impaired renal or hepatic system	**Interventions, dose:** **D1:** Treated (with low dose long-term corticosteroids) **D2:** Untreated (with low dose long-term corticosteroids) Prednisone: corticosteroids, less than or equal to 15mg/d of PRE (or equivalent dose of an alternative steroid) **N:** **D1:** 112 **D2:** 112 **Mean age, yrs:** **D1:** 51.8 **D2:** 51.7 **Sex, % female:** **D1:** 75 **D2:** 75 **Race, % white:** **D1:** 98.2 **D2:** 98.2	**Mean disease duration, yrs:** **D1:** 4.9 +/-6.3 **D2:** 4.9 +/-6.7 **TJC, mean:** NR **SJC, mean:** NR **Average no of SAARDs:** **D1:** 0.47 +/-0.82 **D2:** 0.13 +/-0.37 **Corticosteroid use, %:** **D1:** 100 **D2:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF:** **D1:** 77.7 **D2:** 58.0 **ESR:** **D1:** 50 +/-29.7 **D2:** 36.4 +/-30.5	• n for Treated and Untreated groups respectively: Fracture 21 and 8; GI bleed or ulcer 11 and 4; cataracts 17 and 5; diabetic complications 8 and 3; herpes zoster 8 and 1; glaucoma 1 and 1; death 2 and 0. • OR of 32.3 (95% CI,4.6, 220) (*P* = 0.0004) for pts treated with > 10 up to 15mg/d PRE equivalent; OR of 4.5 (95% CI,2.1, 9.6) (*P* = 0.0001) for pts treated with 5-10mg/d; Prednisone dose <5mg/d did not show a significant increase in risk of having an AE compared to the untreated group; • *Although PRE average dose and cumulative dose had small but significant emsitmated relative risks (OR 1.21, 95%CI,1.0-1.5 for both), PRE use (yes/no) was most highly linked to infection (OR 8.0, 95% CI,1.0-64.0, *P* < 0.05) • Fracture (OR 3.9, 95% CI,0.8-18.1, *P* < 0.09) • First GI event: OR 3.3 (95% CI,0.9-12.1, *P* < 0.07)	**Overall:** **D1:** n =92 AEs **D2:** n =31 **Serious Infections:** **D1:** n =14 **D2:** n =4 **Cardiovascular Events:** **D1:** n =10 (4 myocardial infarctions, 6 strokes) **D2:** n =5 (4 myocardial infarction, 1 stroke)	**Overall Attrition Rate, %:** NA **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Saag, et al., 1994	• Concurrent or alternative rheumatic disorder • Bedridden status • Referral 2nd to a steroid complication		**Extra-articular disease** **D1:** 16.1% **D2:** 6.3%			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Salliot et al., 2006 **Country, Setting:** France, tertiary care **Funding:** NR **Research Objective:** To evaluate rate of infections in rheumatic pts treated with TNF-alpha blockers in daily practice and to determine potential risk factors of infections **Study Design:** Case series **Overall N:** 709 w/ follow-up at least once and 623 w/ with a control period **Study Duration:** NR	**Inclusion Criteria:** • Pts receiving a TNF-alpha blocker and with a follow-up • Those with control period before txt initiation **Exclusion Criteria:** NA	**Interventions, dose:** **D1:** Follow up **D2:** Follow up and control **N:** **D1:** 709 **D2:** 623 **Mean age, yrs:** **D1:** 45.9 **D2:** 46.5 **Sex, % female:** **D1:** 60.4 **D2:** 60.4 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11.8 **D2:** 12.1 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 58.5 **D2:** 58.3 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 43.7 **D2:** 43.6	• 34.5% experienced infection during course of txt; Incidence rate: 48.2 per 100 PY • 6.2 percent experienced a serious infection; incidence rate: 10.4 per 100 PY • Infections by txt: • Any: INF 69.8 ETA 44.1 Adalimumab 37.3 per 100 PY • Serious: INF 10.2 ETA 12.3 Adalimumab 5.3 per 100 PY	**Infections:** **D1:** 50.5 **D2:** 34.2 **D3:** 15.3 **URTI:** **D1:** 13.4 **D2:** 9.4 **D3:** 9.9 **UTI:** **D1:** 5.1 **D2:** 1.1 **D3:** 1.6	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schaible et al., 2000 **Country, Setting:** US; safety database of efficacy trials **Funding:** Centocor **Research Objective:** Long term safety of infliximab **Study Design:** Observational **Overall N:** 963 **Study Duration:** Up to 3 yrs	**Inclusion Criteria:** 12 clinical trials **Exclusion Criteria:** NR	**Interventions:** Infliximab N:963 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Acute infusion reactions (headache, fever, chills, urticaria, chest pain: infliximab 17% versus placebo 7%; *P* = NR • 0.5% of infliximab pts had severe infusion reactions • Less than 2% discontinued treatment because of infusion reactions **Infections:** • Infliximab 26% over 27 wks of follow-up versus placebo 16% over 20 wks of follow-up) • Incidence of serious infections per patient-yr infliximab 0.064 versus placebo 0.114	See outcomes	**Overall Attrition Rate, %:** **ITT Analysis:** Not applicable **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schiff et al., 2006 **Country, Setting:** Mulitnational, multicenter **Funding:** Abbott Labs **Research Objective:** To assess safety of adalimumab in global clinical trials and postmarketing surveillance among pts with rheumatoid arthritis **Study Design:** Retrospective cohort study; postmarketing surveillance **Overall N:** 10,050 (12506 PY) **Study Duration:** Varied	**Inclusion Criteria:** • Pts from RCTs, open label extensions, and two phase IIIb open label trials were and post-marketing spontaneous reports of adverse events in US **Exclusion Criteria:** NA	**Interventions, dose:** NR **N:** 10,050 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**Rates per 100 PY:** • TB: 0.27 • Histoplasmosis: 0.03 • Demyelinating diseases: 0.08 • Lymphoma: 0.12 • SLE/lupus-like syndrome: 0.10 • Congestive heart failure: 0.28	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Setoguchi et al., 2006 **Country, Setting:** US and Canada, 3 databases **Funding:** Novartis and NIH **Research Objective:** To estimate association between treatment with biologic DMARDs and development of cancer in pts with RA **Study Design:** Observational **Overall N:** 7,830 **Study Duration:** 1994 to 2004 in US 1996 to 2003 in Canada	**Inclusion Criteria:** • Age ≥ 65 • 1 claim with a diagnosis of RA and who were dispensed at least 1 prescription of any DMARD or corticosteroid after first RA diagnosis **Exclusion Criteria:** • Diagnosis of any cancer (except nonmelanoma skin cancer) or human immuno-deficiency virus infection	**Interventions:** **D1:** Biologic DMARD **D2: MTX** **N:** **D1:** 1152 **D2:** 7306 **Mean age (yrs):** **D1:** 71.4 **D2:** 73.4 **Sex, % female:** **D1:** 75.3 **D2:** 73.1 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 51.3 **D2: 41.5** **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• RA pts vs. overall population • Non-Hodgkin's lymphoma-PY 33,335.0 Observed 58 Expected 26.0 SIR 2.2 95% CI,1.71-2.87 • Multiple myeloma-PY yrs 33,410.0 Observed 19 Expected 9.3 SIR 2.0 95% CI,1.26-3.12 • Melanoma-PY 33,377.7 Observed 29 Expected 12.8 SIR 2.3 95% CI,1.55-3.22 • Colorectal cancer-PY 32,844.9 Observed 118 Expected 97.3 SIR 1.2 95% CI,1.01-1.45 • Lung cancer-PY 31,532.8 Observed 169 Expected 95.6 SIR 1.8 95% CI,1.52-2.05 • Urinary tract/bladder cancer-PY 33,367.0 Observed 54 Expected 26.4 SIR 2.0 95% CI,1.55-2.65 • Biologics vs. MTX • Unadjusted Lymphoproliferative HR 1.20 (95% CI,0.57-2.51) Hematologic HR 1.45 (95% CI,0.76-2.74) Solid HR 0.91 (95% CI,0.66-1.25)Overall HR 1.00 (95% CI,0.75-1.33)	See health outcomes	**Overall Attrition Rate, %:** NA **ITT Analysis:** Not applicable Observational study **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Shin et al 2006 **Country, Setting:** US **Funding:** NR **Research Objective:** Review occurence and clinical features of Guillan Barre syndrome and Miller Fisher Syndrome during TNF alpha antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 16 cases **Study Duration:** NR	**Inclusion Criteria:** • TNF alpha antagonist therapy in AERS database **Exclusion Criteria:** NA	**Interventions, dose:** NR ETA INF **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Guillain-Barre was temporally associated with INF in 10 pts, ETA in 5 pts. This compares to an annual incidence of Guillain Barre Syndrome of 1-3/100,000 population	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Slifman, 2003 **Country, Setting:** Multinational, multicenter **Funding:** NR **Research Objective:** To evaluate postlicensure cases of opportunistic infection, including Listeria monocytogenes, in pts treated with TNFs **Study Design:** Database analysis; AERS **Overall N:** 15 cases **Study Duration:** Varied	**Inclusion Criteria:** • Age: 17 to 80 • Pts with Listeria monocytogenes treated with ETA or INF for RA or Crohn's disease • Concurrent use of immuno-suppressant drugs allowed **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** INF or ETA ETA: varied INF: varied **N:** **D1:** 15 **Median age, yrs:** **D1:** 69.5 **Sex, % female:** **D1:** 53.3 **Race, % white:** **D1:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RA:** **D1:** 64%	• For all ages and indications, the estimated rate of cases (reporting rates) of listeriosis reported to FDA within first yr of starting txt with inf was 43 cases per 1,000,000 persons (8/186,500) • RA pts treated with inf (US cases only), estimated rate of cases of listeriosis reported to FDA was 61 cases per 1,000,000 persons (5/82,000) • In 2000, annual incidence of listeriosis in US for all ages was estimated to be 3 cases per 1,000,000 • 6 deaths reported (5 INF, 1 ETA) • Among reports from US only, this series included 8 cases of Listeria infection, all of which were associated with INF txt	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Smolen et al., 1999; Larsen 2001; Scott 2001 **Country, Setting:** Multinational, multicenter **Funding:** Hoechst Marion Roussel **Research Objective:** Efficacy and safety of novel DMARD leflunomide was compared to placebo and sulfasalazine **Study Design:** RCT **Overall N:** 266 (358 including placebo arm) **Study Duration:** 24 wks (12 and 24 month followup)	**Inclusion Criteria:** • Age: ≥ 18 • Active RA defined by: ≥ 6 tender and swollen joints, based on a 28-joint count, physician and pt global assessments of RA activity of "fair, poor, or very poor", CRP > 2.0 mg/dL or ESR > 28 mm/h • Functional class I – III • Other DMARDs discontinued ≥ 4 wks • Stable doses of NSAIDS permitted -acetylsalicylic acid, oral steroids (prednisolone ≤ 10 mg/day), and up to 3 intra-articular steroid injections, not exceeding 60 mg triamcinolone • Intra-articular steroid injections not permitted during first 6 mos **Exclusion Criteria:** • Pregnant or lactating	**Interventions:** **D1:** LEF **D2:** SSZ **N:** **D1:** 133 **D2:** 133 **Mean age, yrs:** **D1:** 58.3 **D2:** 58.9 **Sex, % female:** **D1:** 75.9 **D2:** 69.2 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.6 **D2:** 7.4 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 60.2 **D2:** 48.9 **Corticosteroid use, %:** **D1:** 28.6 **D2:** 27.8 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **RF positive:** **D1:** 79% **D2:** 80%	**At 24 weeks** **ACR 20, %:** **D1:** 55 **D2:** 56 **ACR 50, %:** **D1:** 33 **D2:** 30 **Improving HAQ scores, change (%):** **D1:** -0.50 (45) **D2:** -0.29 (29) (*P* = 0.0086) **Change in Sharp; number, change (SD):** **D1:** 87 1.23 (2.85) **D2:** 84 2.32 (10.11) **Larsen score change:** **D1:** 0.01 **D2:** 0.01 (*P* = NS) **At 1 year** **Change in Sharp; number, change (SD):** **D1:** 60 0.97 (6.11) **D2:** 53 1.38 (2.88) **Larsen score change:** **D1:** 0.02 **D2:** 0.02 (*P* = NS) **At 2 years** **Larsen score change:** **D1:** -0.07 **D2:** -0.02 (*P* = NS) Similar ACR20 response rates D1: 48; D2: 44; *P*=NR	**SAEs:** **D1:** 5 **D2:** 7 **Headache:** **D1:** 7 **D2:** 11 **Nausea:** **D1:** 10 **D2:** 17 **URTI:** **D1:** 14 **D2:** 15 **Diarrhea:** **D1:** 17 **D2: 9** **Alopecia:** **D1:** 8 **D2: 5** **Rash:** **D1:** 10 **D2: 9** **Withdrawal due to AEs:** **D1:** 14 **D2: 19** 2 cases of reversible agranulocytosis in SSZ	**Overall Attrition Rate, %:** 33% at 24 wks **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial **Country, Setting:** Multinational, unversity hospitals **Funding:** Centocor **Research Objective:** To compare benefits of initiating txt with MTX and anti-TNFá with those of MTX txt alone in pts with RA of < 3 yrs duration **Study Design:** RCT **Overall N:** 1049 **Study Duration:** 54 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3 mos and < 3 yrs • > 10 swollen joints, and > 12 tender joints • 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS • 20 mg MTX (required) **Exclusion Criteria:** • Prior txt with: MTX, received other DMARDs within 4 wks of entry • Used ETA, INF, ADA or other anti-TNF-á agent • History of TB; HIV, hepatitis B or C virus, CHF, or lymphoma or other malignancy	**Interventions, dose:** **D1:** MTX (20 mg/wk) + placebo **D2:** MTX + INF (3 mg/kg/wk) **D3:** MTX + INF (6 mg/kg/wk) **N:** **D1:** 282 **D2:** 359 **D3:** 363 **Mean age, yrs:** **D1:** 50 **D2:** 51 **D3:** 50 **Sex, % female:** **D1:** 75 **D2:** 71 **D3:** 68 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 0.9 **D2:** 0.8 **D3:** 0.9 **TJC, mean:** **D1:** 34 **D2:** 32 **D3:** 33 **SJC, mean:** **D1:** 22 **D2:** 21 **D3:** 22 **DMARD use, %:** **D1:** 35 **D2:** 29 **D3:** 32 **Corticosteroid use, %** NR **MTX naive, %:** Overall: 100 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** Overall: 100 **Baseline DAS, mean:** NR **JSN:** **D1:** 3.0 **D2:** 2.9 **D3:** 2.9	**At weeks 30 to 54** **HAQ:** **D1:** 0.68 **D2:** 0.80 **D3:** 0.88; (**D2** vs. **D1**; *P* = 0.03) (**D3** vs. **D1**; *P* < 0.001) **At 54 weeks** **HAQ > 0.22, %:** **D1:** 65.2 **D2:** 76.0 **D3:** 75.5 (**D2** vs. **D1**; *P* = 0.003) (**D3** vs. **D1**; *P* < 0.004) **ACR20, %:** **D1:** 53.6 **D2:** 62.4 **D3:** 66.2 (**D2** vs. **D1**; *P* = 0.028) (**D3** vs. **D1**; *P* < 0.001) **ACR50, %:** **D1:** 32.1 **D2:** 45.6 **D3:** 50.4 (**D2** vs. **D1**; *P* = 0.001) (**D3** vs. **D1**; *P* < 0.001) **ACR70, %:** **D1:** 21.2 **D2:** 32.5 **D3:** 37.2 (**D2** vs. **D1**; *P* = 0.002) (**D3** vs. **D1**; *P* < 0.001)	**SAEs:** **D1:** 11 **D2:** 14 **D3:** 14 **Serious Infections:** **D1:** 2.1 **D2:** 5.6 **D3:** 5.0 **Infusion or injection reaction:** **D1:** 7 **D2:** 21 **D3:** 15 **TB:** **D1:** 0 **D2:** 0.8 **D3:** 0.3 **Nausea:** **D1:** 18 **D2:** 20 **D3:** 17 **URTI:** **D1:** 21 **D2:** 25 **D3:** 28	**Overall Attrition Rate, %:** 14.9 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)	within past 5 yrs (excluding excised skin cancers)		**HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5	**ACR-N, %:** **D1:** 26.4 **D2:** 38.9 **D3:** 46.7 (*P* < 0.001) **Modified Sharp:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 (*P* < 0.001) **Increase in radiographic score, %:** INF: 39 vs. MTX 61 (*P* < 0.001) **Employability:** INF+MTX (OR 2.4, *P* < 0.001) MTX (*P* = 0.56) Combo has higher probability of improvement than MTX alone **Net increase in employability:** MTX+INF: 8% MTX-only: 2% **Employability status changed from employable to unemployable, %:** INF: 8 MTX-only: 14 (*P* = 0.05) **SF-36 Physical component summary scores** **D1:** 11.7 **D2:** 13.2 **D3:** 10.1 D3 vs. D1, *P* =0.10 D3 vs. D2; *P* =0.003		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: St. Clair, 2004; Smolen, 2006 ASPIRE Trial (continued)				**Modified Sharp/van der Heijde Score change:** **D1:** 3.7 **D2:** 0.4 **D3:** 0.5 *P* < 0.001 **Erosion Score change:** **D1:** 3.0 **D2:** 0.3 **D3:** 0.1 *P* < 0.001 **JSN Score change:** **D1:** 0.6 **D2:** 0.1 **D3:** 0.2 *P* < 0.001		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 **Country, Setting:** US and Canada, multicenter (47 university & private rheumatology practices) **Funding:** Hoescht Marion Roussel **Research Objective:** Efficacy and safety of LEF with placebo and MTX in active RA **Study Design:** RCT **Overall N:** 482 (active arms-364) **Study Duration:** 12 mos (w/ 1 year followup)	**Inclusion Criteria:** • Age: 18 or older • Diagnosed according to ACR criteria; DMARDs discontinued at least 30 days prior • Duration of condition at least 6 mos • 10 mg stable prednisone (or equivalent) • NSAIDs if dosages stable at least 30 days prior to enrollment **Exclusion Criteria:** • Pregnant or lactating • Prior treatment with: MTX • Inflammatory joint disease not caused by RA, • History of clinically significant drug or alcohol abuse, or admitted to consumption of more than 1 alcoholic drink per day	**Interventions:** **D1:** LEF (20 mg/week) **D2:** MTX (7.5 to 15 mg/week) **N:** **D1:** 182 **D2:** 182 **Mean age, yrs:** **D1:** 54.1 **D2:** 53.3 **Sex, % female:** **D1:** 72.5 **D2:** 75.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.0 **D2:** 6.5 **TJC, mean:** **D1:** 15.5 **D2:** 15.8 **SJC, mean:** **D1:** 13.7 **D2:** 13.0 **DMARD use, %:** **D1:** 55.5 **D2:** 56.0 **Corticosteroid use, %:** **D1:** 53.8 **D2:** 52.7 **MTX naive, %:** Both groups 100 **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **NR** **RF positive:** **D1:** 64.8 **D2:** 59.4 **MHAQ:** **D1:** 0.8 **D2:** 0.8	**At 12 mos** **ACR 20, %** **D1:** 52 **D2:** 46 **ACR 50, %** **D1:** 34 **D2:** 23 **ACR 70, %** **D1:** 20 **D2:** 9 **MHAQ mean change** **D1:** -0.3 **D2:** -0.2 **Sharp score change** **D1:** 0.53 (n:131) **D2:** 0.88 (n= 138) (*P* = 0.05) **Mean change HAQ-DI** **D1:** -0.45 (n= 164) **D2:** -0,26 (n= 168) (*P* ≤ 0.01) **Mean change SF-36 physical component** **D1:** 7.6 (n= 157) **D2:** 4.6 (n=162) **Work productivity mean change** **D1:** 9.8 (n= 138) **D2:** 7.5 (n= 148) **Discontinuation rate, %:** **D1**: 22 **D2**: 10.4 (*P* = NR)	**SAEs:** **D1:** 1.1 **D2:** 2.7 **Infections:** **D1:** 56.6 **D2:** 59.9 **Abdominal Pain:** **D1:** 13.7 **D2:** 15.4 **Nausea:** **D1:** 20.9 **D2:** 19.2 **Back pain:** **D1:** 8 **D2:** 2 **Diarrhea:** **D1:** 36.8 **D2:** 21.6 **Oral Ulcers:** **D1:** 6.8 **D2:** 10.5 **GI Events:** **D1:** 5.5 **D2:** 1.7 **Elevated Transaminases:** **D1:** 7.1 **D2:** 4.4 **Adherence:** Non-adherence as the reason for reason for withdrawal **D1**: 1 **D2**: 1	**Overall Attrition Rate, %:** 51% at 1 year **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999; Cohen 2001; Strand, Tagwell 1999 (continued)				**At 2 yrs** **ACR 20, %** **D1:** 79 **D2:** 67 (*P* = 0.049) **ACR 50, %** **D1:** 34 **D2:** 28 **ACR70, %** **D1:** 17 **D2:** 12 **Sharp score change** **D1:** 1.6 (n= 71) **D2:** 1.2 (n= 66) **HAQ DI change** **D1:** -0.6 (n= 97) **D2:** 0.37 (n=101) **Discontinuation rate, %:** **D1**: 27 **D2**: 17	**At 24 months** **SAEs, %:** **D1:** 18.9 **D2:** 18.9	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al., 2004 **Country, Setting:** US, 2 large databases **Funding:** Aventis **Research Objective:** Assess risk of hepatic events associated with the use of LEF and other DMARDS compared to MTX **Study Design:** Observational **Overall N:** 41,885 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Age: 18 and older • Previous use of DMARDs: after 9/1/98 • ICD 9 code for RA **Exclusion Criteria:** •< 3 mos eligibility in health insurance plan •Pts with outcome 3 mos before cohort study	**Interventions, dose:** NR **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• When compared to MTX, No increased risk with LEF(rate ratio 0.9, 95% CI, 0.2-4.9), or with traditional DMARDS (RR 2.3; 95% CI, 0.8-6.5) • There is an increased risk with biologic DMARDS (RR =5.5; 95% CI, 1.2-24.6) • Rate of nonserious hepatic events was also increased with biologic DMARDS (RR 1.5; 95% CI, 1.0-2.3), but not LEF (RR =0.9; 95% CI, 0.7-1.3) and traditional DMARDS (RR 1.1; 95% CI, 0.8-1.4)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA: cohort **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al. 2006 **Country, Setting:** Canada, PharMetrics claims database **Funding:** Sanofi-Aventis; Canadian Institutes of Health Research **Research Objective:** To assess risk of ILD in pts with RA treated with LEF. **Study Design:** Observational **Overall N:** 62,734 **Study Duration:** Sept 1, 1998 through Dec 31, 2003	**Inclusion Criteria:** • Age: 18 or older • DMARD-treated cohort defined as all subjects who received at least 1 prescription for a DMARD on or after September 1, 1998, mo LEF was approved in US **Exclusion Criteria:** • No DMARD prescription • Subjects with outcome of interest during 1-yr period prior to cohort entry	**Interventions, dose:** **D1:** Cases of ILD **D2:** Controls **N:** **D1:** 74 **D2:** 7400 **Mean age, yrs:** **D1:** 62 **D2:** 61 **Sex, % female:** **D1:** 70 **D2:** 74 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Risk of ILD in pts treated with LEF compared with those not treated with LEF; adjusted OR 1.9, 95% CI,1.1-3.6 (all ORs reported here were adjusted for the concurrent use of the other DMARDs, the other anti-RA drugs, as well as sex and comorbid conditions) • Increase was less and was not significant with use of MTX (OR 1.4; 95% CI,0.8-2.3) • No increase in risk of ILD with LEF among pts who had no previous MTX use and no interstitial lung disease prior to cohort entry (37 cases and 4,259 controls); OR 1.2; 95% CI,0.4-3.1. This group did have an increased risk of ILD with MTX treatment (OR 3.1; 95% CI,1.5-6.4). Among those who had previously taken MTX or who had a previous diagnosis of ILD (37 cases and 3,141 controls), the risk of ILD was elevated with LEF treatment (OR 2.6; 95% CI,1.2-5.6) but was decreased with MTX treatment (OR 0.4; 95% CI,0.2-0.9)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA: nested case control design **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Svennsson et al., 2003 **Country, Setting:** Sweden, multicenter (5 rheumatologic units covering both urban and rural districts) **Funding:** Swedish Rheumatism Association and Vardal Foundation **Research Objective:** To study and compare outcomes of 2 different DMARD/corticosteroid options in txt of early RA in clinical practice **Study Design:** RCT **Overall N:** 245 **Study Duration:** 2 yrs	**Inclusion Criteria:** • Diagnosed according 1987 revised ACR • Duration of condition: less than 2 yrs • Considered to be in need of Css or DMARDS by treating physician's judgment • NSAIDS and analgesics allowed **Exclusion Criteria:** • Prior txt with: DMARDS or Cxs • Per authors--regarded as not suitable for various medical or non-medical reasons	**Interventions:** **D1:** PNL + MTX **D2:** SSZ + PNL at lowest possible dose **Overall:** PNL: 7.5 to 15 mg daily for 1 to 3 mos. with subsequent reduction to lowest possible dose MTX: 5 to 15 mg per wk SSZ: 2 to 3 grams daily **N:** **D1:** 113 **D2:** 108 **Mean age (yrs):** **D1:** median 54 **D2:** median 52 **Sex, % female:** **D1:** 59 **D2:** 67 **Race, % white:** **NR Mean disease duration, yrs:** **D1:** 6 mos. **D2:** 7 mos	**TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 0 **D2:** 0 **Corticosteroid use, %:** **D1:** 0 **D2:** 0 **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **DAS28 median:** **D1:** 5 **D2:** 4.9 **Larsen:** **D1:** 5 **D2:** 3 **HAQ:** **D1:** 0.9 **D2:** 0.9 **RF +:** **D1:** 71 **D2:** 39	No significant differences between txt groups for individual response, remission, function, or radiologic progression **Response (EULAR individual response criteria for good/moderate/no response, %)** **D1**: 30/40/30. **D2**: 33/30/37% (*P* = 0.319) **Remission, %** D1: 29 D2: 19 (*P* = 0.095) **Mean change in HAQ** **D1**: 0.35 **D2**: -0.38 (*P* = 0.752) **Mean change in Larsen score** 6.2 vs. 4.1 (*P* = 0.298) **Completers, %** **D1**: 81% **D2**: 53% Survival analysis between 2 groups (using withdrawals due to AEs or inefficacy as terminal event) showed a highly significant difference in survival times between 2 groups (*P* = 0.0005)	**Overall:** **D1:** 9.9 **D2:** 31.6	**Overall Attrition Rate, %:** 39.6 **ITT Analysis:** No another type of analysis was used (define): Although they state it was an ITT analysis, statistical analysis based on 221 of the 245 pts with available data for clinical outcomes and for about 72% of the cases for Larsen score (based on available **Quality Rating:** Poor for efficacy, fair for adverse events

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: van Riel et al., 2006 **Country, Setting:** Multinational, multicenter **Funding:** Wyeth **Research Objective:** Evaluate efficacy and safety of ETA monotherapy vs. ETA + MTX in RA pts with inadequate response to MTX **Study Design:** RCT, open-label **Overall N:** 315 **Study Duration:** 16 wks	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed according to ACR criteria • Functional class of: I-III • Previous use of DMARDs • Inadequal control of RA symptoms on MTX ≥ 12.5 mg/wk for ≥3 mos **Exclusion Criteria:** • DMARDS other than MTX within 12 wks of screening; prednison ≥10 mg/d • Corticosteroid injections within 6 wks • 'Significant' concurrent medical illness	**Interventions, dose:** **D1:** ETA (25 mg s.c. twice wkly) **D2:** ETA (25 mg s.c. twice wkly) + MTX (≥12.5 mg/wk) **N:** **D1:** 159 **D2:** 155 **Mean age, yrs:** **D1:** 53 **D2:** 54 **Sex, % female:** **D1:** 79.2 **D2:** 76.8 **Race, % white:** **D1:** 99.4 **D2:** 98.7	**Mean disease duration, yrs:** **D1:** 10.0 **D2:** 9.8 **TJC, mean:** **D1:** 14.6 **D2:** 14.7 **SJC, mean:** **D1:** 11.2 **D2:** 11.9 **DMARD use, %:** NR **Corticosteroid use, %** **D1:** 49.1 **D2:** 55.5 **MTX naive, %:** Overall: 0 **Txt resistant, %:** Overall: 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.2 **D2:** 6.3 **HAQ:** **D1:** 1.6 **D2:** 1	**DAS28 improvement of > 1.2 units, %:** D1: 72.8 D2: 75.2 Difference -2.3 (95% CI, -13.1-8.2; *P* = 0.658) **EULAR response maintained, %:** **D1**: 80.0 **D2:** 82.4 (*P* = NR) **ACR 20, %:** **D1**: 71.0 **D2**: 67.1 Difference 3.9 (95% CI, -6.4-14,2; *P* = 0.46) **ACR 50, %:** **D1**: 41.9 **D2:** 40.1 Difference 1.8,(95% CI, -9.2-12.8 ; *P* = 0.75) **ACR 70, %:** **D1**: 17.4 **D2** : 18.4 Difference -1.0 (95% CI, -9.6-7.6; *P* = 0.82)	**Overall:** **D1:** 62.9 **D2:** 70.3 **SAEs:** **D1:** 5.0 **D2:** 4.5 **Infections:** **D1:** 24.5 **D2:** 32.3 **Serious Infections:** **D1:** 0.6 **D2:** 0.3 **Infusion or injection reaction:** **D1:** 6.3 **D2:** 6.5 **Dizziness:** **D1:** 0.6% **D2:** 0 **Headache:** **D1:** 8.8 **D2:** 6.5 **URTI:** **D1:** 8.2 **D2:** 12.9	**Overall Attrition Rate, %:** 17.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wallis et al., 2004 **Country, Setting:** Multinational, multicenter **Funding:** NR **Research Objective:** The relationship between the use of tumor necrosis factor antagonists and onset of granulomatous infection was examined **Study Design:** Database analysis;AERS **Overall N:** 649 cases **Study Duration:** various	**Inclusion Criteria:** • All pts treated with INF or ETA • Other meds allowed • Concurrent use of immuno-suppressant drugs **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** INF (various) **D2**: ETA (various) **N:** **D1:** 566 cases (>233,000 treated) **D2:** 83 cases (>113,000 treated) **Mean age, yrs:** **D1:** 60 **D2:** 58 **Sex, % female:** **D1:** 66 **D2:** 59 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 41 **D2:** 66 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 43 **D2:** 41	**Granulomatous infections, rate per 100,000** **D1**: 239 **D2**: 74 (*P* < .001) **D1** risk of granulomatous infection was 3.25-fold greater among pts than **D2**. **Tuberculosis infections, rate per 100,000** **D1**: 144 **D2**: 35 (*P* < .001)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wasserman et al., 2004 **Country, Setting:** Canada, Quaternary care center **Funding:** Schering-Plough **Research Objective:** Description of infusion-related reactions to INF (during or within 1 hour of infusion) in pts with active rheumatoid arthritis **Study Design:** Case series **Overall N:** 113 pts, 1,183 infusions **Study Duration:** Mean 60.6 wks	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed according to ACR; failed at least 3 DMARDs • Active disease; stable doses of corticosteroids (10 mg/d) and/or NSAIDs **Exclusion Criteria:** • Biologically-based therapies • Current signs and symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, GI, endocrine, pulmonary, cardiac, neurological, or cerebral disease • History of lymphopro-liferative disease • Any known malignant disease • Screened for TB	**Interventions, dose:** **D1:** INF INF: 3 mg/kg wks 0,2,6 then every 8, dose could be increased to 5 mg/kg at wk 14 based on clinical grounds **N:** **D1:** 113 pts; 1,183 infusions **Mean age, yrs:** **D1:** 45.7 **Sex, % female:** **D1:** 87 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 13.6 **TJC, mean:** **D1:** 21.3 **SJC, mean:** **D1:** 10.8 **DMARD use, %:** NR **PRE use, %:** **D1:** 59 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 100	• 104 infusion-related reactions out of 1183 infusions performed (8.8%) and 60 of 113 pts (53%) experienced at least one reaction during course of txt • Infusion related reactions; Allergic-45 (3.8%); Cardiopulmonary-35 (3.0%); Misc.-24 (2.0%) • Reactions following pretxt or not with diphenhydramine at infusions 3 and 4 • Pretreated 14.7% vs. Not pretreated 14.3%	**Overall:** **D1:** 8.8 **Headache:** **D1:** 9	**Overall Attrition Rate, %:** **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 **Country, Setting:** US, Rheumatology practices (509) **Funding:** Immunex Corporation **Research Objective:** To evaluate effectiveness of select biologics, MTX (MTX), and other DMARDs in management of adult RA in routine clinical practice **Study Design:** Prospective cohort study **Overall N:** 5,397 **Study Duration:** 12 mos	**Inclusion Criteria:** • Age: 18 or older • Diagnosed with RA according to ACR criteria: 1987 ACR • Pts requiring a change in RA txt **Exclusion Criteria:** • Pregnant or lactating • Active infection, • Concurrent enrollment in a clinical trial	**Interventions, dose:** **D1:** MTX (10 to 15 mg/wk) **D2:** ETA (50 mg/wk) **D3:** ETA (50 mg/wk) +MTX **D4:** INF (3.8 mg/8wks) **D5:** INF (3.8 mg/8wks) + MTX (15 mg/wk) **D6:** LEF (20 mg/d) **D7:** LEF (20 mg/d) +MTX (15 mg/wk) **D8:** MTX (15 mg/wk) +HCQ (400 mg/d) **D9:** MTX (15 mg/wk) +HCQ (400 mg/d) +SSZ (2000 mg/d) **N:** **D1:** 941 **D2:** 1251 **D3:** 1783 **D4:** 120 **D5:** 540 **D6:** 204 **D7:** 191 **D8:** 325 **D9:** 42 **Mean age, yrs:** **D1:** 56.8 **D2:** 53.2 **D3:** 52.6 **D4:** 60.2 **D5:** 58.5 **D6:** 57.7 **D7:** 55.5 **D8:** 53.8 **D9:** 47.8	**Mean disease duration, yrs:** **D1:** 3.5 **D2:** 9.2 **D3:** 7.7 **D4:** 10.6 **D5:** 9.5 **D6:** 10.1 **D7:** 7.4 **D8:** 4.6 **D9:** 7.2 **TJC, mean:** **D1:** 13 **D2:** 13.4 **D3:** 13.3 **D4:** 14.8 **D5:** 3.9 **D6:** 12.8 **D7:** 12.2 **D8:** 11.8 **D9:** 10.1 **SJC, mean:** **D1:** 11.3 **D2:** 11.1 **D3:** 11.5 **D4:** 13.9 **D5:** 12.0 **D6:** 11.8 **D7:** 11.4 **D8:** 9.2 **D9:** 10.2	**mACR20, %:** **D1:** 37 **D2:** 41 **D3:** 43 **D4**: 26 **D5:** 35 **Adjusting for baseline covariates** **D3:** vs. **D1**(OR 1.29, 95% CI, 1.09-1.52; *P* < 0.01) **D2** vs. **D1** (OR 1.23, 95% CI, 1.02-1.47; *P* < 0.05) **D1** vs. **D5** (OR 0.96 CI 0.76-1.21 p = 0.72) **D1** vs. **D4** (OR 0.66, 95% CI, 0.43-1.02; *P* = 0.06) **Mean change HAQ improvement, %** **D1:** 7 **D2:** 17 (*P* < 0.001) **D3:** 17 (*P* < 0.001) **mACR20 response** **D5** vs. **D1**: (OR 0.68, 95% CI, 0.48-0.96; *P* < 0.05) **D6** vs. **D1** (OR 0.76, 95% CI, 0.54-1.06; *P* = 0.11) **D8** vs, **D1**: (OR 0.94, 95% CI, 0.72-1.23; *P* = 0.64) **D9** vs. **D1**: (OR 0.57, 95% CI, 0.27-1.18; *P* = 0.13) **SJC % improvement** **D1** vs **D1**: 34 (N/A) **D2** vs. **D1**: 53 (*P* < 0.0001) **D4** vs. **D1**: 29 (*P* = NS) **D3** vs. **D1**: 55 (*P* < 0.0001) **D5** vs **D1**:48 (*P* < 0.01)	NR	**Overall Attrition Rate, %:** 33.2 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)		**Sex (% female** **D1:** 75 **D2:** 75 **D3:** 79 **D4:** 71 **D5:** 77 **D6:** 76 **D7:** 78 **D8:** 80 **D9:** 79 **Race, % white:** **D1:** 77 **D2:** 81 **D3:** 81 **D4:** 78 **D5:** 81 **D6:** 78 **D7:** 82 **D8:** 83 **D9:** 79	**DMARD use, %:** **D1:** 25 **D2:** 75 **D3:** 96 **D4:** 85 **D5:** 96 **D6:** 75 **D7:** 95 **D8:** 78 **D9:** 88 **Corticosteroid use, %** **D1:** 53 **D2:** 48 **D3:** 51 **D4:** 63 **D5:** 57 **D6:** 48 **D7:** 56 **D8:** 50 **D9:** 48 **MTX naive, %:** NR **Treatment resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**TJC % improvement** **D1**: 34 (N/A) **D2** vs. **D1**: 53% (*P* < 0.001) **D4** vs **D1**: 29% (*P* = NS) **D3** vs **D1**: 55% (*P* < 0.0001) **D5** vs **D1**: 48% (*P* = NS) **HAQ % improvement amongst pts < 65 yrs** **D2:** 22 **D4:** 4 (*P* = NR)		

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Weaver et al., 2006 (continued)			**RF factor positive:** **D1:** 72 **D2:** 65 **D3:** 69 **D4:** 68 **D5:** 69 **D6:** 75 **D7:** 73 **D8:** 71 **D9:** 71			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Weinblatt et al., 2006 **Country, Setting:** NR **Funding:** Abbott Labs **Research Objective:** To evaluate efficacy and safety of adalimumab plus MTX (MTX) given for up to 4 yrs in pts with active, longstanding rheumatoid arthritis **Study Design:** Uncontrolled open-label extension of ARMADA trial **Overall N:** 262 in extension **Study Duration:** up to 4 yrs (6 mos blinded)	**Inclusion Criteria:** • Age: ≥ 18 yrs • Diagnosed with RA according to ACR criteria • Previous use of DMARDs • MTX for at least 6 mos • 9 tender and 6 swollen joints **Exclusion Criteria:** NR	**Interventions, dose:** Adalimumab + MTX **N:** Overall: 262 **Mean age, yrs:** Overall: 55 **Sex, % female:** Overall: 76 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR NR	• Serious infections occurring during open label txt and blinded period were similar (2.03 vs. 2.30 events per 100 PY, respectively) • Rates of all other adverse events were similar between blinded and extension phases	**Serious Infections:** **D1:** 2.03/ 100 pts **CHF**: **D1:** 0.11/ 100 pts **Malignancies:** **D1:** 19 cancers: • 5 non-melanoma skin • 4 GI • 2 prostate	**Overall Attrition Rate, %:** • 38% • 162/262 used for analysis with a mean txt time of 3.4 yrs however 147 completed 4 yrs of txt **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Weinblatt et al., 2006 **Country, Setting:** Multinational Multicenter ASSURE Trial **Funding:** Bristol-Myers Squibb **Research Objective:** To assess safety of ABA in pts with active RA who had been receiving 1 traditional nonbiologic and/or biologic DMARDs **Study Design:** RCT **Overall N:** 1456 **Study Duration:** One yr	**Inclusion Criteria:** • Age: ≥ 18 • Diagnosed according to ACR criteria • I class I-IV • DMARDs • Stable, low-dose oral Css and/or stable doses of NSAIDs • Stable CHF, asthma, COPD, and DM **Exclusion Criteria:** • Pregnant or lactating • History of TB • Impaired renal or hepatic system • Mycophenolate mofetil, CYP, other calcineurin inhibitors, D-penicillamine, cyclophos-phamide, apheresis unstable or uncontrolled diseases, or any autoimmune disorder as the main diagnosis • Bacterial infections • Active herpes zoster < 2 mos, hepatitis B or C	**Interventions, dose:** **D1:** Non-bio and ABA **D2:** Non-bio and placebo **D3:** Bio and ABA **D4:** Bio and placebo ABA: 500 mg a body weight <60 kg, 750 mg for 60-100 kg, and 1 gram for >100 kg **N:** **D1:** 856 **D2:** 418 **D3:** 103 **D4:** 64 **Mean age, yrs:** **D1:** 52.2 **D2:** 52.0 **D3:** 54.6 **D4:** 52.8 **Sex, % female:** **D1:** 83.1 **D2:** 83.7 **D3:** 75.7 **D4:** 75.0 **Race, % white:** **D1:** 83.9 **D2:** 83.3 **D3:** 97.1 **D4:** 92.2	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9.5 **D3:** 11.3 **D4:** 11.3 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **HAQ:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5 **D4:** 1.6	• ABA and placebo groups exhibited similar frequencies of adverse events (90% and 87%, respectively), serious adverse events (13% and 12%, respectively), and discontinuations due to adverse events (5% and 4%, respectively) • Serious infections were more frequent in the ABA group than in the placebo group (2.9% vs. 1.9%) • Serious adverse events occurred more frequently in the subgroup receiving ABA plus a biologic agent (22.3%) than in other subgroups (11.7-12.5%) • Sub analysis of Pts w/ COPD and DM (placebo vs. ABA)(%) COPD • Overall AEs 88.2 vs.97.3 • Respiratory oriented 23.5 vs. 23.5 • SAEs 5.9 vs. 27 DM • Overall AEs 90.3 vs. 93.8 • Infections 58.1 vs. 50.8 • SAEs 12.9 vs. 21.5 Change in HAQ from baseline • Placebo -0.25 vs. ABA-0.46 ($P < 0.001$)	**Overall:** **D1:** 89.7 **D2:** 86.1 **D3:** 95.1 **D4:** 89.1 **SAEs:** **D1:** 11.7 **D2:** 12.2 **D3:** 22.3 **D4:** 12.5 **Infections:** **D1:** 54.9 **D2:** 53.6 **D3:** 65.0 **D4:** 57.8 **Serious Infections:** **D1:** 2.6 **D2:** 1.7 **D3:** 5.8 **D4:** 1.6 **Malignancies:** **D1:** 3.2 **D2:** 3.8 **D3:** 6.8 **D4:** 1.6	**Overall Attrition Rate, %:** 15 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Westhovens et al., 2006 START Trial **Country, Setting:** Multinational, multicenter **Funding:** Centocor **Research Objective:** The risk of serious infections in INF therapy, and safety in combination with background txts during 1 yr in pts with RA with various comorbidities **Study Design:** RCT **Overall N:** 1084 **Study Duration:** 54 wks of which 22 wks wast RCT then open label extension	**Inclusion Criteria:** • Adults w/ RA according to ACR criteria • MTX ≥ 3 mos • Chloroquine, AZA, penicillamine, oral or intramuscular gold • HCQ, SSZ, LEF, CYP, oral Css, or NSAIDS **Exclusion Criteria:** • TB • Opportunistic or serious infections, HIV, lympho-proliferative disease or malignancy • CHF investigational drug (3 mos or 5 half-lives, whichever was greater), with cyclophos-phamide, nitrogen mustard, chlorambucil, or other alkylating agents more than 5 mg/kg cyclosporine, or biologic	**Interventions, dose:** **D1:** Placebo + MTX (up to 25 mg/wk) **D2:** INF 3 mg/kg (at wks 0, 2, 6, and 14) + MTX (up to 25 mg/wk) **D3:** INF 10 mg/kg (at wks 0, 2, 6, and 14) + MTX (up to 25 mg/wk) **D4: D2 + D3** **N:** **D1:** 363 **D2:** 360 **D3: 361** **Mean age, yrs:** **D1:** median 52 **D2:** 53 **D3: 52** **Sex, % female:** **D1:** 83.2 **D2:** 80.0 **D3: 77.8** **Race, % white:** NR	**Median disease duration, yrs:** **D1:** 8.4 **D2:** 7.8 **D3:** 6.3 **TJC, mean:** **D1:** 22 **D2:** 22 **D3:** 22 **SJC, mean:** **D1:** 15 **D2:** 15 **D3:** 15 **DMARD use, %:** **D1:** 70 **D2:** 70.8 **D3:** 69.8 **Corticosteroid use, %:** **D1:** 59.2 **D2:** 59.2 **D3:** 59 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**At week 22** **ACR20 response, %** **D1**: 26 **D2**: 58 **D3:** 61 (*P* < 0.0001) **ACR50 response, %** **D1**: 9.7 **D2**: 32.1 **D3:** 35.4 (*P* < 0.0001) **ACR70 response, %** **D1**: 4.7 **D2**: 14.0 **D3:** 16.1 (*P* < 0.0001) **DAS28 , (+/-)** **D1:** 4.4 (1.4) **D2 and D3**: 3.4 (1.3) (*P* < 0.001) **Remission, %** **D1**: 14 **D2**: 31 **D3:** 32 (*P* < 0.0001)	**Overall:** **D1:** 66.2 **D2:** 69.7 **D3:** 72.3 **D4:** 71.0 **SAEs:** **D1:** 7.5 **D2:** 7.8 **D3:** 7.5 **D4:** 7.8 **Serious Infections:** **D1:** 1.7 **D2:** 1.7 **D3:** 5.0 **D4:** 3.3 **Cardiovascular Events:** **D1:** 3.3 **D2:** 4.5 **D3:** 5.9 **D4:** 5.2 **Headache:** **D1:** 6.1 **D2:** 9.7 **D3:** 10.2 **D4:** 10.0 **Hepatotoxicity (ALT increase):** **D1:** 2.8 **D2:** 3.6 **D3:** 5.3 **D4:** 4.4	**Overall Attrition Rate, %:** 17.1 **ITT Analysis:** Yes **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Westhovens et al., 2006 (continued)			**Median HAQ score:** **D1:** 1.5 **D2:** 1.5 **D3:** 1.5 **% RF positive:** **D1:** 80.7 **D2:** 82.8 **D3:** 76.8		**Malignancies:** **D1:** 1.7 **D2:** 4.2 **Nausea:** **D1:** 8.0 **D2:** 6.4 **D3:** 6.4 **D4:** 6.4 **URTI:** **D1:** 10.5 **D2:** 9.7 **D3:** 11.9 **D4:** 10.8 **UTI:** **D1:** 0 **D2:** 0 **D3:** 0.6 **D4:** 0.3	

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 **Country, Setting:** US, 908 practices **Funding:** National Data Bank for Rheumatic Diseases (US) funded by pharma **Research Objective:** The rate of and standardized incidence ratio for lymphoma in pts with RA and in RA patient subsets by txt group **Study Design:** Prospective cohort study **Overall N:** 18,572 **Study Duration:** Up to 3 yrs	**Inclusion Criteria:** • Participants in National Data Bank for Rheumatic Diseases (NDB) long-term study of outcomes of RA • Cases were identified from this group as those who developed lymphoma during the 2 ½ yr observational period **Exclusion Criteria:** • Cases were rejected if not enough information could be obtained to verify patient's lymphoma	**Interventions, dose:** **D1:** INF (varied) **D2:** ETA (varied) **D3:** MTX (varied) **D4:** No MTX/ No Biologics **N:** **D1:** 6433 **D2:** 2729 **D3:** 5593 **D4:** 4474 **Mean age, yrs:** **D1:** 60.7 **D2:** 56.4 **D3:** 61.2 **D4:** 60.4 **Sex, % female:** **D1:** 77.3 **D2:** 79.3 **D3:** 75.7 **D4:** 75.7 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 13.7 **D2:** 14.1 **D3:** 13.5 **D4:** 13.5 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 1.2 **D2:** 1.2 **D3:** 1.1 **D4:** 1.0	• SIR for whole population regardless of txt was 1.9 (95%CI, 1.3-2.7); indicating a greater risk for lymphoma in pts with RA • SIR for pts taking biologics (INF or ETA) was 2.9 (95%CI, 1.7-4.9). • No significant differences were observed between txt groups • Only 233 pts received AKA and no lymphomas occurred in this group • Overall, lymphoma incidence rate per 100,000 PY was 99 (95%CI,69-142); for various durations of RA, rates were: 0-5 yrs: 171 (95%CI,82-360), 5-10 yrs: 70 (95%CI,29-168), 10-15 yrs: 20 (95%CI,3-145), >15 yrs: 121 (95% CI, 74-198)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 (continued)			**VAS QoL:** **D1:** 65.8 **D2:** 64.3 **D3:** 66.7 **D4:** 65.9 **Pain:** **D1:** 4.2 **D2:** 4.3 **D3:** 3.7 **D4:** 3.9			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 **Country, Setting:** US, multicenter (National Data Bank for Rheumatic Diseases) **Funding:** Centocor, Inc **Research Objective:** To determine frequency of heart failure in pts with RA, and to determine its predictors, particularly use of anti-TNF therapy **Study Design:** Retrospective cohort study **Overall N:** 15,739 (RA plus OA subjects) **Study Duration:**	**Inclusion Criteria:** • Participation in National Data Bank for Rheumatic Diseases study of outcomes of arthritis; patient at participating rheumatology clinic **Exclusion Criteria:** • NR	**Interventions, dose:** **D1:** Any Anti-TNF **D2:** INF **D3:** ETA **D4:** No anti-TNF **D5:** Total Population Overall **N:** NR **Mean age, yrs:** **D1:** 60 **D2:** 61.5 **D3:** 56.7 **D4:** 61.5 **D5:** 51 **Sex, % female:** **D1:** 78 **D2:** 77 **D3:** 80 **D4:** 76 **D5:** 77 **Race, % white:** **D1:** 95 **D2:** 96 **D3:** 92 **D4:** 92 **D5:** 94	**Mean disease duration, yrs:** **D1:** 14.2 **D2:** 13.8 **D3:** 15.2 **D4:** 15.5 **D5:** 14.9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** Overall: 86 **PRE use (%)** **D1:** 47 **D2:** 49 **D3:** 39 **D4:** 33 **D5:** 39 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 3.7 **D2:** 3.7 **D3:** 3.6 **D4:** 3.5 **D5:** 3.6	**Heart Failure** • 461 cases in 13,171 pts with RA (overall risk of 3.5%); after adjusting for demographic characteristics; Risk: 3.9% (95% CI,= 3.4% to 4.3%) • Among all cases of heart failure, pts receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI,-1.9 --0.5%) • Overall, adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in remaining pts (*P* = 0.03) • Frequency of heart failure was 5.2% in men and 3.0% in women • In examining incident cases of heart failure in pts under age 50, no increase was found (0/1569 pts using anti-TNF vs. 3/1401 not using anti-TNF therapy)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 (continued)			**MTX use:** **D1:** 67 **D2:** 76 **D3:** 44 **D4:** 47 **D5:** 56			

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe et al., 2006 **Country, Setting:** US, Rheumatology Clinics **Funding:** Bristol-Meyers-Squibb **Research Objective:** To evaluate txt of RA and risk of hospitalization for pneumonia **Study Design:** Prospective cohort study **Overall N:** 16,788 **Study Duration:** 3.5 yrs	**Inclusion Criteria:** • Participants in NDB longitudinal study of RA outcomes including 5,317 enrolled as part of an INF safety registry and 1,852 as part of a LEF safety registry • Other meds allowed **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** Cohort Prednisone MTX LEF SSZ Hydroxychlorquine ETA INF Adalimumab Other various RA txts **N:** NR **Mean age, yrs:** **D1:** 62 **Sex, % female:** **D1:** 77.2 **Race, % white:** **D1:** 89.7% white, 4.8% black, 3.0% Hispanic, 1.0 Asian/Pacific Islander, 1.1% American Indian or Alaskan native, 0.5% Other	**Mean disease duration, yrs:** **D1:** 16.3 **TJC, mean:** NR **SJC, mean:** NR **DMARD use mean (lifetime #):** **D1:** 3.3 **Corticosteroid use, %:** **D1:** 38.1 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Effect of txt variables on risk of pneumonia (adjusted for demographic variables-age, sex, smoking, education, and enrollment) • Prednisone HR 1.7 [95% CI, 1.5-2.1]) • LEF HR 1.3 [95% CI, 1.0-1.5], *P* = 0.036) • •SSZ HR 0.7 [95% CI, 0.4-1.0], *P* = 0.053) • ETA HR 0.8 [95% CI, 0.6-1.0], *P* = 0.051) • INF HR 1.1 [95% CI, 0.9-1.4], *P* = 0.322) • Adalimumab HR 1.1 [95% CI, 0.6-1.9], *P* = 0.747) • MTX HR 1.0 [95% CI, 0.8-1.2], *P* = 0.927) • Hydroxychloroquine HR 0.9 [95% CI, 0.7-1.2], *P* = 0.481)	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe, 2004 **Country, Setting:** Multinational, multicenter **Funding:** Centocor, Inc **Research Objective:** To determine baseline rate of TB in RA prior to introduction of INF and to determine rate of TB among those currently receiving INF **Study Design:** Prospective cohort study with historic control **Overall N:** 17,242 Study 1: 10,782 Study 2: 6,460 **Study Duration:** 3 yrs	**Inclusion Criteria:** • Diagnosed with RA according to ACR criteria • Use of INF **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** Study 1 **D2: Study 2** **INF:** varied **N:** **D1:** 10782 **D2:** 6640 **Mean age, yrs:** **D1:** 59.8 **D2:** 61.4 **Sex, % female:** **D1:** 76.9 **D2:** 73.5 **Race, % white:** **D1:** 90.9 **D2:** 94.4	**Mean disease duration, yrs:** **D1:** 13.2 **D2:** 14 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 54.6 **D2:** 50.4 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47.9 **D2:** 74.6	• In pre-INF group, 1 case of TB developed during 16,173 PY of follow-up, yielding a rate of 6.2 cases (95% CI,1.6-34.4) per 100,000 patient yrs • In INF-group, TB incidence rate among pts was 61.9 cases per 100,000 patient yrs • None of TB pts had undergone a TB skin test and no cases of TB occurred in 44-59% that had received test	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005 **Country, Setting:** Germany, clincal **Funding:** Essex Pharma, Wyeth Pharma, Amgen, and Abbott **Research Objective:** To compare drug continuation rates in pts. with RA who start on a biological agent or on a DMARD after previous DMARD failure **Study Design:** Retrospective cohort study **Overall N:** 1,523 **Study Duration:** 1 yr	**Inclusion Criteria:** • Age: 18 to 75 • Diagnosed with RA according to ACR criteria • Previous use of DMARDs: at least 2 **Exclusion Criteria:** NR	**Interventions (dose):** **D1:** ETA **D2:** INF **D3:** AKA **D4:** Total Control Group **D5:** LEF **D6:** LEF + MTX Dosages NR **N:** **D1:** 511 **D2:** 343 **D3:** 70 **D4:** 599 **D5:** 120 **D6:** 141 **Mean age, yrs:** **D1:** 53.7 **D2:** 53.6 **D3:** 54.3 **D4:** 56.5 **D5:** 58 **D6:** 57.4 **Sex, % female:** **D1:** 77.9 **D2:** 71.1 **D3:** 77.1 **D4:** 82.8 **D5:** 85.8 **D6:** 78.0 **Race, % white:** NR	**Mean disease duration (yrs):** **D1:** 9 **D2:** 8.5 **D3:** 13 **D4:** 6 **D5:** 9 **D6:** 7 **TJC, mean:** **D1:** 13.3 **D2:** 12.6 **D3:** 12.6 **D4:** 10 **D5:** 10.6 **D6:** 10.9 **SJC, mean:** **D1:** 10.4 **D2:** 10.7 **D3:** 10.2 **D4:** 7.7 **D5:** 7.4 **D6:** 8.5 **DMARD use (#):** **D1:** 3.9 **D2:** 3.7 **D3:** 4.2 **D4:** 2.1 **D5:** 2.4 **D6:** 2.2 **Corticosteroid use, %:** NR **MTX naive, %:** NR	**Continuation rates** **D1** and **D2** similar **D3** significantly lower **Txt continuation at 1 yr, %** **D1**: 68.6 ETA+ MTX : 71.6 **D2**: 65.4 **D6**: 66.2 **D3**: 59 AKA vs. ETA*; P* = 0.004; ANA vs. INF*; P* = 0.03 **Txt discontinuation because of adverse events, %:** **D1**: 12.6% ETA+MTX 13.3 **D2**: 18.7 INF+MTX: 18.2 **D3**: 16.3 **Txt discontinuation because of lack of efficacy, %:** **D1:** 19.9 ETA + MTX :16.9; **D2:** 45 INF+MTX: 17.9 **D3:** 29.6	NR	**Overall Attrition Rate, %:** N/A **ITT Analysis:** N/A: registry **Quality Rating:** Good

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005 (continued)			**Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 6.1 **D2:** 6 **D3:** 6.1 **D4:** 5.4 **D5:** 5.5 **D6:** 5.6 **MTX use:** **D1:** 91.2 **D2:** 92.1 **D3:** 78.6 **D4:** 68.7 **D5:** 94.2 **D6:** 90.7			

Evidence Table 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Bongartz, 2006, multinational, Mayo foundation, Abbott & Centocor **Study Design:** Systematic literature search with meta-analysis **Aims of the Review:** • To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in pts with RA by performing a meta-analysis • To derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy **Number of Pts:** 5014 (9 trials)	**Studies included:** • Keystone (2004) • St Clair (2004) • Furst (2003) • Lipsky (2000) • van de Putte (2003) • Weinblatt (2003) • Maini (1998) • van de Putte (2004) • Westhovens (2004) **Characteristics of included studies:** • RCTs of INF and ADA in which pts had ACR-diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF antibody + traditional DMARD vs. placebo + traditional DMARD) • Both pt and observer were masked • Trial had to be at least 12 wks in duration **Characteristics of included populations:** • Pts with an ACR diagnosis of RA who were randomized to receive Anti-TNF or placebo **Characteristics of interventions:** Anti-TNF (dosing varied) or Control	• In pts with RA, anti-TNF treatment leads to increased risk of serious infections and a dose-dependent increased risk of malignancies. Serious infections reported in 126 anti-TNF- treated pts vs. 26 control group pts (OR, 2.0; 95% CI, 1.3-3.1) • Malignancies reported in 24 / 3493 (0.8%) pts who received > 1 dose of anti-TNF vs. 2 / 1512 (0.2%) pts on control • Pooled OR for malignancies in anti-TNF group vs. placebo group = 3.3 (95% CI, 1.2-9.1) • Number needed to harm was 154 (95% CI 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (39-125) within a treatment period of 3 to 12 months	Overall AEs reported: • Malignancy: Anti-TNF (23/3192) Control (3/1428) OR = 3.3 (95% CI 1.2 – 9.1) • Serious Infections: Anti-TNF (126/3493) Control (26/1512) OR = 2.0 (1.3-3.1)	**Publication Bias Assessed**: Not reported **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes - briefly describe in box: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the European League Against Rheumatism and the American College of Rheumatology – through December 2005 **Quality Rating:** Fair		

Evidence Table 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Gartlehner et al., 2006 US **Study Design:** Metaanalysis (random effects model); systematic review **Aims of the Review:** To assess comparative efficacy and safety of biologic agents for RA **Number of Patients:** ADA: 2,354 ETA: 1,151 INF: 704 AKA:1,039 (#'s refer to 17 sudies used for adjusted indirect comparisons of efficacy)	**Studies included:** • 26 controlled trials • 18 additional studies assessed safety **Characteristics of included studies:** • Often limited to 1 year of follow-up • Reported on DAS-28 • Radiographic progression, functional capacity, and QOL **Characteristics of included populations:** • Narrowly defined populations • Mean age 53.4 • 76% female • 89% caucasion **Characteristics of interventions:** • All efficacy studies except 1 were funded by the pharmaceutical industry • All 12 weeks plus of duration (for observational studies it was 3 months or greater and 100 or more patients)	• Adjusted indirect comparison indicate no significant differences in efficacy between antiTNF drugs • Anti-TNF drugs appear to be more efficacious than AKA but do not differ among each other. Inddirect comparisons of INF and of anti-TNF drugs as a class compared to AKA yielded a statistically significant greater efficacy on ACR 20 [RR 0.58 (95%CI 0.38-0.90) and RR 0.61 (95% CI 0.39-0.96), respectively], but not ACR 50 • Few studies assessed longterm radiographic outcomes. In general, rate of radiographic progression was significantly lower in patients treated with biologics than in placebo-treated patients, regardless of concomitant DMARD therapy. Similarly, QoL improved significantly for patients treated with biologics	• Because of lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about comparative safety of biologics • Higher rates of injection site reactions for AKA than ADA and ETA (56% vs. 19% vs. 25%)	**Publication Bias Assessed**: Yes **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes - briefly describe in box: Searched Medline, Embase, Cochrane and International Pharmaceutical Abstracts from 1980-2006. Also explored CDER database. **Quality Rating:** Good		

Evidence Table 9. KQ3. Rheumatoid arthritis systematic reviews: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, country, funding: Osiri et al., 2002 Multinational Cochrane Collaboration **Study Design:** Systematic review of RCTs and CCTs **Aims of the Review:** • To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA • Meta-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts **Number of Pts:** 1,144 LEF 312 to Placebo 680 to MTX 132 to SSZ Only 920 used in meta-analysis 2 yr extension: LEF:158 SSZ: 60 MTX 101	**Studies included:** • 6 trials **Characteristics of included studies:** • Randomized, double-blind, placebo and/or active controlled **Characteristics of included populations:** • All with active RA **Characteristics of interventions:** • 5,10 or 25 mg/d vs placebo or MTX or SSZ	• LEF significantly better than placebo at 6,12 and 24 mos. • LEF vs. MTX • ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77) • No significant differences at 2 yrs but more responders with MTX than with LEF; OR 1.28 (0.98-1.67) • ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS	• Total withdrawals lower in LEF group (10% greater than Placebo (70/416 vs 18/311)); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos; AEs+ GI sympotms, elevated liver funcitn tests, alopecia, and infections	**Publication Bias Assessed**: NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good		

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Antoni et al., 2005; Kavanaugh et al., 2006 IMPACT Study **Country, Setting:** Multinational 9 clinical sites **Funding:** NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network **Research Objective:** Efficacy and tolerability of INF for the articular and dermatologic manifestations of active PsA **Study Design:** RCT **Overall N:** 104 **Study Duration:** 50 wks (1-16 wks RCT 16-50 open, all treated with INF)	**Inclusion Criteria:** • Age ≥ 18 • Failure of 1 or more DMARD • Active peripheral polyarticular arthritis • MTX ≥ 15 mg/wk w/ folic acid supplementation • LEF, SSZ, HCQ, intramuscular gold, penicillamine, or azathioprine stable for 4 wks • oral corticosteroids (dosage of 10 mg PRE equivalent/d or less) • NSAIDs stable for at least 2 wks **Exclusion Criteria:** • Monoclonal antibody or fusion protein • History of TB: positive tests for RF or latent TB • investigational drug within 3 mos	**Interventions:** **D1:** Placebo **D2:** INF (5mg/kg at wks 0,2,6,14, then every 8 wks) **N:** **D1:** 52 **D2:** 52 **Mean age, yrs:** **D1:** 45.2 **D2:** 45.7 **Sex, % female:** **D1:** 42.3 **D2:** 42.3 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 11 **D2:** 11.7 **TJC, mean:** **D1:** 20.4 **D2:** 23.7 **SJC, mean:** **D1:** 14.7 **D2:** 14.6 **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 5.4 **D2:** 5.5	**ACR50** **D1**: 0/52 (0.0%) **D2**: 24/52 (46.2%) **ACR70** **D1**: 0/52 (0.0%) **D2**: 15/52 (28.8%) **Tender joints, number** **D1**: -23.6 **D2**: 55.2 **Swollen joints, number** **D1**: -1.8 **D2**: 59.9 **DAS** **D1**: 2.8 **D2**: 45.5 *P* < 0.001 **HAQ** **D1**: -1.6 **D2**: 49.8 *P* < 0.001 **PsARC, %** **D1**: -12 **D2**: +86 *P* < 0.001 **At week 16** **ACR20** **D1**: 5/52 (9.6%) **D2**: 34/52 (65.4%) *P* < 0.001	**Overall:** **D1:** 65 **D2:** 73 **D3:** 84 **Headache:** **D1:** 3 **D2:** 4 **URTI:** **D1:** 5 **D2:** 1	**Overall Attrition Rate (%):** 5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				PsARC, % **D1**: 21 **D2**: 75 *P* < 0.001 **PASI75, %** **D1**: 0 **D2**: 68 *P* < 0.001 **At 50 weeks** **Total modified vdH-S score sowing no worsening** **D1**: 85% (Placebo/INF) **D2**: 84% (INF/INF) **Change in erosion scores** **D1**: 0.536 (Placebo/INF) **D2**: 0.921 (INF/INF) (*P* = 0.780) **Change in JSN** **D1** :-0.47 **D2**: -0.51 (*P* = 0.211)		

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Antoni, 2005; Kavanaugh et al., 2006 **Country, Setting:** Multinational 36 sites in clinics IMPACT2 Study **Funding:** Centocor Inc and Schering-Plough **Research Objective:** Efficacy, health related quality of life and physical function in pts with PsA **Study Design:** RCT **Overall N:** 200 **Study Duration:** 14 to 24 wks (pts with inadequate response entered early escape at wk 16)	**Inclusion Criteria:** • Diagnosed with PsA • Diagnosed at least 6 mos before first infusion of study drug • Inadequate response to current or previous DMARDs or NSAIDs • Pts had to have active plaque psoriasis with at least 1 qualifying target lesion at least 2 cm in diameter • Negative test for RF in their serum • Stable doses of MTX, oral corticosteroids, NSAIDs **Exclusion Criteria:** • TNF α inhibitors; active or latent TB • Chronic or clinically significant infection, malignancy, or CHF	**Interventions:** **D1:** Placebo **D2:** INF (5 mg/kg at wks 0, 2, 6, 14, 22) **N:** **D1:** 100 **D2:** 100 **Mean age, yrs:** **D1:** 46.5 **D2:** 47.1 **Sex, % female:** **D1:** 49 **D2:** 29 **Race, % white:** NR	**Mean disease duration, yrs:** **D1:** 7.5 **D2:** 8.4 **TJC, mean:** **D1:** 25.1 **D2:** 24.6 **SJC, mean:** **D1:** 14.4 **D2:** 13.9 **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 10 **D2:** 15 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 45 **D2:** 47 **PASI:** **D1:** 10.2 **D2:** 11.4	• Placebo vs. INF (%): • ACR 50 at wk 14 3 vs. 36 (P < 0.001) and wk 24 4 vs. 41 (P < 0.001) • ACR70 at wk 14 1 vs. 15 (P < 0.001) and wk 24 2 vs. 27 (P < 0.001) • PsARC at wk 14 27 vs. 77 (P < 0.001) and wk 24 32 vs. 70 (P < 0.001) • •HAQ improvement at wk 14 - 18.4 vs. 48.6 (P < 0.001) and wk 24 -19.4 vs. 46 (P < 0.001) • •SF-36 (change from baseline) • Physical wk 14 1.1 vs. 9.1 (P < 0.001) and wk 24 1.3 vs. 7.7 (P < 0.001) • Mental wk 14-1.2 vs. 3.8 (P = 0.001) and wk 24 0.4 vs. 3.9 (P = 0.047) • ACR20 at Wk 14 11 vs. 58 (P < 0.001) and Wk 24 16 vs. 54 (P < 0.001) • PASI 50: wk 14: 9 vs. 82 (P <0.01), wk 24: 8 vs. 75 (P <75 (P<0.01); PASI 75 wk 14: 2 vs. 64 (P < 0.01), wk 24: 1 vs. 50 (P < 0.01); • improvement wk 14: 0 vs. 41 (P < 0.01), wk 24: 0 vs. 39 (P < 0.01) • median productivity at 14 wks 9.2% vs. 67.5% (P < 0.0001) • missed workdays at 14 wks 13% vs. 3.7% (P = 0.138)	**Overall:** **D1:** 67 **D2:** 67 **SAEs:** **D1:** 6 **D2:** 9 **Infusion or injection reaction:** **D1:** 6 **D2:** 7 **Dizziness:** **D1:** 5 **D2:** 4 **Headache:** **D1:** 5 **D2:** 6 **URTI:** **D1:** 14 **D2:** 10	**Overall:** **Attrition Rate (%):** Wk 14: NR Wk 24: 7.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kaltwasser et al., 2004 and Nash et al., 2006 **Country, Setting:** Multinational Multi-center (31) **Funding:** Aventis **Research Objective:** Efficacy and safety of LEF versus placebo in pts with PsA and psoriasis **Study Design:** RCT **Overall: N:** 190 (ITT = 186) **Study Duration:** 24 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA • NSAIDs or Css (prednisone dose of 10 mg/day or steroid equivalent administered orally) • Discontinue DMARDs, biologics and systemic antipsoriatic txt 28 days **Exclusion Criteria:** • Pregnant or lactating; leflunomide • Impaired renal or hepatic system • Nonpsoriatic inflammatory joint disease or arthritis onset < 16 yrs • RH factor +, rheumatoid nodules, serious infections, malignancy, or CVD, HIV, hepatitis B or C antigen positivity, guttate, pustular, or erythrodermic forms of psoriasis, body weight <45 kg • Impaired bone marrow function; history of drug or alcohol abuse	**Interventions:** **D1:** Placebo **D2:** LEF **N:** **D1:** 91 **D2:** 95 **Mean age, yrs:** Drug 1: 46.9 Drug 2: 48.6 Overall **Sex, % female:** **D1:** 37.4 **D2:** 42.1 **Race, % white:** **D1:** 95.6 **D2:** 97.9	**Mean disease duration, yrs:** **D1:** 10 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **D1:** 49.5 **D2:** 61.1 **Corticosteroid use, %:** **D1:** 9.9 **D2:** 15.8 **DMARD naive, %:** **D1:** e 50.5 **D2:** 38.9 **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• 56 of 95 leflunomide-treated pts (58.9%; 95% CI, 48.4-68.9) and 27 of 91 placebo-treated pts (29.7% [95% CI, 20.6-40.2]) were classified as responders by PsARC (*P* < 0.0001) Change in HAQ total score • Placebo (N:90) -0.05 ± 0.46 (*P* = 0.0267) • Leflunomide (N:94) -0.19 ± 0.51 Change in PASI score • Placebo (N:90) -0.6 ± 6.1 *P* = 0.0030 • Leflunomide (N:92) -2.1 ± 5.9 Change in DLQI total score • Placebo (N:89) -0.2 ± 5.1 *P* = 0.0173 • Leflunomide (N:90) -1.9 ± 5.1	**Overall:** **D1:** 76.1 **D2:** 85.4 **SAEs:** **D1:** 5.4 **D2:** 13.5 **Serious Infections:** **D1:** 0 **D2:** 0 **Diarrhea:** **D1:** 13.0 **D2:** 24.0 **Headache:** **D1:** 7.6 **D2:** 11.5 **Nausea:** **D1:** 8.7 **D2:** 9.4	**Overall Attrition Rate (%):** 47.9% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2000 **Country, Setting:** US, single center in Seattle **Funding:** Immunex Corp. **Research Objective:** To study efficacy and safety of etanercept in pts with psoriatic arthritis and psoriasis **Study Design:** RCT **Overall N:** 60 **Study Duration:** 12 wks	**Inclusion Criteria:** • Age 18 to 70 • Diagnosed with PsA according to: > 3 swollen, tender, or painful joints • Inadequate response to NSAIDs • Hepatic transasminase concentrations no greater than 2x upper limit of normal • Hemoglobin 85 g/L or higher • Platelet count 125,000 per mL or more and serum creatinine 152-4 mmol/L or below • MTX < 25 mg/wk and stable for 4 wks • Corticosteriods if the dose < 10 mg/d of PRE, stable for at least 2 wks and maintained at a constant dose throughout study **Exclusion Criteria:** • Evidence of skin conditions other than psoriasis	**Interventions:** **D1:** Placebo **D2:** ETA (25mg 2x wkly) **N:** **D1:** 30 **D2:** 30 **Mean age, yrs:** **D1:** 43.5 **D2:** 46 **Sex, % female:** **D1:** 40 **D2:** 47 **Race, % white:** **D1:** 83 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.5 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 40 **D2:** 20 **MTX naive, %:** NR **Txt resistant, %:** Overall 100 **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX:** **D1:** 47 **D2:** 47	• PsARC ETA 26 (87%) vs. Placebo 7 (23%) *P* < 0.0001 95% CI, 44-83; ACR50 ETA 15 (50%) vs. Placebo 1 (3%) *P* = 0.0001 95% CI, 28-66; • ACR70 ETA 4 (13%) vs. Placebo 0 (0%) *P* = 0.0403 95% CI, 1-26; • HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) *P* < 0.001 • •ACR20 was achieved by 73% ETA treated pts compared with 13% placebo treated pts (*P* < 0.0001) • Median % improvements in tender and swollen joint counts at 12 wks ETA 75% and 72% respectively vs. placebo 5% worsening and 19% improvement; disability according to HAQ significantly more improved in ETA than placebo (83% vs. 3%, *P* < 0.0001) • 26% of ETA vs. 0 of placebo pts achieved 75% improvement in PASI at 12 wks (*P* = 0.0154); similar differences between ETA and placebo also seen at 25% and 50% improvements in PASI scores	**SAEs:** **D1:** 0 **D2:** 3.3 **Infusion or injection reaction:** **D1:** 20 **D2:** 3 **Headache:** **D1:** 13 **D2:** 10 **URTI:** **D1:** 57 **D2:** 57	**Overall Attrition Rate (%):** 6.6% **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2004; Mease et al., 2006 **Country, Setting:** US 17 sites **Funding:** Immunex **Research Objective:** Safety, efficacy, and effect on radiographic progression of ETA in pts with PsA **Study Design:** RCT **Overall N:** 205 **Study Duration:** 24 wks (with 48 wk open-label phase)	**Inclusion Criteria:** • Age 18 70 • Diagnosed with PsA ≥ 3 swollen and 3 tender joimts • Inadequate response to NSAID • At least one of PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis • Stable plaque psoriasis with a qualifying lesion • MTX therapy (stable 2 mo ≤ 25 mg/wk) • Css (stable 4 wks ≤ 10 mg/d of prednisone) **Exclusion Criteria:** • Oral retinoids, topical vitamin A or D analog preparations, and anthralin	**Interventions:** **D1:** placebo **D2:** ETA (25 mg 2x wkly) **N:** **D1:** 104 **D2:** 101 **Mean age, yrs:** **D1:** 47.3 **D2:** 47.6 **Sex, % female:** **D1:** 55 **D2:** 43 **Race, % white:** **D1:** 91 **D2:** 90	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 15 **D2:** 19 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use, %:** **D1:** 41 **D2:** 42 **Sharp:** **D1:** 18.3 **D2:** 25.89	• At 12 wks, 59% of ETA pts met ACR20 criteria compared with 15% placebo pts (*P* < 0.0001) • 23% of ETA pts eligible for psoriasis evaluation achieved at least 75% improvement in psoriasis area and severity index, compared with 3% of placebo pts (*P* = 0.001) • 12 mos; the mean annualized rate of change over one yr of txt in modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo (*P* = 0.0001) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group (*P* < 0.0001) • 72% & 70% of ETA achieved PsARC at 12 and 24 wks, respectively, compared with 31% and 23% of placebo pts	**SAEs:** **D1:** 3.9 **D2:** 4 **Infusion or injection reaction:** **D1:** 9 **D2:** 36 **Headache:** **D1:** 5 **D2:** 8 **URTI:** **D1:** 23 **D2:** 21 **UTI:** **D1:** 6 **D2:** 6	**Overall Attrition Rate (%):** 19.5 **ITT Analysis:** Yes **Quality Rating:** Fair

Evidence Table 10. KQ3. Psoriatic arthritis trials: Harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mease et al., 2005 **Country, Setting:** Multinational, multi-clinic (50) ADEPT Study **Funding:** Abbott Laboratories **Research Objective:** Safety and efficacy of ADA compared with placebo in txt of active psoriatic arthritis **Study Design:** RCT **Overall N:** 313 **Study Duration:** 24 wks	**Inclusion Criteria:** • Age ≥ 18 • Moderate to severe PsA • Active psoriatic skin lesions or a documented history of psoriasis • Inadequate response or intolerance to NSAIDs • MTX ≥ 3 mos with stable dose 4 wks **Exclusion Criteria:** • CYP, tacrolimus, DMARDs, or oral retinoids (4 wks) • Topical txts for psoriasis within 2 wks, other than medicated shampoos or low-potency topical steroids • Anti-TNF • History of TB • Central nervous system demyelinating disease • Listeriosis, or severe infection within 30 ds or oral antibiotics within 14 ds	**Interventions:** **D1:** placebo **D2:** ADA (40mg every other wk) **N:** **D1:** 162 **D2:** 151 **Mean age, yrs:** **D1:** 49.2 **D2:** 48.6 **Sex, % female:** **D1:** 45.1 **D2:** 43.7 **Race, % white:** **D1:** 93.8 **D2:** 97.4	**Mean disease duration, yrs:** **D1:** 9.2 **D2:** 9.8 **TJC, mean:** **D1:** 25.8 **D2:** 23.9 **SJC, mean:** **D1:** 14.3 **D2:** 14.3 **Mean number previous DMARDS:** **D1:** 1.5 **D2:** 1.5 **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant, %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline PASI (mean):** **D1:** 8.3 **D2:** 7.4 **MTX use:** **D1:** 50 **D2:** 51 **Baseline HAQ:** **D1:** 1.0 **D2:** 1.0	• PsARC ADA 60% wk. vs.placebo 23% • ACR50 ADA, 39% vs. placebo, 6% (*P* < 0.001) • ACR70 ADA, 23% vs. placebo, 1% (*P* < 0.001) • The PASI75 ADA 59% vs. placebo 1% (*P* < 0.001) (N:69 per group). • HAQ DI change placebo -0.1 ± 0.4 vs. ADA -0.4 ± 0.5 (*P* < 0.001) • ACR20 ADA 57% vs. placebo 15% (between-group difference 42%, 95% CI, 31-52%; *P* < 0.001). • Mmean change in modified total Sharp was -0.2 for ADA versus placebo (*P* < 0.001) • Erosion scores (mean change ADA 0.0 vs. placebo 0.6) and JSN scores (mean change ADA -0.2 vs. placebo 0.4) (*P* < 0.001 for both) • SF-36: SF-36 PCS; change in baseline to wk 12 for placebo vs ADA; 1.4 vs 9.3 (*P* < 0.001) • Change in baseline to wk 24; 1.4 vs 9.3 (*P* < 0.001) • SF-36 MCS • Change in baseline to wk 12 ; 1.2 vs 1.6 (*P* NS) • Change in baseline to wk 12; 0.6 vs 1.8 (*P* NS)	**Infusion or injection reaction:** **D1:** 3.1 **D2:** 6.6 **Headache:** **D1:** 8.6 **D2:** 6.0 **URTI:** **D1:** 14.8 **D2:** 12.6 **UTI:** NR	**Overall Attrition Rate (%):** 7.6 **ITT Analysis:** Yes **Quality Rating:** Fair.

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Chakravarty et al., 2003 **Country, Setting:** US, Rheumatology practices (175) **Funding:** Not reported **Research Objective:** To describe prescribing practices of rheumatologists with respect to treatment of RA in women of childbearing age and pregnancy outcomes **Study Design:** Case reports from Mail Survey to Rheumatologists **Overall N:** 175 (29%) physicians returned survey **Study Duration:** NR	**Inclusion Criteria:** • Age • Childbearing age • Women **Exclusion Criteria:**	**Interventions:** NR Methotrexate Leflunomide EtanerceptInfliximab **N:** NR **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant, %):** NR **Patients with Early RA (≤3 years):** NR **Baseline DAS, mean:** NR **Other:** NR	• 39 MTX • 10 LEF • 13 ETA • 2 INF MTX: • 21 full term healthy infants • 7 spontaneous abortions, including one in which fetus had congenital malformation • 8 elective abortions • 3 resulted in congenital malformations (2 live, 1 spontaneous abortion) • All attributed to MTX exposure Of 10 with LEF2 had been prescribed cholestyramine 6 with known outcomes: • 2 fullterm, healthy infants • 1 preterm delivery • 2 underwent elective abortions upon recommendation by their rheumatologist • 1 miscarriage 15 with ETA: Of 8 with known outcomes • 6 fullterm healthy infants, • 1 terminated • 1 patient took both ETA and MTX had a spontaneous abortion	NR	**Overall Attrition Rate, %:** N/A **ITT Analysis:** N/A: Observational study **Quality Rating:** Poor

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Chakravarty et al., 2003 (continued)				• Only 2 pregnancies reported in patients taking INF for RA-1 a fullterm healthy baby • Outcome of other not stated • Combined rate of congenital abnormalities in women on MTX was 17% according to answered questionaires compared to an average of 2 to 3% from a California cohort of 1.6 million infants		

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Jacobsson et al., 2005 **Country, Setting:** Sweden, population-based (2 Swedish registers) **Funding:** NR **Research Objective:** The risk of cardiovascular disease (CVD) in pts with RA treated with TNF inhibitors, compared to a standard RA population **Study Design:** Retrospective cohort study **Overall N:** 983 (combined cohort) **Study Duration:** NR	**Inclusion Criteria:** • Age-: 20 to 79 yrs • Diagnosed according to 1987 ACR criteria • Case cohort • South Swedish Arthritis Txt Group (SSATG): pts with RA treated with anti-TNF agents and included in SSATG register between 2/1/99 and 12/31/01 **Exclusion Criteria:** • Previous hospital discharge due to CVD	**Interventions, dose:** **D1:** Anti-TNF exposed **D2:** Not Anti-TNF exposed **N:** **D1:** 531 **D2:** 452 **Median age, yrs:** **D1:** 55 **D2:** 61 **Sex, % female:** **D1:** 78 **D2:** 75 **Race, % white:** NR	**Median disease duration, yrs:** **D1:** 12 **D2:** 11 **TJC, mean:** NR **SJC, mean:** NR **Median # of previous DMARDs used (IQR):** **D1:** 4 (2-5) **D2:** 2 (1-4) **PNL use, %:** **D1:** 75 **D2:** 22 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **Median HAQ:** **D1:** 1.50 **D2:** 1.13 **VAS patient global assessment median:** **D1:** 69 **D2:** 48	• Decreased incidence and RR for the development of first-time CVD event when controlling for disease severity in pts with RA treated with TNF blocking therapy • Controlling for disability (HAQ), age-sex adjusted rate ratio was 0.46 (95% CI,0.25 -0.85; *P* = 0.013) in anti-TNF treated vs. not treated • Anti-TNF group, 13 CVD events (in 656 PY at risk); age-adjusted incidence rate = 14 events/1000 PY • Unexposed comparison group, 85 CVD events (in 2056 PY at risk); age-adjusted incidence rate = 35.4 events/1000 PY • Relative risk = 0.62 (95% CI, 0.34 to 1.12; *P* = 0.111) • SMR revealed increased risk of new onset CVD in those not treated with TNF blockers in relation to background population of Malmo (SMR = 228, 95% CI,179 to 277) TNF blockers, risk of new onset CVD was lower, with CIs enclosing unity with background population (SMR = 157, 95% CI,72 -242)	**Cardiovascular Events:** **D1:** n =13 (6 MI, 4 cerebrovascular disease, and 3 other) **D2:** n =85 (33 MIs, 15 cerebrovascular disease, 12 CHF, 2 ruptured aortic aneurysm, and 23 other)	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Katz et al., 2004 **Country, Setting:** US and Europe, safety database **Funding:** NR- but data came from manufacturer **Research Objective:** To report first large evaluation of INF exposure during pregnancy **Study Design:** AERS database analaysis **Overall N:** 131 direct and 15 indirect exposure (partner) **Study Duration:** From 1 to 9 infusions	**Inclusion Criteria:** • Pts either were treated with INF or their partners • Other meds allowed: 5-aminosalicylate 6-mercaptopurine/ azathioprine, corticosteroids, metronidazole • MTX • Ciprofloxacin • NSAIDs • Proton pump inhibitors • H2 antagonists • Narcotics • Cyclosporine **Exclusion Criteria:** • NA	**Interventions, dose:** **D1:** INF direct **D2:** INF indirect **N:** **D1:** 131 **D2:** 15 **Mean age, yrs:** **D1:** 33 **D2:** 33 **Sex, % female:** **D1:** 100 **D2:** 100 **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 31 **D2:** 40 **MTX naive, %:** NR **Txt resistant, %:** NR **Pts. with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **MTX use:** **D1:** 8 **D2:** 20	• INF exposure during pregnancy results in outcomes which are not different than US population of pregnant women. No increase in adverse events was detected • Comparing the general population with INF treated, there is no statistical difference • Direct exposure- 67% (64/96) live births (95% CI: 56.3, 76.0), 15% (14/96) miscarriages (95% CI: 8.2, 23.2), and 19% (18/96) therapeutic terminations (95% CI: 11.5, 28.0) among the 96 women. (General population rates live births occurred in 67%, miscarriages in 17%, and therapeutic termination in 16%) • Indirect exposure resulted in 90% live births (9/10) and 10% miscarriage (1/10)	NR	**Overall Attrition Rate, %:** 27 **ITT Analysis:** N/A **Quality Rating:** Fair

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kwon, 2003 **Country, Setting:** USA, multicenter (FDA's MedWatch program) **Funding:** US Food and Drug Administration **Research Objective:** To describe adverse event reports of heart failure after TNF antagonist therapy **Study Design:** Database analysis; AERS **Overall N:** 47 cases **Study Duration:** long-term therapy	**Inclusion Criteria:** •Pts who reported heart failure as an adverse event while taking ETA or INF therapy in US since licensure of drugs until February 2002 •New onset failure and exacerbation of preexisting heart failure included **Exclusion Criteria:** • Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded	**Interventions, dose:** **D1:** New Onset Heart Failure without risk factors **D2:** New Onset Heart Failure with risk factors **D3:** Heart failure exacerbation ETA: any INF: any **N:** NR **Mean age, yrs:** **D1:** 59 **D2:** 67 **D3: 70** **Sex, % female:** **D1:** 74 **D2:** 42 **D3: 44** **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** **D1:** 8 **D2:** 10 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR **%ETA:** **D1:** 12 **D2:** 14 **D3:** 3 **%INF:** **D1:** 7 **D2:** 5 **D3:** 6	• 38 pts (81%) developed new-onset heart failure • 9 (19%) experienced heart failure exacerbation of which: 19 pts had no documented risk factors, 10 pts were under age 50 • Of pts under 50, after cessation of TNF antagonist therapy 3 pts experienced complete resolution of heart failure, 6 pts showed improvement, and 1 patient died	NR	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schaible et al., 2000 **Country, Setting:** US, safety database of efficacy trials **Funding:** Centocor **Research Objective:** Long term safety of infliximab **Study Design:** Observational **Overall N:** 963 **Study Duration:** Up to 3 yrs	**Inclusion Criteria:** 12 clinical trials **Exclusion Criteria:** NR	**Interventions:** Infliximab N:963 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Treatment resistant %:** NR **Patients with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	• Acute infusion reactions (headache, fever, chills, urticaria, chest pain: infliximab 17% versus placebo 7%; *P* = NR • 0.5% of infliximab pts had severe infusion reactions • Less than 2% discontinued treatment because of infusion reactions **Infections:** • Infliximab 26% over 27 wks of follow-up versus placebo 16% over 20 wks of follow-up) • Incidence of serious infections per patient-yr infliximab 0.064 versus placebo 0.114	See outcomes	**Overall Attrition Rate, %:** **ITT Analysis:** Not applicable **Quality Rating:** Fair

Evidence Table 8. KQ3. Rheumatoid arthritis trials: harms, tolerability, adverse effects, or adherence (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schiff et al., 2006 **Country, Setting:** mulitnational Multicenter **Funding:** Abbott Labs **Research Objective:** To assess safety of adalimumab in global clinical trials and postmarketing surveillance among pts with rheumatoid arthritis **Study Design:** Retrospective cohort study; postmarketing surveillance **Overall N:** 10,050 (12506 PY) **Study Duration:** Varied	**Inclusion Criteria:** • Pts from RCTs, open label extensions, and two phase IIIb open label trials were and post-marketing spontaneous reports of adverse events in US **Exclusion Criteria:** NA	**Interventions, dose:** NR **N:** 10,050 **Mean age, yrs:** NR **Sex, % female:** NR **Race, % white:** NR	**Mean disease duration, yrs:** NR **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** NR **Corticosteroid use, %:** NR **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** NR	**Rates per 100 PY:** • TB: 0.27 • Histoplasmosis: 0.03 • Demyelinating diseases: 0.08 • Lymphoma: 0.12 • SLE/lupus-like syndrome: 0.10 • Congestive heart failure: 0.28	NA	**Overall Attrition Rate, %:** NA **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 **Country, Setting:** US, Multicenter (National Data Bank for Rheumatic Diseases) **Funding:** Centocor, Inc **Research Objective:** To determine frequency of heart failure in pts with RA, and to determine its predictors, particularly use of anti-TNF therapy **Study Design:** Retrospective cohort study **Overall N:** 15,739 (RA plus OA subjects) **Study Duration:** 2 years	**Inclusion Criteria:** • Participation in National Data Bank for Rheumatic Diseases study of outcomes of arthritis; patient at participating rheumatology clinic **Exclusion Criteria:** • NR	**Interventions, dose:** **D1:** Any Anti-TNF **D2:** INF **D3:** ETA **D4:** No anti-TNF **D5:** Total Population Overall ETA INF **N:** NR **Mean age, yrs:** **D1:** 60 **D2:** 61.5 **D3:** 56.7 **D4:** 61.5 **D5:** 51 **Sex, % female:** **D1:** 78 **D2:** 77 **D3:** 80 **D4:** 76 **D5:** 77 **Race, % white:** **D1:** 95 **D2:** 96 **D3:** 92 **D4:** 92 **D5:** 94	**Mean disease duration, yrs:** **D1:** 14.2 **D2:** 13.8 **D3:** 15.2 **D4:** 15.5 **D5:** 14.9 **TJC, mean:** NR **SJC, mean:** NR **DMARD use, %:** **Overall: 86** **PRE use (%)** **D1:** 47 **D2:** 49 **D3:** 39 **D4:** 33 **D5:** 39 **MTX naive, %:** NR **Txt resistant %:** NR **Pts with Early RA (≤3 yrs):** NR **Baseline DAS, mean:** **D1:** 3.7 **D2:** 3.7 **D3:** 3.6 **D4:** 3.5 **D5:** 3.6	• 461 cases of heart failure in 13,171 pts with RA (overall risk of 3.5%); after adjusting for demographic characteristics the risk was 3.9% (95% CI,= 3.4% to 4.3%) • Among all cases of heart failure, pts receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI,-1.9 --0.5%) • Overall, adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in remaining pts (*P* = 0.03) • Frequency of heart failure was 5.2% in men and 3.0% in women • In examining incident cases of heart failure in pts under age 50, no increase was found (0/1569 pts using anti-TNF vs. 3/1401 not using anti-TNF therapy)	NR	**Overall Attrition Rate, %:** NR **ITT Analysis:** NA **Quality Rating:** Fair

Evidence Table 11. KQ4. Rheumatoid arthritis trials: benefits and harms for selected subpopulations (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 (continued)			**MTX use:** **D1:** 67 **D2:** 76 **D3:** 44 **D4:** 47 **D5:** 56			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Bathon et al., 2006 United States, supported by Immunex Corporation, wholly owned subsidiary of Amgen, Inc., and by Wyeth, Collegeville, PA, USA **Study Design:** Pooled analysis Aims of the Review: To evaluate safety and efficacy of ETA treatment in elderly (age 65 yrs) and younger adult subjects (age < 65 yrs) with RA Number of Pts: 1,353 2 longterm extensions (N = 1,049)	**Studies included:** • RCTs • Weinblatt et al., 1999 • Moreland et al., 1999 • Bathon et al., 2000 • Keystone et al., 2004 **Characteristics of included studies:** • 4 RCTs and 2 long-term observational extensions • Dosing arms included ETA 25 mg twice weekly vs placebo, MTX • Studies 1 and 2 were LRA extensions and conducted in DMARD-failure RA subjects and MTX-incomplete responders, respectively • Study 3, early study compared MTX and ETA therapy • Study 4 included subjects who had failed at least 1 DMARD other than MTX • Characteristics of included	• Elderly subjects had similar or less response to treatment than younger subjects (ACR 20, ACR 50, ACR 70) • Elderly ETA-treated subjects had similar or slightly lower, ACR responses compared with younger ETA treated subjects across all timepoints • ACR 20/50/70 responses after 6 mos of ETA treatment were 70%/45%/15% for elderly subjects and 65%/39%/15% in younger subjects • For LRA extension, ACR responses were similar between age groups • ACR 20/50/70 responses were 70%/47%/11% in elderly subjects and 75%/53%/29% in younger subjects after 72 mos ETA treatment in extension • Study 3, ACR responses tended to be lower in elderly group compared with younger group in both MTX and ETA treatment arms • After 24 mos ETA treatment, ACR 20/50/70 responses were 54%/22%/14% for elderly ERA subjects	• Rates of serious adverse events tended to be higher in elderly than younger subjects; however, rates of safety events observed in elderly ETA-treated subjects did not exceed rates in elderly placebo or MTX-treated subjects			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		populations: • Adults with RA • 14% to 22% across treatment arms were elderly **Characteristics of interventions:** ETA (25 mg) twice weekly and comparison (placebo or MTX)	and 77%/54%/32% for younger subjects			

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Bathon et al., 2006 United States; Supported by Immunex Corporation, wholly owned subsidiary of Amgen, Inc., and by Wyeth, Collegeville, PA, USA (continued)		• In Study 3 extension, ACR 20/50/70 responses were 60%/40%/19% in elderly subjects and 79%/58%/40% in younger subjects after 48 mos of treatment in extension • In Study 4, elderly subjects had greater separation between efficacy responses achieved with ETA and MTX versus either monotherapy compared with younger subjects • After 12 mos treatment with combiation ETA and MTX, ACR 20/50/70 responses were 77%/68%/39% • For both age groups, treatment with ETA resulted in improved efficacy and function compared with control treatment, and combination therapy with ETA plux MTX resulted in greater efficacy than eitehr ETA or MTx used alone • Efficacy responses of elderly subjects were sustained for up to 6 yrs • Radiographic progression, M-SHS after 1 year of treatment was lower in subjects treated with both ETA and MTX compared with subjects treated with either agent used alone and this pattern was similar in both age groups				

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Fleischmann et al., 2003, multinational, Immunex corporation (last author, George Spencer-Green, is full-time employee at Immunex) **Study Design:** Pooled analysis **Aims of the Review:** To compare safety and efficacy of ETA in pts with RA who were ≥ 65 yrs to those < 65 yrs in open-label and RCTs **Number of Pts:** 1,128 Improvement in signs and symptoms was assessed for those who were able to receive ETA continuously for at least 1 yr (n=1059)	**Studies included:** All 9 are not clearly identified; 4 that are: • Moreland et al., 1997 • Weinblatt et al., 1999 • Moreland et al., 1999 • Bathon et al., 2000 **Characteristics of included studies:** • 4 double-blind RCT • 5 open-label trials • 8 trials evaluated pts with long-standing disease who failed previous DMARD therapy and 1 evaluated pts with recent onset RA (≤ 3 yrs) who never received MTX **Characteristics of included populations:** • Adults with RA • 83% < 65 yrs old • 17% > 65 • 8 trials evaluated pts with long-standing disease who failed previous DMARD therapy and 1 evaluated pts with recent onset RA (≤ 3 yrs) who never received MTX **Characteristics of interventions:** • ETA twice weekly for all pts	• 17% of pts were ≥65 yrs old at time of study entry At 1 yr: • 69% of pts < 65 and 66% of pts ≥ 65 met ACR20 (P = 0.480) • 40% of pts ≥ 65 met ACR50 and 17% met ACR70, compared to 44% and 20% for < 65 group, respectively (P values NR) • Subgroup analysis of those with early RA showed no difference in ACR20 response between those ≥ 65 and those < 65 (51% vs. 58%, P = 0.265) • Same for subgroup of those with late RA (58% vs. 63%, P = 0.321)	• Any infection (< 65 vs. ≥ 65: 1.56 events/PY vs. 1.36, P = 0.036) • Injection site reactions (4.31 events/PY vs. 1.47, P < 0.001), headaches (0.37 vs. 0.18, P < 0.001), and rhinitis (0.19 vs. 0.10, P = 0.006) occurred at higher rates in younger pts (< 65) • Rates of other AEs were comparable between 2 groups: rash, diarrhea, nausea, and abdominal pain	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** NR **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Poor		

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995, Multinational, NIH grants **Study Design:** Systematic review **Aims of the Review:** To evaluate whether age and renal impairment affect rate of side effects or efficacy of MTX in RA pts **Number of Pts:** 496	**Studies included:** 11 MTX clinical trials: • Weinblatt, et al., 1985 • Furst, et al., 1989 • Schmid, et al., unpublished study • Williams, et al., 1985 • Wilke, et al., unpublished study • Weinblatt, et al., 1990 • Williams, et al., 1992 • Suarez et al 1988 • Morassut, et al., 1989 • Hamdy, et al., 1987 • Bell, et al., 1988. **Characteristics of included studies:** • RCTs • Placebo control or comparative trial • MTX as 1 treatment arm • Adult RA pts • Trial completed (although not necessarily published) by end of 1991, and trial 12 weeks or longer (to end or to crossover) **Characteristics of included populations:** • Adult RA pts treated with MTX **Characteristics of interventions:** • All pts treated with MTX (doses NR)	• Study compares subgroups of pts treated with MTX • Neither age nor renal impairment had any effect on efficacy of MTX • Odds of major clinical improvement by age were 1.0 for < 60 yr old group (referent), 1.4 (0.7, 2.6) for 60-64, 1.0 (0.5, 2.2) for 65-69, and 0.7 (0.3, 1.7) for ≥ 70 (efficacy regression analyses controlled for age group, sex, renal function, study of origin, initial tender joint count, grip strength, steroid dose, NSAID used at baseline, and maximum MTX dose) • Odds of major clinical improvement by creatinine clearance were 1.0 for ≥99.8 ml/min (referent), 0.6 (0.3, 1.0) for 78.6-99.9 ml/min, 1.1 (0.6, 2.0) for 62.6-78.6 ml/min, and 1.0 (0.5, 2.1) for < 62.6 ml/min • Age did not affect rate of toxicity. Those in the oldest group were not at a higher risk of side effects from MTX	• No significant difference for liver toxicity between different creatinine clearance groups 1.0 (referent) 1.8 (1.0, 3.4) 1.2 (0.6, 2.3) 1.8 (0.8, 3.7) • Toxicity regressions adjusted for age, sex, creatinine clearance, baseline NSAID use (yes/no), maximum MTX dose, and study of origin	**Publication Bias Assessed:** NR **Heterogeneity Assessed:** Yes **Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** Yes **Quality Rating:** Fair		

Evidence Table 12. KQ4. Rheumatoid arthritis systematic reviews: benefits and harms for selected subpopulations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995 Multinational NIH grants (continued)		• Pts with renal impairment had worse toxicity scores and a higher overall rate of toxicity; mean worst toxicity scores were 2.2 (referent), 3.0 (*P* = < 0.05), 2.9 (*P* = < 0.05), and 3.3 (*P* = < 0.01) for ≥ 99.8 ml/min (referent), 78.6-99.9 ml/min, 62.6-78.6 ml/min, and < 62.6 ml/min. groups respectively; Rates of any toxicity were 55%, 64%, 65%, and 72% for groups respectively (*P* NR) • They report that pts with renal impairment were at higher risk of severe toxicity and for respiratory toxicity; however, 95% CI crosses 1 for all but 1 group; for severe toxicity odds for 4 groups were 1.0 (referent), 3.0 (0.7, 13.0), 5.7 (1.4, 23.6), and 4.5 (0.9, 22.6); for respiratory toxicity, 1.0 (referent), 5.9 (0.6, 57.0), 5.6 (0.5, 60.4), and 6.9 (0.5, 88.8)				

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Appendix G: Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the U.S. Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer-based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Observational Studies:

Assessment of Internal Validity

1. Were both groups selected from the same source population?

2. Did both groups have the same risk of having the outcome of interest at baseline?

3. Were subjects in both groups recruited over the same time period?

4. Was there any obvious selection bias?

5. Were ascertainment methods adequate and equally applied to both groups?

6. Was an attempt made to blind the outcome assessors?

7. Was the time of followup equal in both groups?

8. Was overall attrition high ($\geq$ 20%)?

9. Was differential attrition high ($\geq$ 15%)?

10. Did the statistical analysis consider potential confounders or adjust for different lengths of followup?

11. Was the length of followup adequate to assess the outcome of interest?

Appendix H: Characteristics of Studies With Poor Internal Validity

Study	Design	Sample Size	Intervention	Reason for Exclusion
†Bathon et al., 2006[1]	Pooled data analysis	2,402	Etanercept	Selection bias
de Nijs et al., 2001[2]	Cross-sectional	410	Corticosteroids	Selection bias
Faarvang et al., 1993[3]	RCT	91	Hydroxychloroquine Sulfasalazine	No ITT analysis; high LTF
†Fleischmann et al., 2003[4]	Pooled data analysis	1128	Etanercept	Selection bias
‡Flendrie et al, 2003[5]	Retrospective cohort study	230	Adalimumab Etanercept Infliximab	High differential LTF; no ITT analysis
Flendrie et al., 2005[6]	Observational	162	Leflunomide infliximab	High LTF; selection bias
Hansen et al., 1999[7]	RCT	102	DMARDs Prednisolone	High attrition; no ITT analysis
‡Langer et al., 2003[8]	Post-marketing surveillance	454	Anakinra	No comparison group; no ITT analysis
‡Moreland et al., 2006[9]	Pooled retrospective analysis	714	Etanercept	High LTF; completers analysis only
‡O'Dell et al., 2006[10]	Prospective open-label study	119	Etanercept Hydroxychloroquine Sulfasalazine	Bias due to poor ITT design
‡Svensson et al, 2003[11]	Open-label RCT	245	Methotrexate Prednisolone Sulfasalazine	High post-randomization exclusions; high differential LTF

ITT, intention to treat; LTF, loss to followup; RCT, randomized controlled trial.
†Included for subgroups
‡Rated fair for adverse events

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Appendix I: Clinical and Self-Reported Scales and Instruments Commonly Used in Studies of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis

Introduction

This appendix provides a brief overview of the various scales and self-reported measures that investigators used to assess outcomes in all the studies reviewed in this systematic review. The main outcome categories involve radiologic assessments of joint damage (erosion or narrowing) and various instruments that patients or subjects used to report on functional capacity or quality of life; the latter fall into two groups, one related to general health measures and one related to condition- or disease-specific instruments. General measures used in rheumatoid and psoriatic arthritis studies are described first; then the disease-specific measures used in rheumatoid and psoriatic arthritis studies are described separately.

Radiographic Measures

Radiographic assessment of joint damage in hands (including wrists) or both hands and feet are critical to clinical trials in rheumatoid arthritis. The damage can be both joint space narrowing and erosions, and the underlying construct is sometimes referred to as radiographic progression (i.e., changes, whether positive or negative) as detected by radiography and interpretation. Several approaches exist, but the two commonly used are the Sharp Score (and variants) and the Larsen Score. These and other scoring methods have recently been reviewed by Boini and Guillemin;[1] additional citations or sources are given in the brief descriptions below.

Sharp Score and Sharp/van der Heijde Score

The Sharp Score is a means of evaluating joint damage in joints of the hands, including both erosion and joint space narrowing.[2] Although it has undergone modifications since its introduction, the version proposed in 1985 has become the standard approach. In this method, 17 joint areas in each hand are scored for erosions; 18 joint areas in each hand are scored for joint space narrowing. The score per single joint for erosions ranges from 0 to 5 and for joint space narrowing from 0 to 4. In both cases, a higher score is worse. Erosion scores range from 0 to 170 and joint space narrowing scores range from 0 to 144. Thus, the "total Sharp Score" is the sum of the erosion and joint space narrowing scores, or 0 to 314.

The Sharp/van der Heijde (SHS) method, introduced in 1989, overcame one drawback to the Sharp Score, namely its focus on only hands, given that feet can also be involved early in rheumatoid arthritis. Therefore, the SHS method was developed to take account of erosions and joint space narrowing in both hands and feet.[3,4] As with the Sharp Score, higher scores reflect worse damage. Erosion is assessed in 16 joints in each hand and 6 joints in each foot. Each joint is scored from 0 to 5 with a maximal erosion score of 160 in the hands and 120 in the feet. Joint space narrowing and subluxation are assessed in 15 joints in the hands and 6 joints in the feet.

Each joint is scored from 0 to 4 with a maximal score of 120 in the hands and 48 in the feet. The erosion and joint space narrowing scores are combined to give a total SHS score with a maximum of 448 (weighted toward hands because more joints are scored).

Numerous variants on the Sharp or SHS scores have been developed, differing subtly in terms of the numbers of joints measured and other details.[5] Generally, all the Sharp methods are very detailed assessments and the approach, although reliable and sensitive to change, is considered time-consuming and tedious. For a speedier approach, Larsen and colleagues developed a simpler approach.

Larsen Scale for Grading Radiographs

The Larsen Scale is an overall measure of joint damage, originally devised in the 1970s and updated most recently in the late 1990s.[6-10] It produces both a score for each joint (hands and feet) and an overall score that reflects measurement and extent of joint damage. Scores range from 0 ("normal conditions," i.e., intact bony outlines and normal joint space) to 5 ("mutilating abnormality," i.e., original bony outlines have been destroyed), so higher scores reflect greater damage. Scores can range from 0 to 250.

General Health Measures

Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ) is a widely used self-report measure of functional capacity; it is a dominant instrument in studies of patients with arthritis (particularly trials of drugs in patients with rheumatoid arthritis), but it is considered a generic (not disease-specific) instrument. Detailed information on its variations, scoring, etc., can be found at www.chcr.brown.edu/pcoc/EHAQDESCRSCORINGHAQ372.PDF (accessed for this purpose 1/18/2007) or www.hqlo.com/content/1/1/20 (accessed for this purpose 1/18/2007) and in the seminal reports by Fries et al.[11] and Ramey et al.[12]

The full, five-dimension HAQ consists of four domains: disability, discomfort and pain, toxicity, and dollar costs, plus death (obtained through other sources). More commonly, "the HAQ" as used in the literature refers to the shorter version encompassing the HAQ Disability Index (HAQ-DI), the HAQ pain measure, and a global patient outcome measure. The HAQ-DI is sometimes used alone.

The HAQ-DI, with the past week as the time frame, focuses on whether the respondent "is able to…" do the activity and covers eight categories in 20 items: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The four responses for the HAQ-DI questions are graded as follows: without any difficulty = 0; with some difficulty = 1; with much difficulty = 2; and unable to do = 3. The highest score for any component question in a category determines the category score. The HAQ-DI also asks about the use of aids and devices to help with various usual activities. Two composite scores can be calculated, one with and one without the aids/devices element; both range from 0 to 3.

The HAQ pain domain is measured on a doubly-anchored horizontal visual analog scale (VAS) of 15 cm in length; one end is labeled "no pain" (score of 0) and the other is labeled "very severe pain" (score of 100). Patients mark a spot on the VAS, and scores are calculated as the

length from “no pain” in centimeters (cm) multiplied by 0.2 to yield a value that can range between 0 and 3.

With respect to interpretation, HAQ-DI scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.

The HAQ global health status scale measures quality of life (essentially, as how the patient is feeling) with a 15 cm doubly-anchored horizontal VAS scored from 0 (very well) to 100 (very poor).

Medical Outcomes Study Short Form 36 Health Survey

The Medical Outcomes Study Short Form 36 Health Survey (SF-36) is an internationally known generic health survey instrument. Information can be found at www.sf-36.org/tools/sf36.shtml (accessed for this purpose 2/18/2007) and in a large number of articles documenting its psychometric properties.[13-19] It comprises 36 items in eight independent domains tapping functioning and well-being: physical functioning, role-physical, bodily pain, and general health in one grouping (physical health) and vitality, role-emotional, social functioning, and mental health in another grouping (mental health). The SF-36 provides a separate scale score for each domain (yielding a profile of health) and two summary scores, one for physical health and one for mental health. Each scale is scored from 0 to 100 where higher scores indicate better health and well-being.

A “version 2” of the SF-36 was introduced in the late 1990s to correct some drawbacks in formatting, wording, and other issues and to update the norm-based scoring with 1998 data. It can be fielded in two versions varying by recall period: 4-week recall (the usual approach) and 1-week recall (acute). More recently, it has been tested and used for computer adaptive testing according to item response theory principles.

EuroQol EQ-5D Quality of Life Questionnaire

A third generic quality-of-life instrument is the EuroQol EQ-5D Quality of Life Questionnaire, typically known just as the EQ-5D. More information can be found at http://www.euroqol.org/ (accessed for this purpose 1/18/2007) and in key descriptive articles,[20] one of which is about patients with rheumatoid arthritis.[21]

The EQ-5D covers health status in five domains (three questions each): mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. It is intended for self-response but can be used in other administration modes. Each item can take one of three response levels – no problems, some moderate problems, extreme problems – identified as level 1, 2, or 3, respectively. This yields a profile of one level for each of the five domains; this is essentially a five-digit number, and no arithmetic properties attach to these values. Users can convert health states in the five-dimensional descriptive system into a weighted health state index by applying scores from EQ-5D "value sets" elicited from general population samples to the profile pattern (e.g., 1, 2, 3, 3, 1).

The EQ-5D also has a global health VAS scale (20 cm) scored from 0 to 100.

Rheumatoid Arthritis Measures

American College of Rheumatology 20/50/70

The American College of Rheumatology (ACR) criteria are concerned with *improvement* in counts of tender and swollen joints and several domains of health.[22] A principal aim of these criteria is use in studies (particularly trials) of drugs for rheumatoid arthritis. More information can be found at www.rheumatology.org/publications/response/205070.asp and www.hopkins-arthritis.som.jhmi.edu/edu/acr/acr.html#remis_rheum (both accessed for this purpose 1/18/2007). Originally these latter involved patient assessment, physician assessment, erythrocyte sedimentation rate, pain scale, and functional questionnaire.

Today, based on work done in the mid 1990s,[23] values for clinical trial patients are defined as improvement in both tender and swollen joint counts and in three of the following: patient's assessment of pain; patient's global assessment of disease activity, patient's assessment of physical function (sometimes referred to as physical disability), the physician's global assessment of disease activity, and acute phase reactant (C-reactive protein, or CRP). The 20, 50, or 70 designations (sometimes called the ACR Success Criteria) refer to improvements in percentage terms to 20 percent, 50 percent, or 70 percent in the relevant dimensions. A physician's global assessment of 70 percent improvement is considered remission.

Thus, patients are said to meet ACR 20 criteria when they have at least 20 percent reductions in tender and swollen joint counts and in at least three of the domains. ACR 50 and ACR 70 criteria are defined in a manner similar to that for ACR 20, but with improvement of at least 50 percent and 70 percent in the individual measures, respectively. The table illustrates, in a study context, how a patient might be said to have an ACR 50 response.

Outcomes Measured	Baseline	Endpoint
Tender joints count *	12	6
Swollen joints count *	8	3
Patient's pain score*	60	20
Patient's physical function (disability) score	80	60
Physician's global activity score*	50	20
C-reactive protein*	3.6	1.4

* At least 50 percent improvement between baseline and endpoint measurements.

Ritchie Articular Index

This is a long-standing approach to doing a graded assessment of the tenderness of 26 joint regions, based on summation of joint responses after applying firm digital pressure.[24] Four grades can be used: 0, patient reported no tenderness; +1, patient complained of pain; +2, patient complained of pain and winced; and +3, patient complained of pain, winced, and withdrew. Thus, the index ranges from 0 to 3 for individual measures and 0 to 78 overall, with higher scores being worse tenderness.

Certain joints are treated as a single unit, such as the metacarpal-phalangeal and proximal interphalangeal joints of each hand and the metatarsal-phalangeal joints of each foot. For example, the maximum score for the five metacarpal-phalangeal joints of the right hand would be 3, not 15. No weights are used for different types of joints (e.g., by size), because the issue is one of measuring changes (improvements) in tenderness; this is especially relevant for rheumatoid arthritis.

Disease Activity Score

The Disease Activity Score (DAS) is an index of disease activity first developed in the mid 1980s. The history of its development and current definitions, scoring systems, and other details can be found at http://www.das-score.nl/www.das-score.nl/ (accessed for this purpose 1/19/2007) and in recent articles.[4,25] The DAS originally included the Ritchie Articular Index (see above), the 44 swollen joint count, the erythrocyte sedimentation rate, and a general health assessment on a VAS. A cut-off level of the DAS of 1.6 is considered to be equivalent with being in remission.

More recently, an index of RA disease activity using only 28 joints – the DAS 28 – has been developed, focusing on joint counts for both tenderness (TJC) and swelling (SJC). It also uses either the patient's or a physician's global assessment (PGA) of disease activity (on a 100 mm VAS) and the erythrocyte sedimentation rate (ESR) or C-reactive protein. The formula for calculating a DAS 28 score is as follows: = $(0.56 \times TJC^{1/2}) + (0.28 \times SJC^{1/2}) + (0.7 \times \ln [ESR]) + (0.014 \times PGA [in mm])$. Numerous formulas to calculate a variety of DAS and DAS 28 scores exist (see the website above), such as when a global patient assessment of health is unavailable.

The DAS 28 yields a score on a scale ranging from 0 to 10. A DAS 28 of 2.6 is considered to correspond to remission; a DAS 28 of 3.2 is a threshold for low disease activity; and a DAS 28 of more than 5.1 is considered high disease activity

Psoriatic Arthritis Measures

Psoriatic Arthritis Response Criteria

The psoriatic arthritis response criteria (PsARC) was initially designed for use in a clinical trial that compared sulphasalazine to placebo in the setting of the Veterans Administration.[26] It has since been used as the primary or secondary outcome in all the studies that examined biologics versus placebo in the treatment of PsA. The PsARC includes improvement in at least two of the following, one of which had to be a joint count, and no worsening of any measure: tender or swollen joint count improvement of at least 30%, patient global improvement by one point on a five-point Likert scale, or physician global improvement on the same scale.[26]

American College of Rheumatology 20

The ACR 20 (American College of Rheumatology 20 percent response) is the other outcome that is used as the primary outcome in clinical trials of biologics. The measurement is similar to that of the ACR 20 used for rheumatoid arthritis with modifications made that increased the number of joints tested from 68 tender and 66 swollen to 76 and 78, respectively, with the addition of distal interphalangeal joints of the feet and carpometacarpal joints of the hands.[26] The outcomes from the ACR 20 are generally poorer when compared to the PsARC due to the variation in items measured; this is due in part to the need to see an improvement in tender *and* swollen joints in the ACR 20 versus an improvement in tender *or* swollen joint counts.

The Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) was developed to measure the effect of treatments in clinical trials of psoriasis and is utilized to capture the psoriasis component found in psoriatic arthritis. The scale was originally published in 1978 in a trial of 27 patients suffering from severe chronic generalized psoriasis that were treated with Ro 10-9359, a retinoic acid derivative.[27] The PASI is a composite index of disease severity incorporating measures of scaling, erythema, and induration, and it is weighted by severity and affected body surface area. A PASI >12 defines severe, PASI 7-12 moderate, and PASI <7 mild psoriasis.

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