AHRQ Comparative Effectiveness Review Surveillance Program

CER #55:
Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Original release date: **April, 2012**

Surveillance Report: **May, 2013**

Key Findings:

- For Key Question 1, conclusion on comparative effectiveness of biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is probably out of date. Conclusions on comparative effectiveness of biologic DMARDs vs oral DMARDs, biologic DMARD combinations, and early RA strategies are possibly out of date.
- For Key Question 2, on functional capacity, conclusions are still valid.
- For Key Question 3, on safety, conclusions on combinations which include corticosteroids are out of date; conclusions on biologic DMARDs are probably out of date.
- For Key Question 4, on subgroups, conclusions are up to date, with the exception that one new meta-analysis found tocilizumab + methotrexate (MTX) combo did not increase risk of tuberculosis (TB) reactivation.

Summary Decision

This CER's priority for updating is **High**

Authors:
Margaret Maglione, MPP
Susanne Hempel, PhD
Sydne Newberry, PhD
Aneesa Motala, BA
Roberta Shanman, MS
Paul Shekelle, MD, PhD

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

S. Louis Bridges, Jr., MD, PhD
University of Alabama

Katrina Donahue, MD, PhD
RTI-UNC Evidence-based Practice Center

Marian McDonagh, Pharm D
Oregon Health Sciences University

Christopher Ritchlin, MD, MPH
University of Rochester

Contents

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

1. Introduction

Comparative Effectiveness Review (CER) #55, Drug Therapy for Rheumatoid Arthritis in Adults: An Update, was released in April 2012.[1] It was therefore due for a surveillance assessment in October, 2012. At that time, we contacted experts involved in the original CER to get their opinions on whether the conclusions had changed and whether the CER needed to be updated again. We conducted an electronic literature search update. We also conducted searches of the US Food and Drug Administration (FDA) and UK Medicines and Healthcare Regulatory Agency (MHRA) databases for safety alerts on medications.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original CER, we conducted a limited literature search. The limited search included the five major medical journals (Annals of Internal Medicine, Journal of the American Medical Association, British Medical Journal, Lancet, and the New England Journal of Medicine), as well as these specialty journals: Rheumatology, Annals of Rheumatic Diseases, Arthritis and Rheumatism, Arthritis Research Therapy, Clinical Rheumatology, and Journal of Rheumatology. Our search covered the time period January 2011 to October 2012; the original CER update searched through January 2011. We conducted this search simultaneously with an update search for CER #54, on treatment of psoriatic arthritis.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER. We screened the titles and abstracts and obtained full text copies of publications accordingly.

2.3 Expert Opinion

We shared the conclusions of the original report with nine experts in the field, including the original project leader and all original technical expert panel members, for their assessment of the need to update the report and their recommendations of any relevant new studies. Four subject matter experts, including the CER author, responded. Appendix C shows the questionnaire matrix used.

2.4 Check for qualitative and quantitative signals

After abstracting details and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

We constructed a summary table that included the key questions, the original conclusions, the findings of the new literature search, the expert assessments, and any FDA or MHRA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 667 titles on treatment of psoriatic or rheumatoid arthritis. In addition to the electronic database searches, we followed up suggestions from the topic experts for studies not already included in the original report. We reference-mined articles that met inclusion criteria as well as systematic reviews identified by the literature searches to identify additional articles that may have been published since the publication of the report. After title and abstract review, we further reviewed the full text of 130 journal articles on rheumatoid arthritis. The remaining titles were rejected because they studied psoriatic arthritis or they clearly did not meet inclusion criteria for any of the review questions

Of the 130 articles that went through full text screening, 93 were rejected because they did not meet the inclusion criteria of the original report (trial of one drug versus placebo, open label extension using only one drug, N < 100, non-systematic review, commentary, same study published in more than one journal, etc) or were new publications of studies already included in the CER (ten articles). As per the original CER, four studies that met other inclusion criteria but were judged to be of poor quality were excluded. Because of the high number of remaining articles, we also rejected five cohort studies with less than 5,000 patients. The 18 remaining articles were abstracted into an evidence table (Appendix B) for this assessment.[4-21]

3.2 Expert Opinion

The lead author of the CER and three other experts completed the questionnaire matrix. Their responses are summarized in Table 1 below. In sum, several experts felt that the conclusions on the comparative effectiveness of the various biologic DMARDs were out of date.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update.

Eighteen large studies were abstracted. Three were active-controlled clinical trials, six were systematic reviews with meta-analyses, and nine were cohort studies of at least 5,000 patients. The majority studied the comparative safety of different biologic DMARDs or non-inferiority of a specific biologic DMARD compared to the others.

Our search of FDA and MHRA databases identified several new warnings for biologic DMARDs. In addition, in November 2012, tofacitinib became the first Janus kinase (JAK) inhibitor approved by the FDA for rheumatoid arthritis. This drug is not a biologic. There are at least five RCTs of this drug which report both ACR20 and DAS28 response; these RCTs could be incorporated into an updated comparative effectiveness meta-analysis.

Three of the four experts felt the conclusions on comparative safety and effectiveness of biologic DMARDs, particularly tumor necrosis factor (TNF) inhibitors, were possibly out of date. The results of our limited literature search support their opinion. Our literature search also identified studies that may make other conclusions out of date. Thus, we have classified this CER as a **high** priority for update.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?				
Oral DMARD vs. Oral DMARD				
Leflunomide vs. MTX: No differences in ACR 20 or radiographic responses. (Low) Leflunomide vs. sulfasalazine: Mixed ACR response rates. (Insufficient) Leflunomide vs. sulfasalazine: No differences in radiographic changes. (Low) Sulfasalazine vs. MTX: No differences in ACR 20 response, disease activity scores and radiographic changes. (Moderate)	No new head to head trials of oral DMARDs identified.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Oral DMARD Combinations vs. Oral DMARD				
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: In patients with early RA, no differences in ACR 20 response rates or radiographic changes. (Moderate) Oral DMARD plus prednisone vs. oral DMARD: Mixed results for disease activity. (Insufficient) Less radiographic progression in patients on DMARD plus prednisone. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints (Low)	No trials of oral DMARD combos vs oral DMARD monotherapy identified.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Biologic DMARDs vs. Biologic DMARDs				
Abatacept vs. Infliximab: Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. (Low) Biologic vs. biologic (Mixed treatment comparisons): No significant differences in disease activity (ACR 50) in MTC analyses	A new systematic review designed to investigate the non-inferiority of abatacept[16] showed abatacept +MTX is superior to MTX alone and comparable to the other biologic DMARDs in ACR50 and DAS28 response. Another meta-analysis[18] reported that certolizumab is superior to infliximab,	See Key Question 3 on adverse events.	Three experts feel the conclusion is probably out of date. One expert did not know.	Conclusion is probably out of date, per expert opinion and some new evidence.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
patients resistant to MTX. (Low) Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. (Low) Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. (Low)	Certolizumab was equivalent to golimumab and tocilzumab in ACR20 response rate. A new RCT[21] reported equivalent ACR20 response rates with abatacept + MTX and adalimumab + MTX.			
Biologic DMARDs vs. Oral DMARDs				
Anti-tumor necrosis factor drugs vs. MTX: In patients with early RA, no clinically significant differences in clinical response between adilimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. (Moderate)	No new studies identified.	See Key Question 3 on adverse events.	Two experts feel the conclusion is still valid. One expert feels the conclusion may be out of date. One expert does not know.	Conclusion is possibly out of date, per opinion of one expert.
Biologic DMARD Combinations				
Biologic DMARD plus biologic DMARD vs. biologic DMARD: No additional benefit in disease activity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy (Low) Biologic DMARDs plus MTX vs. biologic DMARDs: Better improvements in disease activity from combination therapy of biologic DMARDs (adilimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. (Moderate) In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly	One RCT of etanercept + MTX vs etanercept alone reported significantly higher response rates on ACR20, ACR50, and ACR70 for the combo therapy group.[17]	See Key Question 3 on adverse events.	Two experts feel the conclusion is still valid. One expert feels the conclusion may be out of date. One expert does not know.	Conclusion is possibly out of date, per opinion of one expert who reported that several trials conducted in Japan should be published soon. New evidence supports prior conclusion on biologic DMARD plus MTX vs biologic

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
greater clinical remission, and less radiographic progression in the combination therapy group. (Low) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No difference in clinical response rates between etanercept plus sulfasalazine and etanercept monotherapy. (Low) Biologic DMARD plus MTX vs. MTX: Better clinical response rates from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. (High)				DMARD, but could increase the SOE (currently moderate).
Strategies in Early RA				
Two oral DMARDs plus prednisone vs. oral DMARD: In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. (Low) Three oral DMARDs plus prednisone vs. one oral DMARD: In patients on three oral DMARDs, improved ACR 50 response rates and disease activity scores. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints. (Low)	No new studies of 2+ oral DMARDs in combo were identified.	No issues identified.	Two experts feel the conclusion is still valid. One expert feels the conclusion may be out of date. One expert does not know.	Conclusion still valid.
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high dose prednisone vs. combination with infliximab: Less radiographic progression and lower disease activity scores from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy.	An RCT of rituximab + MTX vs MTX alone in MTX naive early RA patients[19] reported the combination therapy resulted in better outcomes on ACR20, ACR50, ACR70, and radiological measures of joint damage.		Three experts feel the conclusion is still valid. One expert does not know.	Conclusion possibly out of date due to new evidence on using biologic DMARD (rituximab) in MTX naïve early RA patients.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
However no difference in remission at 4 years. (Low)				
KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?				
Oral DMARD vs. Oral DMARD				
Leflunomide vs. MTX: No clinically significant difference for functional capacity. (Low) Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. (Low) Leflunomide vs. sulfasalazine: Greater improvement in functional capacity for leflunomide. (Low) Sulfasalazine vs. MTX: No differences for functional capacity.(Moderate)	No new head to head trials of oral DMARDs identified.	No issues identified.	Two experts feel the conclusion is still valid. Two experts do not know.	Conclusion still valid.
Oral DMARD Combinations vs. Oral DMARD				
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: No differences in functional capacity. (Moderate) Oral DMARD plus prednisone vs. oral DMARD: Greater improvement in functional capacity for one oral DMARD plus prednisone than for oral DMARD monotherapy. (Moderate) No difference in quality of life. (Low)	No trials of oral DMARD combos vs oral DMARD monotherapy identified.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Biologic DMARDs vs. Oral DMARDs				
Anti-tumor necrosis factor drugs vs. MTX: No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. (Low; Insufficient) Faster improvement in quality of life with etanercept than MTX. (Low)	No new studies identified.	See Key Question 3 on adverse events.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Biologic DMARD Combinations				
Biologic DMARD plus biologic DMARD vs. biologic DMARD: No additional benefit in functional capacity from combination of	No studies reported functional capacity outcomes.	See Key Question 3 on adverse events.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. (Low) Biologic DMARDs plus MTX vs. biologic DMARDs: In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life (Low) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. (Low) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No difference in functional capacity and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. (Low) Biologic DMARD plus MTX vs. MTX: Better functional capacity and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. (High for functional capacity, Moderate for quality of life)				
Strategies in Early RA				
Two oral DMARDs plus prednisone vs. oral DMARD: More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. (Low) Three oral DMARDs plus prednisone vs. one oral DMARD: In patients on three oral DMARDs, less work disability.(Low) Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high dose prednisone vs. combination with infliximab: Better functional ability and health-related	No new studies of 2+ oral DMARDs in combo were identified.	No issues identified.	Two experts feel the conclusion is still valid. Two experts do not know.	Conclusion still valid.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. (Low)				
KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?				
Oral DMARD vs. Oral DMARD				
Leflunomide vs. MTX: No consistent differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient) Leflunomide vs. sulfasalazine: No differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient) Sulfasalazine vs. MTX: No differences in tolerability; more patients stayed on MTX long term. (Low) Mixed results for specific adverse events. (Insufficient)	A new meta-analysis concluded that no oral DMARDs were associated with increased risk of malignancies.[6] A new cohort study[5] found that, compared to "other oral DMARDs" hydroxychloroquine was associated with lower risk of diabetes onset. There was no difference in diabetes risk for MTX.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion is possibly out of date if diabetes risk is a concern to stakeholders.
Oral DMARD Combinations vs. Oral DMARD				
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: Withdrawal rates attributable to adverse events higher with combination. (Low) Insufficient evidence for specific adverse events. (Insufficient) Oral DMARD plus prednisone vs. oral DMARD: No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. (Moderate) No differences in specific adverse events, except addition of corticosteroid may increase wound healing complications. (Low)	A case-control study reported that RA patients taking glucocorticoids (GCs) had higher rates of GI perforations than those taking oral or biologic DMARDs without GCs.[9] A cohort study of RA patients using GCs, oral DMARDs, and biologic DMARDs found prednisone associated with dose-dependent increased risk of cardiovascular events.[15] Another cohort study of elderly RA patients found a dose-response increased risk of non-	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion is out of date regarding tx combinations that include corticosteroids.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	serious infection among GC users.[11] A new meta-analysis[12] of 21 RCTs and 42 observational studies found GCs associated with increased risk of infections.			
Biologic DMARDs vs. Biologic DMARDs				
Abatacept vs. Infliximab: Discontinuation rates and severe adverse events higher with infliximab. (Low) Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. (Low) Risk for injection site reactions apparently highest with anakinra. (Low) Mixed results for specific adverse events. (Insufficient)	A new meta-analysis concluded that **no** biologic DMARDs were associated with increased risk of malignancies.[6] A new cohort study reported lower risk for hospitalized infection for abatacept, etanercept, adalimumab, and rituximab than infliximab.[8] Another cohort study reported higher risk for serious infections with infliximab compared to etanercept and adalimumab.[4] A new RCT reported greater dropout due to both any adverse event and serious adverse events with adalimumab + MTX compared to abatacept + MTX.[21]	Tocilzumab – October 2012 - FDA warning re hypersensitivity, anaphylaxis Infliximab – March 2013 - FDA warning re melanoma & merkel cell carcinoma – February 2011 - FDA warning re should not be taken with abatacept due to increased risk of infections Golimumab – Sept 2011 – FDA box warning re serious infections – Dec 2011 – FDA warning re demyelinating disorders – Aug 2012 – FDA warning re hypersensitivity	Two experts feel the conclusion is still valid. One expert feels the conclusion is out of date. One expert does not know.	Conclusion is probably out of date.
Biologic DMARDs vs. Oral DMARDs				
Anti-tumor necrosis factor drugs vs. MTX: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient)	A cohort study[5] reported that anti-TNFs were associated with lower risk of new onset diabetes than oral DMARDs. One cohort study[10] reported no difference in rates of venous thrombotic events between anti-TNFs and oral DMARDs. One cohort study[13] reported that anti-TNFs were associated with greater risk for septic arthritis than oral DMARDs. One cohort study[14] reported	Tocilzumab – October 2012 - FDA warning re hypersensitivity, anaphylaxis Infliximab – March 2013 - FDA warning re melanoma & merkel cell carcinoma – February 2011 - FDA warning re should not be taken with abatacept due to increased risk of infections Golimumab – Sept 2011 – FDA box warning re serious infections – Dec 2011 – FDA	Two experts feel the conclusion is still valid. Two experts do not know.	Conclusion is probably out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	similar rates of serious adverse events and serious infections with etanercept vs MTX.	warning re demyelinating disorders – Aug 2012 – FDA warning re hypersensitivity		
Biologic DMARD Combinations				
Biologic DMARD plus biologic DMARD vs. biologic DMARD: Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. (Moderate) Biologic DMARDs plus MTX vs. biologic DMARDs: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient) Biologic DMARD plus MTX vs. MTX: Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis. (Low) Mixed evidence on differences in the risk for rare but severe adverse events. (Insufficient)	An RCT of rituximab + MTX vs MTX alone[19] reported no difference in adverse events. A new meta-analysis of 6 RCTs of tocilzumab + MTX vs. placebo[7] showed increased risk of infection, but not of malignancy. One RCT of etanercept + MTX vs etanercept alone[17] reported no difference in adverse events.	Tocilizumab – October 2012 - FDA warning re hypersensitivity, anaphylaxis Infliximab – March 2013 - FDA warning re melanoma & merkel cell carcinoma – February 2011 - FDA warning re should not be taken with abatacept due to increased risk of infections Golimumab – Sept 2011 – FDA box warning re serious infections – Dec 2011 – FDA warning re demyelinating disorders – Aug 2012 – FDA warning re hypersensitivity	Two experts feel the conclusion is still valid. Two experts do not know.	Conclusion is probably out of date.
Strategies in Early RA				
Two oral DMARDs plus prednisone vs. oral DMARD: No differences in discontinuation rates. (Moderate) Three oral DMARDs plus prednisone vs. one oral DMARD: No differences in discontinuation rates. (Moderate) Sequential monotherapy starting with MTX	A case-control study of RA patients taking glucocorticoids (GCs) had higher rates of GI perforations than those taking oral or biologic DMARDs without GCs.[9] A new meta-analysis of 6	No issues identified.	Two experts feel the conclusion is still valid. Two experts do not know.	Conclusion is out of date regarding tx combinations that include corticosteroids.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
vs. step-up combination therapy vs. combination with tapered high dose prednisone vs. combination with infliximab: No differences in serious adverse events between groups. (Low)	RCTs of early RA treatment showed no difference in risk of serious infection or risk of malignancy between anti-TNFs vs MTX.[20]			
KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities? Limited good or fair evidence for benefits or harms of subpopulations exists; therefore, the strength of evidence was low and results should be interpreted cautiously.				
Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity.	No new studies identified.		Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
For MTX, the odds for major clinical improvement dropped slightly as the age of clinical trial patients increased; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly.	No new studies identified.	Not applicable.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Those taking anakinra and concomitant diabetic, antihypertensive, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment.	No new studies identified.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion still valid.
Those with high risk comorbidities (cardiovascular events, diabetes, malignancies, renal impairment) and taking anakinra did not experience an increase in serious adverse events or overall infectious events.	A new meta-analysis of 6 RCTs of tocilizumab + MTX vs. placebo[7] showed no increased risk of TB reactivation.	No issues identified.	Three experts feel the conclusion is still valid. One expert does not know.	Conclusion probably out of date regarding safety for TB patients.

Legend: ACR: American College of Rheumatology; DAS: Disease Activity Score; DMARD: Disease-modifying antirheumatic drug; MTC: Mixed-treatment comparisons; MTX: Methotrexate; PCS: Physical Component Score; RA: Rheumatoid Arthritis; SF-36: Short Form 36; SOE: Strength of Evidence; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center; Tx: Treatment

References

1. Donahue KE, Jonas DE, Hansen RA, et al. Drug Therapy for Rheumatoid Arthritis in Adults: An Update. Comparative Effectiveness Review No. 55 (Prepared by RTI-UNC Evidence-based Practie Center under Contract No. 290-02-0016-I.) Agency for Healthcare Research adn Quality. Rockville, MD: Apr April 2012. http://www.ncbi.nlm.nih.gov/22696776.

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID 17638714.

4. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA. 2011 Dec 7;306(21):2331-9. PMID 22056398.

5. Solomon DH, Massarotti E, Garg R, et al. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA. 2011 Jun 22;305(24):2525-31. PMID 21693740.

6. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA. 2012 Sep 5;308(9):898-908. PMID 22948700.

7. Campbell L, Chen C, Bhagat SS, et al. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2011 Mar;50(3):552-62. PMID 21078627.

8. Curtis JR, Xie F, Chen L, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011 Aug;70(8):1401-6. PMID 21586439.

9. Curtis JR, Xie F, Chen L, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. Arthritis Rheum. 2011 Feb;63(2):346-51. PMID 20967860.

10. Davies R, Galloway JB, Watson KD, et al. Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Oct;70(10):1831-4. PMID 21784722.

11. Dixon WG, Kezouh A, Bernatsky S, et al. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis. 2011 Jun;70(6):956-60. PMID 21285116.

12. Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. Arthritis Res Ther. 2011;13(4):R139. PMID 21884589.

13. Galloway JB, Hyrich KL, Mercer LK, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Oct;70(10):1810-4. PMID 21784730.

14. Gibofsky A, Palmer WR, Keystone EC, et al. Rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study: safety and etanercept utilization analyses from the RADIUS 1 and RADIUS 2 registries. J Rheumatol. 2011 Jan;38(1):21-8. PMID 20952478.

15. Greenberg JD, Kremer JM, Curtis JR, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Apr;70(4):576-82. PMID 21109516.

16. Guyot P, Taylor P, Christensen R, et al. Abatacept with methotrexate versus other biologic agents in treatment of patients with active rheumatoid arthritis despite methotrexate: a network meta-analysis. Arthritis Res Ther. 2011;13(6):R204. PMID 22151924.

17. Kameda H, Kanbe K, Sato E, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol. 2011 Aug;38(8):1585-92. PMID 21572151.

18. Launois R, Avouac B, Berenbaum F, et al. Comparison of certolizumab pegol with other anticytokine agents for treatment of rheumatoid arthritis: a multiple-treatment Bayesian metaanalysis. J Rheumatol. 2011 May;38(5):835-45. PMID 21239748.

19. Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2011 Jan;70(1):39-46. PMID 20937671.

20. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum. 2011 Jun;63(6):1479-85. PMID 21360522.

21. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013 Jan;65(1):28-38. PMID 23169319.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2011-10/15/2012

LANGUAGE:
English

SEARCH STRATEGY:
"Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH] OR "rheumatoid arthritis" OR "psoriatic arthritis"
AND
"Adrenal Cortex Hormones"[MeSH] OR corticosteroid* OR adrenal cortex hormone* OR "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH] OR methotrexate* OR leflunomide* OR sulfasalazine* OR hydroxychloroquine* OR "TNFR-Fc fusion protein"[Substance Name] OR TNFR-Fc fusion protein* OR etanercept OR "infliximab"[Substance Name] OR infliximab OR "adalimumab"[Substance Name] OR adalimumab OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR rituximab OR interleukin 1 receptor antagonist protein* OR anakinra OR "CDP870"[Substance Name] OR CDP870 OR CDP-870 OR certolizumab OR cimzia OR "efalizumab "[Substance Name] OR efalizumab OR raptiva OR "alefacept "[Substance Name] OR alefacept OR amevive OR "natalizumab"[Substance Name] OR natalizumab OR tysabri OR actemra OR "tocilizumab"[Substance Name] OR tocilizumab OR "golimumab "[Substance Name] OR golimumab
NOT
editorial[pt] OR letter[pt] OR practice guideline[pt]

NUMBER OF RESULTS: 1987

ENDNOTE FILTERED SEARCHES TO ELIMINATE:
ANIMALS
KEYWORD – "ANIMAL" NOT "HUMAN"
TITLE - MOUSE, MICE, MURINE, RAT, RATS, MONKEY(S)

CHILDREN/ADOLESCENTS –
KEYWORD - "CHILD OR ADOLESCEN" NOT ADULT
TITLE – "CHILD," "ADOLESCEN..."

NUMBER AFTER FILTERING: 1922

ADDITIONAL FILTERING TO INCLUDE ONLY THE FOLLOWING JOURNALS:
ANNALS OF INTERNAL MEDICINE
BMJ
JAMA
LANCET
NEW ENGLAND JOURNAL OF MEDICINE

ANNALS OF THE RHEUMATIC DISEASES
ARTHRITIS AND RHEUMATISM
ARTHRITIS RESEARCH THERAPY
CLINICAL AND EXPERIMENTAL RHEUMATOLOGY
CLINICAL RHEUMATOLOGY
JOURNAL OF RHEUMATOLOGY
RHEUMATOLOGY

NUMBER OF RESULTS AFTER FILTERING FOR JOURNALS: 667

TOTAL RESULTS: 585

Appendix B. Evidence Table

Author, Year	Drug Class	Study Design	Study name	Drugs	Year conducted	N, Population	Efficacy / effectiveness	Safety	Subpopulations (Stage, prior therapy, demographics, comorbidities)
Guyot, 2011[16]	Oral, oral + biologic, biologic	Systematic review - noninferiority of abatacept	NA	TNFi's, MTX	Studies published before January 2010	16 RCTs	Regarding ACR-50 and DAS28 response rates, abatacept plus MTX is superior to MTX alone and comparable to other biologic DMARDs	NA	Patients with inadequate response to MTX
Lopez-Olivo, 2012[6]	Oral vs oral, oral vs biologic, biologic vs biologic	Meta-analysis	NA	TNFi's, non-biologic DMARDS	2000-2011	63 trials; 29,423 patients	NA	No drugs were associated with increased risk of malignancies	NA
Solomon, 2011[5]	Oral vs oral, oral vs biologic	Cohort	NA	Hydroxychlolorquine, MTX, TNFi's, other nonbiologic DMARDs	1996-2008	13,905 patients with RA or psoriasis	NA	adjusted HR for onset of type 1 diabetes, compared to other nonbiological DMARDs: TNFi's 0.62 (95% CI 0.42-0.91) MTX 0.77 (95% CI 0.53-1.13) Hydroxychloroquine 0.54 (95% CI 0.36-0.80)	NA
Tak, 2011[19]	Oral vs oral + biologic	RCT	IMAGE	Rituximab, MTX	2006-2007	755 early stage RA patients	Rituximab plus MTX was associated with significant reduction in	Safety outcomes were similar across groups.	Patients were MTX naïve

Author, Year	Drug Class	Study Design	Study name	Drugs	Year conducted	N, Population	Efficacy / effectiveness	Safety	Subpopulations (Stage, prior therapy, demographics, comorbidities)
							progression of joint damage compared with MTX alone. Both 500 mg and 1000 doses of rituximab, with MTX resulted in better outcomes on ACR20, ACR50, ACR70.		
Davies, 2011[10]	Oral vs biologic	Cohort	NA	TNFi's, non-biologic DMARDS	2001-2009	15,554 RA patients	NA	No difference in rates of venous thrombotic events between TNFi's and nonbiologic DMARDs. Rates were similar across individual drugs	NA
Galloway, 2011[13]	Oral vs biologic	Cohort	NA	TNFi's, non-biologic DMARDS	2001-2009	15,554 RA patients	NA	Adjusted HR for septic arthritis with TNFi's was 2.3 (95% CI 1.2-4.4). Risk did not differ significantly by specific drug.	Risk highest in earliest months of tx
Gibofsky, 2011[14]	Oral vs biologic	Cohort	RADIUS registry	Etanercept	unclear	6,185 RA patients	NA	Rates of serious adverse events, serious infections, and events of medical interest in etanercept patients were similar to those for MTX monotherapy	NA
Thompson,	Oral vs	Meta-	NA	TNFi's, MTX	Studies	6 RCTs with	NA	Risk of serious	No prior DMARD

Author, Year	Drug Class	Study Design	Study name	Drugs	Year conducted	N, Population	Efficacy / effectiveness	Safety	Subpopulations (Stage, prior therapy, demographics, comorbidities)
2011[20]	biologic	analysis			published before June 2009	2,183 early stage RA patients		infection and risk of malignancy in TNFi' users was not statistically different from risk in MTX users. OR 1.28 (95% CI 0.82-2.00) and OR 1.08 (95% CI 0.50-2.32) respectively	or MTX use
Campbell, 2011[7]	Oral + biologic vs placebo	Meta-analysis	NA	Tocilizumab	2000-2009	6 trials; 3,102 patients	NA	Tocilizumab plus MTX associated with increased risk of infection (OR 1.30, 95% CI 1.07-1.58) compared to placebo. No increased incidence of malignancy, TB reactivation or hepatitis was found.	NA
Curtis, 2011a[9]	GCs, Oral, biologic	Case-control	NA	MTX, GCs, NSAIDs, TNFi's, non-biologic DMARDs	2005-2009	40,841 RA patients	NA	Patients receiving glucocorticoids had higher rates of GI perforations. However, diverticulitis was strongest predictor.	NA
Greenberg, 2011[15]	GCs, Oral, biologic	Cohort	CORRO NA registry	TNFi's, non-biologic DMARDS, MTX	2001-2006	10,156 RA patients	NA	TNFi's associated with reduced risk of cardiovascular events. MTX not associated with reduced risk. Prednisone associated with dose-dependent increased risk.	NA
Dixon, 2011a[11]	GCs	Case-control	NA	GCs (glucocorticoids)	1985-2003	16,207	NA	GCs associated	NA

Author, Year	Drug Class	Study Design	Study name	Drugs	Year conducted	N, Population	Efficacy / effectiveness	Safety	Subpopulations (Stage, prior therapy, demographics, comorbidities)
						elderly RA patients		with non-serious infection. Adjusted RR 1.20 (95% CI 1.15-1.25). Dose-response effect was noted.	
Dixon, 2011b[12]	GCs	Meta-analysis	NA	GCs	Studies published before January 2010	21 RCTs and 42 observational studies	NA	In observational studies, GCs associated with increased risk of infections RR 1.67 (95% CI 1.49-1.87)	NA
Kameda, 2011[17]	Biologic vs oral + biologic	RCT	JESMR	MTX, etanercept	2005-2007	151 RA patients	ACR20, ACR50, and ACR70 response rates were significantly higher in patients taking etanercept plus MTX than in those taking etanercept alone	No significant difference in any AEs across groups	Patients with inadequate response to MTX
Curtis, 2011b[8]	Biologic vs biologic	Cohort	NA	TNFi's, other biologic DMARDS	2005-2009	7,847 "tx episodes"	NA	adjusted HR for hospitalized infections was lower for abatacept 0.68 (95% CI 0.48-0.96), adalimumab 0.52 (95% CI 0.39-0.71), etanercept 0.64 (95% CI 0.49-0.84) and rituximab 0.81 (95% CI 0.55-1.20) than infliximab	NA
Grijalva, 2011[4]	Biologic vs biologic	Cohort	NA	TNFi's, non-biologic DMARDS	1998-2007	10,484 RA patients	NA	infliximab was associated with	NA

Author, Year	Drug Class	Study Design	Study name	Drugs	Year conducted	N, Population	Efficacy / effectiveness	Safety	Subpopulations (Stage, prior therapy, demographics, comorbidities)
								significant increase in serious infections compared with etanercept and adlimumb - adjusted HR 1.27 (95% CI 1.08-1.49) and 1.23 (95% CI 1.02-1.48) respectively	
Launois, 2011[18]	Biologic vs biologic	Meta-analysis, non-inferiority of certolizumab	NA	TNFi's, other biologic DMARDs	Studies published before June 2009	19 trials	According to ACR20 response, certolizumab is superior to infliximab, adlimumab, and anakinra, and equivalent to etanercept, golimumab, and tocilzumab	NA	Patients with inadequate response to MTX
Weinblatt, 2013[21]	Biologic vs biologic	RCT	AMPLE	biologic DMARDs	unclear	646 RA patients	Abatacept + MXT had similar ACR20 response rate as adalimumab + MTX	Significantly higher drop-out rate due to both adverse events and serious adverse events with adalimumab + MTX	NA

Legend: ACR: American College of Rheumatology; DAS: Disease Activity Score; DMARD: Disease-modifying antirheumatic drug; MTC: Mixed-treatment comparisons; MTX: Methotrexate; PCS: Physical Component Score; RA: Rheumatoid Arthritis; SF-36: Short Form 36; SOE: Strength of Evidence; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center; TNF: Tumor Necrosis Factor; Tx: Treatment

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?			
Oral DMARD vs. Oral DMARD			
Leflunomide vs. MTX: No differences in ACR 20 or radiographicresponses. (Low) Leflunomide vs. sulfasalazine: Mixed ACR response rates. (Insufficient) Leflunomide vs. sulfasalazine: No differences in radiographic changes. (Low) Sulfasalazine vs. MTX: No differences in ACR 20 response, disease activity scores and radiographic changes. (Moderate)	☐	New Evidence:	☐
Oral DMARD Combinations vs. Oral DMARD			
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: In patients with early RA, no differences in ACR 20 response rates or radiographic changes. (Moderate) Oral DMARD plus prednisone vs. oral DMARD: Mixed results for disease activity. (Insufficient) Less radiographic progression in patients on DMARD plus prednisone. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints (Low)	☐	New Evidence:	☐
Biologic DMARDs vs. Biologic DMARDs			
Abatacept vs. Infliximab: Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference.	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
(Low) Biologic vs. biologic (Mixed treatment comparisons): No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. (Low) Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. (Low) Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. (Low)			
Biologic DMARDs vs. Oral DMARDs			
Anti-tumor necrosis factor drugs vs. MTX: In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. (Moderate)	☐	New Evidence:	☐
Biologic DMARD Combinations			
Biologic DMARD plus biologic DMARD vs. biologic DMARD: No additional benefit in disease activity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy (Low) Biologic DMARDs plus MTX vs. biologic DMARDs: Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. (Moderate) In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. (Low) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No difference in clinical response	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
rates between etanercept plus sulfasalazine and etanercept monotherapy. (Low) Biologic DMARD plus MTX vs. MTX: Better clinical response rates from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. (High)			
Strategies in Early RA			
Two oral DMARDs plus prednisone vs. oral DMARD: In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. (Low) Three oral DMARDs plus prednisone vs. one oral DMARD: In patients on three oral DMARDs, improved ACR 50 response rates and disease activity scores. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints. (Low)	☐	New Evidence:	☐
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered highdose prednisone vs. combination with infliximab: Less radiographic progression and lower disease activity scores from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no difference in remission at 4 years. (Low)	☐	New Evidence:	☐
KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?			
Oral DMARD vs. Oral DMARD			
Leflunomide vs. MTX :No clinically significant difference for functional capacity. (Low) Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. (Low) Leflunomide vs. sulfasalazine: Greater improvement in functional capacity for leflunomide. (Low) Sulfasalazine vs. MTX:No differences for functional capacity.(Moderate)	☐	New Evidence:	☐
Oral DMARD Combinations vs. Oral DMARD			

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: No differences in functional capacity. (Moderate) Oral DMARD plus prednisone vs. oral DMARD: Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. (Moderate) No difference in quality of life. (Low)	☐	New Evidence:	☐
Biologic DMARDs vs. Oral DMARDs			
Anti-tumor necrosis factor drugs vs. MTX: No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. (Low; Insufficient) Faster improvement in quality of life with etanercept than MTX. (Low)	☐	New Evidence:	☐
Biologic DMARD Combinations			
Biologic DMARD plus biologic DMARD vs. biologic DMARD: No additional benefit in functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. (Low) Biologic DMARDs plus MTX vs. biologic DMARDs: In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life (Low) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. (Low) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No difference in functional capacity and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. (Low) Biologic DMARD plus MTX vs. MTX: Better functional capacity and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. (High for functional capacity, Moderate for quality of life)	☐	New Evidence:	☐
Strategies in Early RA			
Two oral DMARDs plus prednisone vs. oral DMARD: More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. (Low)	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Three oral DMARDs plus prednisone vs. one oral DMARD: In patients on three oral DMARDs, less work disability.(Low) Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered highdose prednisone vs. combination with infliximab: Better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. (Low)			
KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?			
Oral DMARD vs. Oral DMARD			
Leflunomide vs. MTX: No consistent differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient) Leflunomide vs. sulfasalazine: No differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient) Sulfasalazine vs. MTX: No differences in tolerability; more patients stayed on MTX long term. (Low) Mixed results for specific adverse events. (Insufficient)	☐	New Evidence:	☐
Oral DMARD Combinations vs. Oral DMARD			
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy: Withdrawal rates attributable to adverse events higher with combination. (Low) Insufficient evidence for specific adverse events. (Insufficient) Oral DMARD plus prednisone vs. oral DMARD: No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. (Moderate) No differences in specific adverse events, except addition of corticosteroid may increase woundhealing complications. (Low)	☐	New Evidence:	☐
Biologic DMARDs vs. Biologic DMARDs			
Abatacept vs. Infliximab: Discontinuation rates and severe adverse events higher with infliximab. (Low) Adjusted indirect comparisons found a more favorable	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. (Low) Risk for injection site reactions apparently highest with anakinra. (Low) Mixed results for specific adverse events. (Insufficient)			
Biologic DMARDs vs. Oral DMARDs			
Anti-tumor necrosis factor drugs vs. MTX: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient)	☐	New Evidence:	☐
Biologic DMARD Combinations			
Biologic DMARD plus biologic DMARD vs. biologic DMARD: Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. (Moderate) Biologic DMARDs plus MTX vs. biologic DMARDs: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient) Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs: No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient) Biologic DMARD plus MTX vs. MTX: Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from metaanalysis. (Low) Mixed evidence on differences in the risk for rare but severe adverse events. (Insufficient)	☐	New Evidence:	☐
Strategies in Early RA			
Two oral DMARDs plus prednisone vs. oral DMARD: No differences in discontinuation rates. (Moderate)	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Three oral DMARDs plus prednisone vs. one oral DMARD: No differences in discontinuation rates. (Moderate) Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered highdose prednisone vs. combination with infliximab: No differences in serious adverse events between groups. (Low)			
KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities? Limited good or fair evidence for benefits or harms of subpopulations exists; therefore, the strength of evidence was low and results should be interpreted cautiously.			
Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity.	☐	New Evidence:	☐
For MTX, the odds for major clinical improvement dropped slightly as the age of clinical trial patients increased; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly.	☐	New Evidence:	☐
Those taking anakinra and concomitant diabetic, antihypertensive, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment.	☐	New Evidence:	☐
Those with highrisk comorbidities (cardiovascular events, diabetes, malignancies, renal impairment) and taking anakinra did not experience an increase in serious adverse events or overall infectious events.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			