Comparative Effectiveness Review

Number 11

Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults

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Prepared by:

RTI-University of North Carolina Evidence-based Practice Center

Investigators
Katrina E. Donahue M.D., M.P.H.
Gerald Gartlehner, M.D., M.P.H.
Daniel E. Jonas, M.D., M.P.H.
Linda J. Lux, M.P.A.
Patricia Thieda, M.A.
Beth Jonas, MD, M.P.H.
Richard A. Hansen, Ph.D.
Laura C. Morgan, M.A.
Stacey C. Williams, B.S.
Kathleen N. Lohr, Ph.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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AHRQ Contacts

Beth A. Collins-Sharp, Ph.D., R.N.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality
Rockville, MD

Carmen Kelly, Pharm.D., R.Ph.
Task Order Officer
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality
Rockville, MD

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Background

Rheumatoid and psoriatic arthritis are among the most disabling forms of arthritis. Rheumatoid arthritis (RA), which affects 1 percent of the U.S. adult population (or upwards of 2 million individuals), is an autoimmune disease that involves inflammation of the synovium (a thin layer of tissue lining a joint space) with progressive erosion of bone, leading in most cases to misalignment of the joint, loss of function, and disability. The disease tends to affect the small joints of the hands and feet in a symmetric pattern, but other joint patterns are often seen. The diagnosis is based primarily on the clinical history and physical examination. Psoriatic arthritis (PsA) affects fewer people than RA (approximately 1 million people in the United States). PsA is associated with the skin disease psoriasis. It has a highly variable presentation, which generally involves pain and inflammation in joints and progressive joint involvement and damage. Like RA, PsA can be disabling.

Treatment of patients with RA and PsA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability. Available therapies for RA include corticosteroids; synthetic disease-modifying antirheumatic drugs, or DMARDs (hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine); and biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab). Three biologics (adalimumab, etanercept, and infliximab) are also classified as anti-tumor necrosis factor (anti-TNF) drugs.

Experts have not arrived at a consensus about the comparative efficacy of different types of combination therapy—synthetic DMARDs, synthetic DMARDs with corticosteroids, or synthetic DMARDs with biologic DMARDs—all often in combination with the synthetic DMARD methotrexate. In addition, there is debate about how early in the disease process combination therapy should be initiated and whether patients will respond to a biologic agent if they have previously failed a different biologic agent. Many questions remain about the risks of these agents across a spectrum of adverse events from relatively minor side effects, such as injection site reactions, to severe and possibly life-threatening problems, such as severe infections or infusion reactions. Finally, very little is known about the benefits or risks of these drugs in different patient subgroups, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities.

Historically, few trials have been conducted on patients with PsA, with only minimal research conducted before biologic agents were introduced; management options tended to be adapted from RA trial evidence. All the same issues noted for RA of short- and long-term risks and safety, as well as performance in population subgroups, have been only minimally addressed to date for PsA.

This report from the RTI-University of North Carolina Evidence-based Practice Center summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, synthetic DMARDs, and biologic DMARDs in the treatment of patients with either RA or PsA. The key questions (KQs) were developed through a public process in conjunction with the Scientific Resource Center at the Oregon Health and Science University. The KQs are as follows:

KQ 1. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission?

KQ 2. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?

KQ 3. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?

KQ 4. What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?

We identified 2,153 citations from our searches. Working from 619 articles retrieved for full review, we included 156 published articles reporting on 103 studies: 22 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 13 placebo-controlled trials, 10 meta-analyses or systematic reviews, 55 observational studies, and 2 poor-quality pooled data analyses on subgroups. Of the 103 included studies, 51 (50 percent) were supported by pharmaceutical companies, 21 (20 percent) were funded by governmental or independent funds, and 11 (11 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 20 studies (19 percent). One-quarter of the individual trials were rated good quality; most were found to be fair quality.

Conclusions

We present our major findings in this section by type of drug comparison and important outcomes (both benefits and harms). Summary Table A summarizes the information for RA. We limit our findings in the Executive Summary to RA because no comparative evidence exists on PsA for any drugs. We also have not presented findings from subpopulation analyses for RA because the strength of evidence for age, sex, and comorbidities is very weak.

Summary Table A. Summary of findings: rheumatoid arthritis

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
	Monotherapy vs. Monotherapy	
Synthetic DMARDs		
Leflunomide vs. methotrexate	No differences in ACR 20 or radiographic responses: *Moderate* Greater improvement in functional status (HAQ-DI) and health-related quality of life (SF-36 physical component) for leflunomide: *Moderate* No differences in work productivity outcomes: *Moderate*	No differences in tolerability and discontinuation rates: *Moderate*
Leflunomide vs. sulfasalazine	Higher ACR 20 and ACR 50 response rates and greater improvement in functional capacity for leflunomide: *Low* No differences in radiographic changes: *Low*	No differences in tolerability and discontinuation rates: *Moderate*
Sulfasalazine vs. methotrexate	No differences in ACR 20 response, disease activity scores, functional capacity, and radiographic changes: *Moderate*	No differences in tolerability; more patients on methotrexate than sulfasalazine long term: *Moderate*
Biologic DMARDs		
Biologic DMARDs vs. biologic DMARDs		
Anti-TNF drugs (adalimumab, etanercept, infliximab) vs. anti-TNF drugs	No differences in ACR 20/50 response rates among anti-TNF drugs: *Moderate*	Insufficient evidence on the comparative risk of harms: *Low*
Biologic DMARDs vs. biologic DMARDs	Indirect comparisons consistently showed anakinra to have lower ACR 20 and ACR 50 response rates than anti-TNF drugs as a class: *Moderate*	Risk for injection site reactions apparently higher for anakinra than for adalimumab and etanercept: *Moderate*
Biologic DMARD vs. synthetic DMARD		
Anti-TNF drugs vs. methotrexate	In patients with early RA, no differences in clinical response, functional capacity, and quality of life between adalimumab or etanercept and methotrexate; better radiographic outcomes in patients on biologic DMARDs than in patients on synthetic DMARDs: *Moderate* In patients who had failed initial RA treatment, greater functional independence and remission for anti-TNF drugs as a class than synthetic DMARDs as a class: *Moderate*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence on differences in the risk for rare but severe adverse events: *Low*

Summary Table A. Summary of findings: rheumatoid arthritis (continued)

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
Combination Therapy vs. Monotherapy		
Synthetic DMARDs vs. Synthetic DMARDs		
Sulfasalazine plus methotrexate vs. monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes: *Moderate* No differences in functional capacity in all patients: *Moderate* In patients with early RA, significantly better disease activity scores with combination therapy: *Low*	No differences in withdrawal rates attributable to adverse events: *Moderate*
1, 2, or 3 synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine) plus prednisone vs. 1 synthetic DMARD	In patients on 1, 2, or 3 synthetic DMARDs plus prednisone, improved ACR 50 response rates, disease activity scores, and less radiographic progression: *Moderate* In patients with early RA, significantly lower radiographic progression and fewer eroded joints: *Low* Better outcomes with the combination strategies for functional capacity: *Low* for each individual comparison, *Moderate* for combination therapy vs. monotherapy	No differences in discontinuation rates: *Moderate*
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional treatment effects from combination of etanercept plus anakinra compared with etanercept monotherapy: *Low*	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy: *Moderate*
Biologic DMARD plus methotrexate vs. biologic DMARD	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARD plus methotrexate than from monotherapy with biologics: *Moderate* In methotrexate-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group: *Low*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence on differences in the risk for rare but severe adverse events: *Low*
Biologic DMARDs plus synthetic DMARD other than methotrexate vs. biologic DMARD	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy: *Low*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence on differences in the risk for rare but severe adverse events: *Low*

Summary Table A. Summary of findings: rheumatoid arthritis (continued)

Key comparisons	Efficacy and strength of evidence	Harms and strength of evidence
Biologic DMARD plus methotrexate vs. methotrexate	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and methotrexate than from methotrexate monotherapy: *Moderate*	No differences in adverse events in efficacy studies: *Low* Insufficient evidence to make conclusion on differences in the risk for rare but severe adverse events: *Low*
Combination Therapy vs. Combination Therapy or Other Treatment Strategy		
Sulfasalazine plus methotrexate plus hydroxychloroquine vs. 2 drugs	In patients previously on monotherapy, higher ACR 20/50 response rates for triple therapy than for 2-drug combinations: *Moderate* In patients with no previous use of study drugs, higher ACR 20/50 response rates in the triple combination therapy group than in methotrexate plus sulfasalazine or methotrexate plus hydroxychloroquine: *Low*	No differences in withdrawal rates attributable to adverse events: *Moderate*
Sequential monotherapy starting with methotrexate vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability from initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus methotrexate than from sequential DMARD monotherapy or step-up combination therapy: *Low*	No differences in serious adverse events between groups: *Low*

Abbreviations: ACR=American College of Rheumatology; DMARD=disease-modifying antirheumatic drug; HAQ-DI= Health Assessment Questionnaire Disability Index; RA=rheumatoid arthritis; SF-36=Medical Outcomes Study Short Form 36; TNF=tumor necrosis factor.

Monotherapy vs. Monotherapy

Synthetic DMARDs. The data show no differences in radiographic outcomes over 2 years for leflunomide and methotrexate. One systematic review that included a meta-analysis of two RCTs suggested that higher proportions of patients on methotrexate than on leflunomide met the American College of Rheumatology (ACR) 20-percent improvement criteria at 1 year (odds ratio [OR], 1.43; 95-percent confidence interval [CI], 1.15-1.77, $P = 0.001$), but statistical significance was lost at 2 years (OR, 1.28; 95-percent CI, 0.98-1.67). However, patients on methotrexate had less improvement in functional status and health-related quality of life than patients taking leflunomide (Short Form [SF]-36 physical component: 4.6 vs. 7.6, $P < 0.01$; Health Assessment Questionnaire Disability Index [HAQ-DI]: -0.26 vs. -0.45, $P < 0.01$). Existing head-to-head evidence (three RCTs) supports no differences in efficacy between methotrexate and sulfasalazine by ACR 20, disease activity score (DAS), and functional capacity.

For leflunomide vs. sulfasalazine, data are limited to one RCT with 2-year followup that reported that leflunomide resulted in a higher proportion of patients reaching ACR 20-percent improvement and ACR 50-percent improvement criteria and greater improvement in functional

capacity (ACR 20: 82 percent vs. 60 percent, $P < 0.01$; ACR 50: 52 percent vs. 25 percent, $P < 0.01$; HAQ: -0.50 vs. -0.29, $P < 0.03$). Radiographic changes were not different for those treated with leflunomide and those treated with sulfasalazine.

No differences in tolerability were reported for leflunomide, methotrexate, and sulfasalazine in three efficacy trials and one meta-analysis of data up to 3 years. Similarly, discontinuation rates because of adverse events did not differ among leflunomide, methotrexate, or sulfasalazine. In the meta-analysis, 2-year withdrawals attributed to adverse events were not significantly different for leflunomide vs. methotrexate (relative risk [RR], 1.19; 95-percent CI, 0.89-1.6) or sulfasalazine (RR, 0.77; 95-percent CI, 0.45-1.33). However, in one meta-analysis of 71 RCTs and 88 observational studies, at 5 years the proportion of patients who were continuing to take methotrexate was higher than the proportion continuing to take sulfasalazine (36 percent vs. 22 percent, P = not reported [NR]).

Biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. No evidence exists on abatacept and rituximab compared with other biologic DMARDs.

Existing direct head-to-head evidence is limited to one nonrandomized, open-label effectiveness trial and two prospective cohort studies comparing etanercept with infliximab. In all three studies, patients on etanercept had a faster onset of action than patients on infliximab, although no differences in effectiveness were apparent between the two agents. The above findings are generally consistent with results from three adjusted indirect comparison models (adalimumab, etanercept, and infliximab) that reported no differences in efficacy among anti-TNF drugs.

Adjusted indirect comparisons also indicated that anakinra has lower efficacy than anti-TNF drugs. Although not all results reached statistical significance, anakinra had consistently lower response rates on ACR 20 (RR, 1.64; 95-percent CI, 1.04-2.56) and ACR 50 (RR, 1.89; 95-percent CI, 0.98-3.57) than anti-TNF drugs as a class.

Biologic DMARD vs. biologic DMARD. Biologic DMARDs were generally well tolerated in efficacy studies. Long-term extension studies of anti-TNF drugs indicated that the rate of adverse events does not increase over time. One nonrandomized, open-label trial directly compared the tolerability of two biologic DMARDs. This 12-month study did not report any differences in harms between etanercept and infliximab.

A good-quality systematic review reported that the mean crude incidence rates of injection site reactions in RCTs and observational studies were substantially higher in patients using anakinra (67.2 percent; 95-percent CI, 38.7-95.7) than in patients on adalimumab (17.5 percent; 95-percent CI, 7.1-27.9) or etanercept (22.4 percent; 95-percent CI, 8.5-36.3).

Otherwise, evidence from placebo-controlled trials and observational studies is insufficient to draw conclusions about the comparative tolerability and safety of biologic DMARDs. One prospective cohort study suggested that adalimumab, etanercept, and infliximab did not differ in the risk for serious infections. Three fair-quality observational studies, however, indicated that infliximab might have a higher risk of granulomatous infections than etanercept.

The evidence on comparative discontinuation rates is limited to three observational studies. In one large, retrospective cohort study, anakinra led to statistically significantly higher overall discontinuation rates (41 percent) than either etanercept (31 percent; $P = 0.004$) or infliximab (35 percent; $P = 0.03$).

Biologic DMARD vs. synthetic DMARD. Three RCTs compared the efficacy of two anti-TNF drugs (adalimumab or etanercept) with that of methotrexate. Two trials enrolled exclusively

methotrexate-naive patients with early RA; the third trial included a mixed population of methotrexate-naive patients and patients who had failed synthetic DMARDs other than methotrexate. In all three studies, results did not indicate substantial differences in clinical response, functional capacity, or quality of life between either adalimumab or etanercept and methotrexate. In the adalimumab study, 25 percent of patients achieved remission in each treatment group. Radiographic outcomes, however, were statistically significantly better in patients treated with biologic DMARDs than in those tapered with methotrexate. For example, in the ERA (Early Rheumatoid Arthritis) study, 72 percent of patients on etanercept and 60 percent of patients on methotrexate had no radiographic progression of the disease ($P = 0.007$). What implications such intermediate outcomes have on the long-term progression of the disease remains unclear. No studies comparing biologics with synthetic DMARDs other than methotrexate were available.

One prospective cohort study enrolled a population who failed initial RA treatment. After 12 months, patients on biologic DMARDs as a class had almost four times higher odds of achieving functional independence (OR, 3.88; 95-percent CI, 1.71-8.79) and almost two times higher odds of achieving remission (OR, 1.95; 95-percent CI, 1.20-3.19) than patients on synthetic DMARDs. In both groups, only half of patients who were in remission at 6 months achieved a sustained remission until 12 months.

In general, adverse events did not differ significantly between biologic and synthetic DMARDs. Studies were too small to assess reliably differences in rare but severe adverse events.

Combination Therapy vs. Monotherapy

Synthetic DMARDs. The data are limited by the number of supporting studies for each drug combination.

Sulfasalzine-methotrexate vs. monotherapy. In two trials lasting 4 years, ACR response rates and radiographic changes did not differ in patients with early RA. Findings of these studies are consistent and do not support a difference in functional capacity between combination therapy and monotherapy. One study in patients with early RA, however, reported improved DAS scores at 18 months with combination therapy (DAS score -0.67 combination, -0.30 sulfasalazine, -0.26 methotrexate; $P = 0.023$ for combination vs. methotrexate).

Synthetic DMARD-corticosteroid vs. monotherapy. Three RCTs examined combination strategies of one or more synthetic DMARDs with corticosteroids against synthetic DMARD monotherapy. These trials suggest better outcomes with the combination strategies, although each study used different outcome measures, including ACR, DAS, and radiographic scores. One RCT comparing a combination involving a synthetic DMARD (either methotrexate or sulfasalazine) and a corticosteroid with a synthetic DMARD monotherapy had a higher remission rate in the combination group than in the monotherapy group (remission defined by DAS 28 < 2.6: 55.5 percent vs. 43.8 percent; $P = 0.0005$). Patients with early RA had significantly lower radiographic progression and fewer eroded joints with the combination treatment than with monotherapy.

One open-label RCT compared synthetic DMARD use with and without prednisolone. It was found that the prednisolone group had a greater improvement in functional capacity. The investigators did not compare the results statistically, and the clinical relevance of the results is uncertain.

Combination studies involving two synthetic DMARDs, including sulfasalazine and methotrexate, vs. one DMARD showed no differences in withdrawal rates because of adverse

events. Combination studies including prednisone with one or more DMARDs also had no differences in discontinuation rates between groups.

Biologic DMARDs. The data are limited by the number of supporting studies for each drug combination.

Biologic combination vs. monotherapy. One RCT did not detect any synergistic effects of a combination treatment of etanercept and anakinra compared with etanercept monotherapy. The incidence of serious adverse events, however, was substantially higher with the combination treatment (14.8 percent vs. 2.5 percent; P = NR).

Two trials indicated that a combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy. The evidence, however, is limited to combinations of anakinra plus etanercept and abatacept plus anakinra, adalimumab, etanercept, or infliximab.

Biologic combination with methotrexate vs. biologic DMARDs alone. Most of the other studies compared combinations of biologic DMARDs and methotrexate with monotherapies of these drugs. Overall, combination therapy of biologic DMARDs and methotrexate achieved better clinical response rates than monotherapies. For example, four RCTs and two prospective cohort studies suggested that a combination of adalimumab, etanercept, infliximab, or rituximab with methotrexate leads to statistically significantly greater improvements than monotherapy of biologic DMARDs. In one trial, significantly more patients on the combination therapy (adalimumab plus methotrexate) than patients on adalimumab monotherapy (59 percent vs. 37 percent; $P < 0.001$) exhibited responses on the ACR 50 after 2 years of treatment. Likewise, more patients on etanercept plus methotrexate than on etanercept monotherapy achieved remission (DAS < 1.6; 35 percent vs. 16 percent; $P < 0.0001$) during the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study. Both RCTs suggested that a combination of either adalimumab or etanercept with methotrexate led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with a biologic DMARD. In methotrexate-naive patients with early, aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression were seen in the combination therapy group.

Biologic DMARD combinations with other synthetics vs. biologic DMARDs. Only one study used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD. A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy. No differences in adverse events were found between combinations of biologic and synthetic DMARDs and biologic DMARD monotherapy.

Biologic DMARD combinations with methotrexate vs. methotrexate alone. Two trials found that a combination of either adalimumab plus methotrexate or infliximab plus methotrexate in patients with early, aggressive RA who were methotrexate naive led to better clinical and radiographic outcomes than methotrexate monotherapy. After 2 years of treatment, 59 percent of patients on adalimumab plus methotrexate met ACR 50 criteria, compared with 43 percent of patients on methotrexate monotherapy ($P < 0.001$). Likewise, significantly more patients in the infliximab plus methotrexate combination groups than in the methotrexate group exhibited remission rates in the ASPIRE (Active controlled Study of Patients receiving Infliximab for Rheumatoid arthritis of Early onset) retrial. Both RCTs and one prospective cohort study found greater improvements in functional capacity and quality of life with combination therapies (adalimumab, infliximab, or etanercept plus methotrexate) than with methotrexate alone.

In general, no statistically significant differences in adverse events existed between combinations of biologic and synthetic DMARDs and synthetic DMARD monotherapy. Studies, however, were too small to assess reliably differences in rare but severe adverse events. An exception was a study with high-dose infliximab plus methotrexate therapy, which led to a statistically significantly higher rate of serious infections than methotrexate monotherapy.

Combination Therapy Comparisons or Other Treatment Strategies

Evidence is insufficient to draw firm conclusions about whether one combination strategy is better than any other. Two RCTs reported more improved response rates at 2 years for the combination of sulfasalazine, methotrexate, and hydroxychloroquine than for one or two drugs in patients who had previously been on monotherapy. ACR 20 response rates were 78 percent for triple therapy, as contrasted with 60 percent for methotrexate and hydroxychloroquine ($P = 0.05$) and 49 percent for methotrexate and sulfasalazine ($P = 0.002$). Groups did not differ in withdrawal rates.

In patients with early RA, data are limited to one effectiveness trial. It reported less radiographic progression over 12 months with either (1) methotrexate, sulfasalazine, and high-dose tapered prednisone or (2) methotrexate and infliximab vs. (3) sequential DMARD therapy or (4) step-up combination therapy (median modified Sharp/van der Heijde score change: 2.0, 2.5, 1.0, and 0.5, respectively; $P = 0.003$ for group 1 vs. group 3, $P < 0.001$ for group 1 vs. group 4, $P = 0.007$ for group 2 vs. group 3, $P < 0.001$ for group 2 vs. group 4). Patients treated with initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab and methotrexate had statistically significantly better functional ability (Dutch version of the HAQ) at 12 months than those treated with sequential DMARD therapy starting with methotrexate. The magnitude of difference was small, however. The groups did not differ in serious adverse events.

Remaining Issues

Most of the trials were conducted in RA patients; data are limited for PsA patients. Common problems for both RA and PsA include the lack of effectiveness information—i.e., studies and findings with a high level of applicability to community populations. Future investigations need to take into account factors such as varying adherence because of administration schedules, costs, and adverse events. Information about the performance of these drugs in subgroups of patients defined by health status, sociodemographics, or other variables is also needed.

To address problems with current literature, future studies should use designs of longer duration and followup, enroll patients representing key subgroups (or report on them when they are enrolled), and ensure that quality of life (or other patient-oriented outcomes) is measured in addition to clinician-oriented measures, such as joint erosion.

The gaps in information for specific RA therapies are substantial. With respect to comparative efficacy, future studies should focus on head-to-head trials assessing combination therapies involving synthetic DMARDs in comparison with those involving biologic DMARDs. Adequately powered, long-term RCTs must also examine different treatment strategies with and without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in patients with RA. Additionally, no head-to-head RCTs have compared one biologic DMARD with another; this is a significant hole in the literature that future research should fill. However, this is less likely to occur because of

the expense of biologic DMARDs. Investigators may find large registries helpful in identifying the same kinds of patients treated with different agents.

With respect to study design, studies of longer duration and followup will be beneficial, given that RA is a progressive, chronic condition. Such studies will also help to clarify whether early initiation of any regimen can improve the long-term prognosis of RA and, particularly, whether early use of biologic DMARDs is beneficial.

Minimal research was conducted on PsA before biologic DMARDs were introduced, so the gaps in this knowledge base are larger than those in RA. Going forward, head-to-head comparisons of any of the drug therapies to treat PsA are needed, probably with particular attention to biologic DMARDs. Issues similar to those for RA with respect to long-term outcomes and early initiation are also important for PsA.

Addendum

We updated our literature search in September 2007 and identified 243 new citations. We obtained the full text for 22 references and included 16 published articles on 10 new studies. We report relevant new data below but, overall, these studies do not change the conclusions of this report.

Rheumatoid Arthritis

Biologic comparisons. We found eight new studies on biologics that met our eligibility criteria;[1-8] five of these were observational studies assessing the safety of biologics.[4-8] Overall, these studies did not change our conclusions or any ratings of the strength of the evidence. Nevertheless, some studies added notable new evidence.

For example, one RCT compared the efficacy of rituximab monotherapy with a combination treatment of rituximab and methotrexate in patients with active RA despite ongoing methotrexate treatment.[3] To date, this is the first study comparing these treatment strategies. Results are similar to trials comparing adalimumab or etanercept monotherapies with combinations of these biologics and methotrexate. During the entire followup and after 2 years, the combination group experienced substantially greater response rates than the rituximab monotherapy group (ACR 50 at 2 years: 20 percent vs. 8 percent).

A prospective, population-based cohort study from Sweden, enrolling more than 1,100 patients, reported statistically significantly higher adherence rates for patients on etanercept and methotrexate than for those on infliximab and methotrexate.[1] After 5 years of treatment, 65 percent of patients on etanercept and 36 percent of patients on infliximab still adhered to therapy. Infliximab led to statistically significantly more withdrawals owing to adverse events than etanercept (data not reported; $P < 0.001$). To date, this study is the longest comparative assessment of two biologic treatments for RA.

Combination strategy comparisons. We found two articles[9,10] containing 2-year followup data for a previously reported RCT comparing complex combination strategies.[11] The 2-year data reinforce our conclusions that patients on initial combination therapy of methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with methotrexate and infliximab had less radiographic progression than sequential monotherapy and step-up combination therapy (median increase in total Sharp/van der Heijde score: 1.0, 1.0, 2.0, and 2.0, respectively). However, all arms had similar disease activity by disease activity score (DAS) values at 2 years regardless of which initial therapy they had received.

Psoriatic Arthritis

We identified six new articles published on studies concerning the treatment of PsA.[12-17] Two were new, formerly unreported studies;[12,13] four of the articles contained additional outcomes on studies previously reported.[14-17] Overall, these studies did not change our conclusions or any ratings of the strength of the evidence.

However, one of the studies added new evidence by comparing biologics with methotrexate, the conventional treatment of PsA.[12] In this prospectively planned observational study in Norway, 6 months of treatment with biologics and biologics plus methotrexate vs. methotrexate alone were compared in 1,022 patients. The group treated with biologics had poorer baseline characteristics than the methotrexate group; once statistical adjustments were made, the differences at 6 months were significantly in favor of the biologics group for the DAS-28 ($P < 0.001$) and other measures.

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Introduction

Background

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults,[1] affecting more than 7 million persons. Noninflammatory arthritic conditions (e.g., osteoarthritis) are most common, but inflammatory arthritides such as spondyloarthropathies (e.g., ankylosing spondylitis, psoriatic arthritis [PsA]), and reactive arthritis) and rheumatoid arthritis (RA) can be equally or more disabling.

Among RA and PsA—*the focus of this review*—the burden of disease is evidenced by decreased quality of life,[2-4] decreased employment rates,[5] and increased direct and indirect costs.[6-9] Annually, approximately 9 million physician office visits and more than 250,000 hospitalizations occur as the result of RA. The mean total annual direct cost to patients with RA is estimated to be $9,519 per person,[6] and most studies have reported indirect costs to be roughly twofold greater than direct costs.[10] Costs associated with PsA are not as well studied, although they are believed to be just slightly lower than those in RA.[8] Indirect costs are believed to increase over time; as the disease progresses so does the loss of function and inability to work.

Clinically, RA and PsA may present similarly. The most notable distinctions are the presence of serum rheumatoid factor in RA and accompanying skin presentations in PsA. Still, the two inflammatory conditions are unique, and they warrant independent descriptions.

Causes and Diagnosis

Rheumatoid Arthritis (RA)

RA is an autoimmune disease that affects 2.1 million adults in the United States. Disease onset generally occurs between ages 30 and 50 years, and incidence is higher in women and older adults. RA presentations range from mild to severe. Some people are affected for as little as a few months, whereas others are affected for a lifetime and suffer severe joint damage and disability.

The hallmarks of the disease are inflammation of the synovium (a membrane that lines the joint capsule and produces lubricating fluid in the joint) with progressive erosion of bone leading to malalignment of the joint. As the inflamed synovium destroys the joint, the surrounding muscles and tendons become weak, leading to disability in most cases. Unlike osteoarthritis, RA can affect areas in addition to joints. Most patients develop anemia. Some patients have dry eyes and mouth (sicca syndrome). Rarely, patients develop inflammation in the lining of the lung (pulmonary fibrosis), various layers of the eye wall (episcleritis and scleritis), small vessels (vasculitis), and the outer covering of the heart (pericarditis).

The exact etiology of RA is not completely understood, but genetic susceptibility has been described in certain populations.[11,12] Studies have shown the importance of T cells, B cells, and cytokines in the pathogenesis of RA.[13,14] Cytokines of particular interest are tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6.

TNF plays a central role in the pathobiology of RA. It is an important regulator of other proinflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a mass of tissue that causes localized joint destruction.[14]

The diagnosis of RA is primarily a clinical one, based on multiple patient symptoms. No single laboratory test confirms RA. Constitutional symptoms including low-grade fever, fatigue, or malaise are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. A serum rheumatoid factor is present in up to 75 percent of patients with RA but is frequently negative in early disease. A more specific marker, anticyclic citrullinated peptide (CCP) antibody, has recently been described and may be a useful marker in patients with early disease.[15] Table 1 presents the diagnostic criteria for RA proposed by the American College of Rheumatology (ACR).[16] Patients are said to have RA if they meet four of the seven criteria in the table.[16]

Table 1. ACR criteria for the diagnosis of rheumatoid arthritis

Criteria
1. Morning stiffness lasting greater than 1 hour
2. Arthritis in 3 or more joint areas
3. Arthritis of the hand joints (metacarpophalangeal [MCP], proximal interphalangeal [PIP], wrists)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes: erosions or unequivocal periarticular osteopenia

Source: Arnett et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar; 31(3):315-24.

Psoriatic Arthritis (PsA)

Psoriasis, a skin disease, affects 2.2 percent of U.S. adults; approximately 10 percent to 30 percent of patients with psoriasis develop PsA. Approximately 55,000 adults in the United States have PsA. PsA can develop at any age but most often appears between 30 and 50 years old. Unlike RA, PsA appears to affect men slightly more often than women.

The presentation is highly variable. In most cases, the psoriasis predates the onset of the PsA, although arthritis has been described as the initial manifestation of psoriatic disease. Common presentations include a symmetric small-joint polyarthritis (RA-like) and an axial arthritis with involvement of the sacroiliac joints, axial skeleton (spine), and large joints. In all cases, symptoms include pain and stiffness in the affected joint, enthesial areas (where tendons insert into bone) with joint line tenderness, swelling, and often loss of range of motion. Pitting of the fingernails often correlates with the extent and severity of the disease. Dactylitis—swelling of a whole digit—is a characteristic clinical finding, and inflammatory eye disease (iritis, uveitis) may occur. More than one-third of patients with PsA will develop dactylitis and enthesopathy (a disease process at the site where muscle tendons or ligaments insert into bones or joints).

The etiology and pathogenesis of psoriasis and PsA are not completely understood, but genetic, immunologic, and environmental factors are all likely to play a role.[17] Several classification systems have been proposed for the diagnosis of PsA,[18] but which one best represents true PsA remains unclear. Table 2 presents the CASPAR (ClASsification of Psoriatic ARthritis) as an example of one classification.[19]

Table 2. CASPAR criteria for the diagnosis of psoriatic arthritis

Inflammatory articular disease (joint, spine, or enthesial areas) with ≥ 3 points from the following	
1.	Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
2.	Typical psoriatic nail dystrophy including onycholysis, pitting, or hyperkeratosis
3.	Negative test result for the presence of rheumatoid factor
4.	Current dactylitis or history of dactylitis
5.	Radiographic evidence of juxtaarticular new bone formation

Source: Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.[19]

Treatment of Rheumatoid Arthritis and Psoriatic Arthritis

Overview

Treatment of patients with RA or PsA is aimed primarily at controlling pain and inflammation and, ultimately, at slowing or arresting the progression of joint destruction.

Corticosteroids. Corticosteroids—sometimes referred to as glucocorticoids or steroids—are used for many inflammatory and autoimmune conditions. As a class, corticosteroids have been used since the discovery of cortisone in the 1940s. Commonly used corticosteroids include betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone. The drugs differ in their relative potency and available modes of administration. Betamethasone and dexamethasone are the most potent of the corticosteroids, whereas cortisone and hydrocortisone are the least potent. Frequently used agents for oral administration are prednisone and methylprednisolone. Methylprednisolone, betamethasone, and triamcinolone are used for intra-articular therapy.

Corticosteroids are a synthetic form of cortisol, a hormone produced by the adrenal glands. They produce their anti-inflammatory and immunosuppressive response by interacting with steroid-specific receptors in the cytoplasm of cells, thereby inhibiting the movement of inflammatory cells into the site of inflammation, inhibiting neutrophil function, and inhibiting prostaglandin production. They are widely prescribed as an oral treatment for RA because of their ability to reduce inflammation and subsequent joint pain and swelling. When used in PsA, corticosteroids are most often given as a joint injection rather than orally.

Synthetic disease-modifying antirheumatic drugs (DMARDs). Synthetic DMARDs such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide modify the course of inflammatory conditions, presumably through their effects on the immune system. Most of the synthetic DMARDs have been used in clinical practice for more than 20 years. MTX was developed in the 1940s as a treatment for leukemia but was not approved for the treatment of arthritis until 1988. Sulfasalazine also has been available since the 1940s; it is a combination salicylate (acetylsalicylic acid) and antibiotic (sulfapyearidine) that originally was used to treat

patients with inflammatory bowel disease. Hydroxychloroquine, approved in the 1950s for the treatment of malaria, is believed to work in arthritis by interfering with antigen presentation and the activation of immune response by increasing the pH within macrophage phagolysosomes. Additionally, hydroxychloroquine possibly inhibits toll-like receptors that mediate proinflammatory cytokine production. Only leflunomide, an isoxazole immunomodulatory agent, was specifically developed for treating inflammatory arthritis; the U.S. Food and Drug Administration (FDA) approved its use in 1998.

Synthetic DMARDs are not members of a single drug family. They are classified together, however, because they all are slow acting with the aim of improving symptoms, reducing or preventing joint damage, and preserving structure and function in patients with inflammatory disease. All the synthetic DMARDs covered in this review can be given orally, although methotrexate can also be injected.

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new category of DMARDs that differ from synthetic DMARDs in that they target specific components of the immune system. The FDA approved the first of the biologics (infliximab) in 1998; this report covers five additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), and rituximab (2006). Of the six agents, all are currently FDA approved for treating RA, but only adalimumab, etanercept, and infliximab are approved for treating PsA.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, etanercept, and infliximab are known as TNF inhibitors (i.e., drugs that block specific proinflammatory mediators known as cytokines). They produce their primary effect by blocking TNF from interacting with cell surface TNF receptors. Adalimumab and infliximab are monoclonal antibodies. Adalimumab is a fully human monoclonal antibody that binds specifically to TNF, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Infliximab is a chimeric (i.e., made from human and mouse proteins) monoclonal antibody that binds specifically to human TNF. Etanercept is not a monoclonal antibody, but rather a TNF-soluble receptor protein. More specifically, it is a soluble dimeric form of the p75 TNF receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). Etanercept exerts its action by binding circulating TNF and preventing it from interacting with a cell surface receptor.

IL-1, another naturally occurring cytokine, has both immune and proinflammatory actions. Anakinra is a human recombinant protein that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agent abatacept produces its immune response by interfering with T lymphocyte activation. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.

Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. Thus, it in effect removes circulating B cells from the pre-B cell stage through the activated B cells. B cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in RA.

Tables 3 and 4 provide detailed information on agents used in the treatment of RA and PsA that we have included in this review. Table 3 documents names, manufacturers, and available dosage forms. Table 4 shows routes of administration, labeled uses, and usual (recommended) adult doses and frequency for RA and PsA.

Table 3. Pharmaceutical treatments for rheumatoid arthritis and psoriatic arthritis

Class	Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
Corticosteroids				
	Betamethasone	Celestone®, Soluspan®	Multiple	Injectable—3 mg/ml and 6 mg/ml Syrup—0.6 mg/5 ml Topical—cream, lotion, ointment (multiple strengths)
	Budesonide	Entocort® EC	AstraZeneca	Tabs—3 mg
	Cortisone	Cortone®	Multiple	Tabs—5 and 25 mg
	Dexamethasone	Decadron®, Maxidex®	Multiple	Injectable—4 and 10 mg/ml Solution—0.5 mg/5 ml, 1 mg/ml Tabs—0.5, 1.5, 2, and 4 mg
	Hydrocortisone	Cortef®, Solu-Cortef®	Multiple	Injectable—100, 250, 500, and 1,000 mg vials Tabs—5, 10, and 20 mg Topical—cream, foam, gel, lotion, ointment, solution (multiple strengths)
	Methylprednisolone	Medrol®, Depo-Medrol®, Solu-Medrol®	Multiple	Injectable (acetate)—20, 40, and 80 mg/ml Injectable (sodium succinate)—40, 125, and 500 mg, 1 and 2 g vials Tabs—2, 4, 8, 16, and 32 mg
	Prednisone	Deltasone®, Sterapred®, LiquiPred	Multiple	Solution—1 and 5 mg/ml Tabs—1, 2.5, 5, 10, 20, and 50 mg
	Prednisolone	Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®	Multiple	Solution/Syrup—5, 6.7, 15, and 20 mg/5 ml Tabs—5 and 15 mg
	Triamcinolone	Aristospan®, Kenacort® Kenalog®	Multiple	Injectable (acetonide)—10 and 40 mg/ml Injectable (hexacetonide)—5 and 20 mg/ml Tabs—4 mg Topical—aerosol, cream, lotion, ointment, paste
Synthetic DMARDs				
	Hydroxychloroquine	Plaquenil®	Multiple	Tabs—200 mg
	Leflunomide	Arava®	Multiple	Tabs—10 and 20 mg
	Methotrexate	Trexall®, Folex®, Rheumatrex®	Multiple	Injectable—25 mg/ml, 20 mg and 1 g vials Tabs—2.5, 5, 7.5, 10, and 15 mg
	Sulfasalazine	Azulfidine®, EN-tabs®, Sulfazine®	Multiple	Suspension—250 mg/5 ml Tabs—500 mg
Biologic DMARDs				
	Abatacept	Orencia®	Bristol Myers Squibb	Injectable—250 mg vial
	Adalimumab	Humira®	Abbott	Injectable—40 mg/0.8 ml syringe
	Anakinra	Kineret®	Amgen	Injectable—100 mg/0.67 ml syringe
	Etanercept	Enbrel®	Amgen Wyeth Immunex	Injectable—50 mg/ml, 25 mg vial

Table 3. Pharmaceutical treatments for rheumatoid arthritis and psoriatic arthritis (continued)

Class	Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
	Infliximab	Remicade®	Centocor	Injectable—100 mg vial
	Rituximab	Rituxan®	Genentech IDEC	Injectable—10 mg/ml vial

DMARD, disease-modifying antirheumatic drug.
*Listed trade names are limited to commonly prescribed U.S. products when multiple are available.

Table 4. Route, labeled use, and usual dose of treatments for rheumatoid arthritis and psoriatic arthritis

Class	Generic Name	Route	Labeled Use*	Usual Adult Dose
Corticosteroids				
	Betamethasone	Injectable Oral Topical	NSA	IM—0.6 to 9 mg/day in 1 or 2 divided doses Intrabursal, intra-articular, intradermal, intralesional—0.25 to 2 ml Oral—2.4 to 4.8 mg/day in 2 to 4 divided doses Topical—1 to 2 times daily as needed
	Budesonide	Oral	Crohn's	Oral—9 mg once daily for up to 8 weeks
	Cortisone	Oral	NSA	Oral—25 to 300 mg/day in 1 or 2 divided doses
	Dexamethasone	Injectable Oral	NSA	IM, IV, oral—0.75 to 9 mg/day in 2 to 4 divided doses
	Hydrocortisone	Injectable Oral Topical	NSA	IM, IV, oral—15 to 240 mg/day in 2 divided doses Intralesional, intra-articular, soft tissue injection—10 to 37.5 mg Topical—2 to 4 times daily as needed
	Methylprednisolone	Injectable Oral	NSA	IM (acetate)—10 to 80 mg every 1 to 2 weeks IM (sodium succinate)—10 to 80 mg daily Intra-articular, intralesional (acetate)—4 to 80 mg every 1 to 5 weeks IV (sodium succinate)—10 to 40 mg every 4 to 6 hours; up to 30 mg/kg every 4 to 6 hours Oral—2 to 60 mg in 1 to 4 divided doses to start, followed by gradual reduction
	Prednisone	Oral	NSA	Oral—Use lowest effective dose (≤ 7.5 mg/day)
	Prednisolone	Oral	NSA	Oral—Use lowest effective dose (5 to 7.5 mg/day)
	Triamcinolone	Injectable Oral Topical	NSA	IM—2.5 to 60 mg Intra-articular, intralesional, intradermal, intrasynovial—1 to 40 mg Oral—8 to 16 mg/day Topical—2 to 4 times daily as needed
Synthetic DMARDs				
	Hydroxychloroquine	Oral	RA	Oral—200 to 400† mg/day in 1 or 2 divided doses
	Leflunomide	Oral	RA	Oral—10 to 20 mg/day in a single dose
	Methotrexate	Injectable Oral	RA	IM, IV, oral—7.5 to 25 mg/week in a single dose
	Sulfasalazine	Oral	RA	Oral—500 to 3,000 mg/day in 2 to 4 divided doses

Table 4. Route, labeled use, and usual dose of treatments for rheumatoid arthritis and psoriatic arthritis (continued)

Class	Generic Name	Route	Labeled Use*	Usual Adult Dose
Biologic DMARDs				
	Abatacept	Injectable	RA	IV—Dosed according to body weight (< 60 kg = 500 mg; 60-100 kg = 750 mg; > 100 kg = 1,000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter
	Adalimumab	Injectable	PsA	SQ—40 mg every other week
			RA	SQ—40 mg every other week; may increase to 40 mg per week in patients not taking concomitant methotrexate
	Anakinra	Injectable	RA	SQ—100 mg/day; dose should be decreased to 100 mg every other day in renal insufficiency
	Etanercept	Injectable	PsA, RA	SQ—25 mg twice weekly or 50 mg once weekly
	Infliximab	Injectable	PsA	IV—5 mg/kg, with or without methotrexate, at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter
			RA	IV—3 mg/kg in combination with methotrexate at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treat as often as every 4 weeks
	Rituximab	Injectable	RA	IV—1,000 mg on days 1 and 15 in combination with methotrexate

DMARD, disease-modifying antirheumatic drug; IM, intramuscular; IV, intravenous; NSA, nonspecific anti-inflammatory (or immunosuppressant) indication; PsA, psoriatic arthritis; SQ, subcutaneous; RA, rheumatoid arthritis.
*Labeled use limited to RA and PsA unless otherwise indicated.
† Initial dose is 400-600 mg/day for 4 to 12 weeks

Disease-Specific Treatments

Rheumatoid arthritis. In RA, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in early or mild disease, but they do not have any disease-modifying properties. For RA, the synthetic DMARD MTX is the cornerstone of treatment, as it has demonstrated good disease control. However, MTX toxicity may limit its use, and many patients do not adequately respond to MTX monotherapy.

Combination therapies serve an important role because treatment with a single DMARD often does not adequately control symptoms. Low-dose systemic corticosteroids (prednisone 7.5-10 mg/day) or intra-articular corticosteroids are used as an adjunct to DMARDs. In patients with persistent disease despite aggressive management with standard agents, biologic agents, often in combination with MTX, are now considered the standard of care.

There is debate as to which types of combination therapy are preferred and how early in the disease process to initiate this intervention. No settled opinion exists as to whether treatment should proceed in a sequential "step-up" approach (progressing from single therapy to combination therapy) or in a "step-down" approach (beginning with combination therapy and stepping down treatment when symptoms are under control). Additionally, uncertainty remains regarding risks and benefits of therapies in patient subgroups.

Two recent reports examined some of the biologic DMARDs in the treatment of RA. The first included a meta-analysis of the benefits and harms of three biologics (adalimumab,

etanercept, and infliximab).[20] It found that these three drugs were more efficacious than placebo for RA patients who are not well controlled by conventional DMARDs, specifically for improving control of symptoms, increasing physical function, and slowing radiographic changes in the joints. The second report used meta-regression techniques and found that anakinra was less effective than infliximab, etanercept, or adalimumab;[21] when the researchers accounted for disease duration and baseline quality-of-life scores, the three biologics appeared better than anakinra. These studies support the overall efficacy of biologics. Nonetheless, examining comparative efficacy and effectiveness with synthetic DMARDs and corticosteroids, as well as long-term outcomes and subpopulations, is warranted.

Psoriatic arthritis. Historically, few PsA trials have been conducted, and management has been adapted from RA trial data. With the introduction of biologic therapy, however, dedicated PsA trials have demonstrated efficacy in this distinct disease. The first line of treatment of PsA is NSAIDs, although in most cases DMARDs are necessary. MTX is particularly useful because it treats the psoriasis in addition to the arthropathy. Corticosteroids may be used to control inflammation, but they do not have much of a role in chronic disease management in psoriatic disease. The tapering or withdrawal of steroids in PsA has been associated with severe flares of skin disease. When chronic disease continues to be active despite the use of MTX, biologics are indicated. Biologics most often are given in combination with synthetic DMARDs (e.g., MTX).

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and harms of corticosteroids, synthetic DMARDS, and biologic DMARDs in the treatment of patients with RA and PsA. We address the following four key questions (KQs):

KQ 1. For patients with rheumatoid or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission?

KQ 2. For patients with rheumatoid or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?

KQ 3. For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?

KQ 4. What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?

For each key question, we evaluated specific outcome measures as reported in Table 5. For efficacy and effectiveness, we focused on head-to-head trials and prospective observational studies comparing one drug to another. For biologic DMARDs, we also included placebo-controlled, double-blinded randomized controlled trials (RCTs). For safety and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and prospective and retrospective observational studies.

Because equipotency among the reviewed drugs is not well established, we assume that comparisons made within the recommended dosing ranges in Table 4 are appropriate. Dose comparisons made outside the recommended daily dosing range are not in our report.

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by key question (RA followed by PsA), and discusses the implications of those results for clinical applications and future research. Appendix A lists our peer reviewers; Appendix B describes our search strategy; Appendix C contains studies included in meta-analyses; Appendix D lists excluded studies; Appendix E presents evidence tables; Appendix F contains abstract-only studies; Appendix G presents the criteria for assessing the quality of individual studies; Appendix H provides characteristics of studies with poor internal validity; and Appendix I describes clinical assessment scales commonly used in arthritis trials.

Table 5. Outcome measures and study eligibility criteria

Key Questions, Outcomes of Interest, and Specific Measures	Study Eligibility Criteria
KQ 1 /KQ 2: Efficacy/effectiveness **KQ 1:** • Patient symptoms • Radiographic joint damage • Remission **KQ 2:** • Functional capacity • Quality of life	**Study Design** • Head-to-head double-blind RCTs • High-quality systematic reviews • Prospective, controlled observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100
KQ 3: Harms, tolerability, adherence, adverse effects	**Study Design** • Head-to-head double-blind RCTs • High-quality systematic reviews • Observational studies, prospective and retrospective **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100
KQ 4 **Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities**	**Study Design** • Head-to-head double-blind RCTs • High-quality systematic reviews • Observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA or PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100

KQ, key question; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Methods

Topic Development

The topic of this report and preliminary key questions arose through a public process involving the public, the Scientific Resource Center (SRC, at www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#RC) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#SG). Investigators from the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) then refined the original questions, in consultation with AHRQ and the SRC through multiple conference calls, into the final set of key questions cited in the introduction.

Literature Search

To identify articles relevant to each key question we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix B. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (rheumatoid arthritis [RA], psoriatic arthritis [PsA]), drug interactions, and adverse events with a list of nine corticosteroids (betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone), four synthetic disease-modifying antirheumatic drugs (DMARDs, including methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and six biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to September 2006 to capture literature relevant to the scope of our topic.

We used the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We also manually searched reference lists of pertinent review articles and letters to the editor. We imported all citations into an electronic database (EndNote 8.0). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the U.S. Food and Drug Administration (FDA).

The SRC contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies (Abbott, Amgen, Bristol-Myers Squibb, Centocor, and Genetech).

Our searches found 1,957 citations, unduplicated across databases. Additionally, we identified 166 articles from manually reviewing the reference lists of pertinent review articles. Twenty-eight other studies came from pharmaceutical dossiers, and two additional studies came from peer review or public comments. The total number of citations in our database was 2,153.

Study Selection

We developed eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to medications inside our scope of interest. Table 5 in the introduction describes the criteria in more detail. Because multiple large RCTs had been conducted in this drug class, we adopted a minimum sample size requirement ($N \geq 100$) to be able to focus on the best available evidence.

Two persons independently reviewed abstracts. If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility criteria to determine which, if any, to exclude at this stage. We did not include studies that met eligibility criteria but were reported as an abstract only. These studies are listed in Appendix F.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. We defined head-to-head trials as those comparing one drug of interest with another. RCTs or prospective cohort studies of at least 3 months' duration and an adult study population with a sample size of at least 100 participants were eligible for inclusion.

For harms (i.e., evidence pertaining to safety, tolerability, and adverse events), we examined data from both experimental and prospective and retrospective observational studies. We included RCTs and observational studies with large sample sizes (≥100 patients), lasting at least 3 months, that reported an outcome of interest.

Initially, we reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness, for example, were clinical response to treatment, remission, functional capacity, and quality of life. In addition, we included radiographic outcomes as intermediate outcome measures. For harms, we looked for both overall and specific outcomes ranging in severity (e.g., serious infections, malignancies, hepatotoxicity, hematological adverse events, infusion and injection reactions, nausea), withdrawals attributable to adverse events, and drug interactions.

We included meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality.[22] We did not abstract individual studies if they had been used in an included meta-analysis; studies in this group that met eligibility criteria are cited in Appendix C. However, we reviewed them to determine whether any other outcomes of interest were reported. Appendix D summarizes reasons for exclusion of studies that were reviewed as full text articles but did not meet eligibility criteria.

Data Extraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating.

We abstracted the following data from included articles: study design, eligibility criteria, intervention (drugs, dose, and duration), additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or mean disease duration), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available. All data

abstraction employed SRS 3.0, TrialStat™ Corporation. Evidence tables containing all abstracted data of included studies are presented in Appendix E.

Quality Assessment

To assess the quality (internal validity) of trials, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[23] and the National Health Service Centre for Reviews and Dissemination.[24] Elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients were analyzed as randomized with missing values imputed), adequacy of blinding, and overall and differential loss to followup.

In general terms, a "good" study has the least bias and results are considered to be valid. A "fair" study is susceptible to some bias, but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To assess the quality of observational studies, we used criteria outlined by Deeks et al.[25] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party. Appendix G details the predefined criteria used for evaluating the quality of all included studies.

Studies that met all criteria were rated good quality. The majority of studies received a quality rating of fair. This category includes studies that presumably fulfilled all quality criteria but did not report their methods to an extent that answered all our questions. Time constraints precluded our contacting study authors for clarification of methodological questions. Thus, the fair-quality category includes studies with quite different strengths and weaknesses. Studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high probability of bias) in one or more categories were rated poor quality and, generally, excluded from our analyses. If no other evidence on an outcome of interest was available, we comment on findings from poor studies. Poor-quality studies and reasons for that rating are presented in Appendix H.

Applicability Assessment

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies.[26] We deemed studies that met at least six of seven predefined criteria to be effectiveness studies (Table 6). The results of effectiveness studies are more applicable to the spectrum of patients that will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies.

Table 6. Criteria for effectiveness studies

Criteria	Relevance to Treatment of RA or PsA
Study population	Primary care population
Less stringent eligibility criteria	Determine case by case
Health outcomes	Response, remission, quality of life, functional capacity, hospitalization
Clinically relevant treatment modalities	> 8 week study duration; flexible dose design; physician-based diagnosis
Assessment of adverse events	Always
Adequate sample size to assess a minimally important difference from a patient perspective	N > 150
Intention-to-treat analysis	Always

PSA, psoriatic arthritis; RA, rheumatoid arthritis.

Rating Strength of a Body of Evidence

We rated the strength of the available evidence in a three-part hierarchy based on an approach devised by the GRADE working group.[27] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates four key elements: study design, study quality, consistency, and directness. It also considers the presence of imprecise or sparse data, high probability of publication bias, evidence of a dose gradient, and magnitude of the effect.

As shown in Table 7, we used three grades: high, moderate, and low (combining the GRADE category of very low with low).[28] Grades reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and harms of drugs to treat RA and PsA. The critical element is the extent to which new evidence might alter the confidence we would have in our findings. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals.

Table 7. Definitions of the grades of overall strength of evidence

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.

Source: Adapted from the GRADE working group (Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. 2004;4(1):38.)

This approach does not incorporate other factors, such as funding sources and comparable dosing, that might be relevant to assess reliably comparative efficacy, effectiveness, and harms. We have assessed these additional factors and highlighted issues that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

Data Synthesis

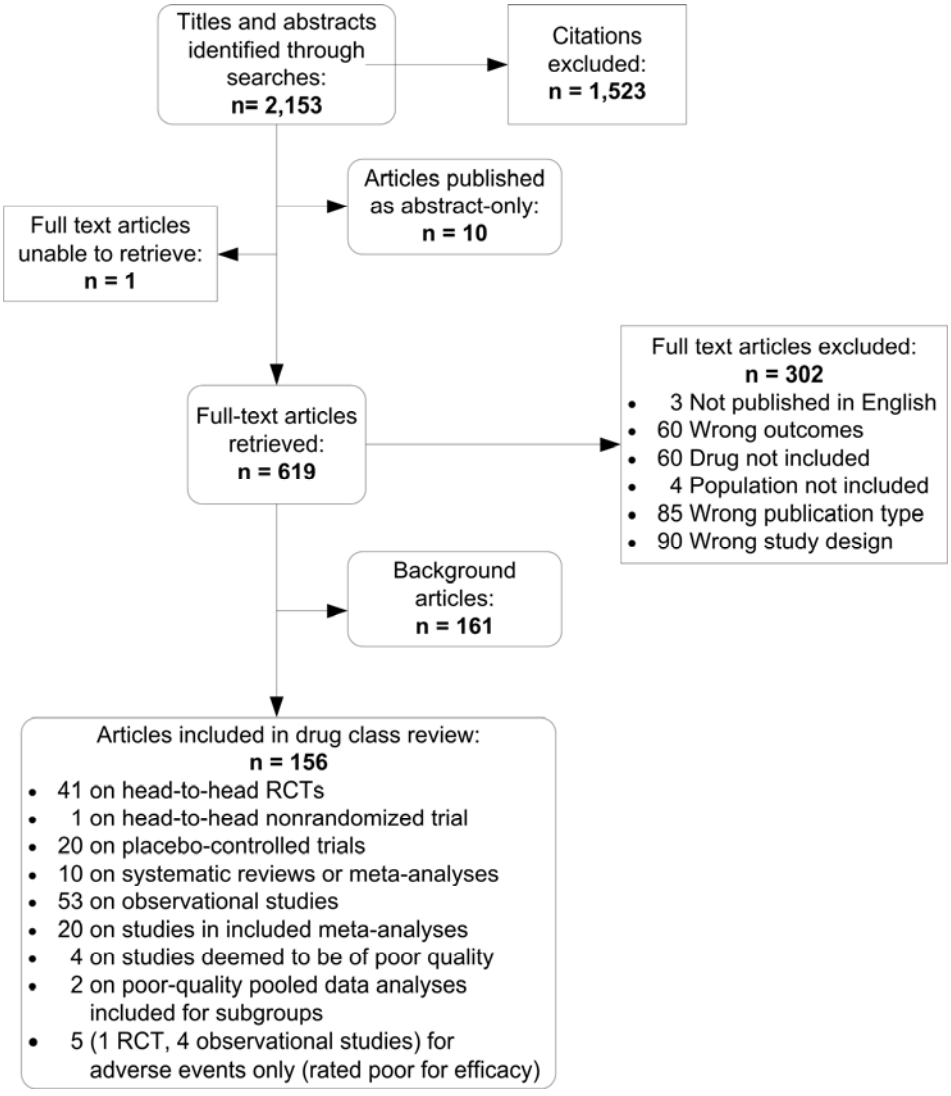
Throughout this report we synthesized the literature qualitatively. Comparisons of the drugs that had not yet been quantitatively analyzed in any of the meta-analyses or indirect comparisons that we included either were limited to fewer than three good or fair RCTs or had noncomparable study populations. Therefore, we did not attempt any quantitative analyses of such comparisons.

As is customary for all comparative effectiveness reviews done for AHRQ, the SRC requested review of this report from three outside rheumatology experts in the field. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and key questions. Our peer reviewers (listed in Appendix A) gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. In addition, the SRC placed the draft report on the AHRQ website (http://effectivehealthcare.ahrq.gov/) and compiled the comments for our review. Twenty-four public reviewers submitted comments. They represented advocacy groups, the pharmaceutical industry, and practicing physicians. Based on these comments, we revised the text where appropriate.

Results

We identified 2,153 citations from our searches (Appendix B). Figure 1 documents the results of the literature search. Working from 619 articles retrieved for full review, we included 161 for background and excluded 302 at this stage (Appendix D). We included 156 published articles reporting on 103 studies: 22 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 13 placebo-controlled trials, 10 meta-analyses or systematic reviews, and 55 observational studies. Our findings include studies rated good or fair, unless a particular study rated poor provides some unique information that we judged to be of interest. We included 2 poor-quality pooled data analyses on subgroups. Most studies were of fair quality; we designate in the text only those of good or poor quality. Evidence tables for included studies, by key question (KQ), can be found in Appendix E.

Figure 1. Results of literature search*



*Number of included articles differs from number of included studies because some studies have multiple publications.

We excluded articles based on eligibility criteria or methodological criteria (quality rating) as explained in Chapter 2. We excluded six studies that originally met eligibility (inclusion) criteria but were subsequently rated as poor quality after full review (Appendix H). The main reasons for poor ratings were high loss to followup and selection bias.

Of the 103 included studies, 51 (50 percent) were supported by pharmaceutical companies; 21 (20 percent) were funded by governmental or independent funds; and 11 (11 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 20 (19 percent) studies.

This chapter is organized by key question and, within each question, by disease (first rheumatoid arthritis [RA] and then psoriatic arthritis [PsA]). We then present findings in order by class of drugs, types of drugs, and combinations of drugs as appropriate to the condition and the particular key question. Generally, the chapter is organized using the following main analytic categories: corticosteroids vs. corticosteroids, synthetic disease-modifying antirheumatic drugs (DMARDs) vs. synthetic DMARDs, synthetic DMARD combinations (with or without corticosteroids) vs. synthetic DMARD combinations, biologics vs. biologics, biologics vs. corticosteroids, biologics vs. synthetic DMARDs, biologics plus synthetic DMARDs vs. biologics, and biologics plus synthetic DMARDs vs. synthetic DMARDs (see Table 3 in the introduction).

Across all key questions and both diseases, we have included head-to-head studies with either active or placebo controls (or both), observational studies, and other systematic reviews. When comparative evidence is available, we discuss it before presenting placebo-controlled trials. This occurs for RA only for KQ 3 and KQ 4 on harms and subgroups. PsA involves only placebo-controlled trials.

Table 8 below gives the numbers of trials or studies for drug class comparisons, only for RA, and reported only from *head-to-head trials or studies;* when some groupings have important subcomparisons, we note these in Table 8 as well. We do not, however, offer an exhaustive list of all *possible* comparisons among corticosteroids, synthetic DMARDs, and biologic DMARDs simply because of the sheer number of potential combinations of drugs within classes and across classes, which cannot be clearly and concisely presented here.

Table 8. Number of head-to-head trials or studies by drug comparison for rheumatoid arthritis

Drug Comparison	Number of Trials or Studies; Quality Rating
Corticosteroids vs. corticosteroids	1; 1 fair
Synthetic DMARDs vs. synthetic DMARDs	7; 1 good, 6 fair
Synthetic DMARD combinations	11; 5 good, 6 fair
Biologic DMARDs vs. biologic DMARDs	8; 2 good, 6 fair
Biologic DMARDs vs. synthetic DMARDs	4; 4 fair
Biologic DMARD + synthetic DMARD combinations	10; 2 good, 8 fair

DMARD, disease modifying anti-rheumatic drug.
*No head-to-head drug comparison studies were available for psoriatic arthritis; all were placebo-controlled studies.

Table 9 lists abbreviations and full names of diagnostic scales and health status or quality-of-life instruments encountered in these studies. For further details about such instruments and scales, see Appendix I**.**

Table 9. Diagnostic scales and quality-of-life instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by
ACR-N	American College of Rheumatology percent improvement from baseline to endpoint	0 to 100 percent	Increase
ACR 20/50/70*	American College of Rheumatology response scores based on 20, 50, or 70 percent criteria for improvement	0 to 100 percent	Increase
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)	0 to 100	Increase
DAS*	Disease Activity Score	0 to 10	Decrease
DAS 28	Disease Activity Score Short Form	0 to10	Decrease
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase
HAQ* (D-HAQ)	Health Assessment Questionnaire (Dutch Version)	0 to 3	Decrease
HAQ-DI	Disability Index of the Heath Assessment Questionnaire	0 to 3	Decrease
Larsen Scale*	Larsen Scale for Grading Radiographs in Rheumatoid Arthritis	0 to 250	Decrease
PASI*	Psoriasis Area and Severity Index	0 to 72	Decrease
PsARC*	Psoriatic Arthritis Response Criteria	0 to 100 percent	Increase
SF-36*	Medical Outcomes Study Short Form 36 Health Survey	0 to 100	Increase
Sharp Scale	Sharp Scoring System for Radiographic Rheumatoid Arthritis	Erosion: 0 to 170 Narrowing: 0 to 144	Decrease
SHS*	Sharp/van der Heijde Method (SHS) for Scoring Radiographs (SHS is frequently modified by individual authors to meet study requirements and needs; there is no standard modified SHS)	Erosion: 0 to 160 for hands; 0 to 120 for feet Joint space narrowing: 0 to 168 Total: 0 to 448	Decrease
SOFI	Signals of Functional Impairment Scale	0 to 44	Decrease

* These key scales are defined in Appendix I.

Key Question 1: Reductions in Symptoms, Limitations of Disease Progression, and Maintenance of Remission

This key question concerned three main topics for both diseases. Specifically, "for patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission?" As noted earlier, we address first the evidence about RA and then the information about PsA. Tables 10 and 11 provide selected study-specific information on outcomes, broken out by primary outcomes in Table 10 and by radiologic outcomes in Table 11, for ease of comparison. Evidence Tables 1 (for head-to-head studies) and 2 (for systematic reviews and meta-analyses) in Appendix E document details about all these studies.

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Corticosteroids vs. Corticosteroids					
Kirwan et al., 2004[29]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	No significant difference between 9 mg BUD and PNL for ACR 20, DAS (ACR 20: 42% vs. 56%; *P* = 0.11)	Fair
Synthetic DMARDs vs. Synthetic DMARDs					
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	At 18 months, no significant difference in DAS for SSZ vs. MTX (-0.30 vs. -0.26; *P* = 0.79); no significant difference in any ACR responses	Fair
Dougados et al., 1999[31]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in DAS between SSZ vs. MTX (-1.15 vs. -0.87; *P* = NS, NR); no significant difference in ACR 20 responses; *P* = NR	Fair
Emery et al., 2000[32]	RCT 999 1 year with optional 2nd year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Lower ACR 20 responses at 12 months (50.5% vs. 64.8%; *P*<0.001); no significant differences in ACR at 2 years (64.3% vs. 71.7%; *P* = NS, NR)	Fair
Haagsma et al., 1997[33]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week	No significant difference in DAS for SSZ vs. MTX (-1.6 vs. -1.7; *P* = NS, NR)	Fair
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week)	Lower ACR 20 responses for LEF vs. MTX at 12 months (OR, 1.43; 95% CI, 1.15-1.77; *P* = 0.001); no significant differences in ACR response rates at 2 years	Good

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Osiri et al., 2003 (cont'd)			LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	Higher ACR 20 and ACR 50 responses for LEF vs. SSZ at 24 months (ACR 20: OR, 0.35; 95% CI, 0.16-0.77; *P* = 0.009) (ACR 50: OR, 0.32; 95% CI, 0.15-0.67*; P* = 0.003); no significant differences in any ACR response rates at 6 and 12 months	
Smolen et al., 1999;[35] Larsen et al., 2001[36]	RCT 358 24 weeks (12 and 24 month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Similar ACR 20 response rates (48% vs. 44%; *P* = NR)	Fair
Strand, et al., 1999[37,38]	RCT 482 12 months (1 year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	At 1 year, ACR 20 numerically higher for LEF but not significant (52% vs. 46%; *P* = NR); at 2 years, ACR 20 difference not significant (79% vs. 67%; *P* = 0.019)	Fair
Synthetic DMARD Combinations vs. Monotherapy or Combinations, With or Without Corticosteroids					
Boers et al., 1997;[39] Landewe et al., 2002[40] COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2 g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Pooled disease index: mean change better in combo group than SSZ alone at 28 weeks (1.4 vs. 0.8; *P* < 0.0001) vs. no longer significant at 52 weeks (1.1 vs. 0.9; *P* = 0.20) (Pooled index included tender joint count, grip strength, ESR, VAS, MACTAR questionnaire)	Good
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland, 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	Combination therapy better than monotherapy MTX or SSZ for DAS (-0.67, -0.30, -0.26; *P* = 0.039 for SSZ + MTX vs. SSZ*; P*= 0.023 for SSZ + MTX vs. MTX) No significant difference in ACR responses	Fair

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Dougados et al., 1999[31] Maillefert et al., 2003[41]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR responses (65 vs. 59 vs. 59; *P* = NS, NR) DAS change (-1.26 vs. -1.15 vs. -0.87; *P* = 0.019) DAS change NS at year 5	Fair
Goekoop-Ruiterman et al., 2005[42] BeSt study	RCT 508 12 months	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1to 5); median duration of symptoms 23 weeks (IQR 14 to 53)	1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	DAS ≤ 2.4: 53%, 64%, 71%, 74%; *P* = 0.004 for 1 vs. 3; *P* = 0.001 for 1 vs. 4; *P* = NS for other comparisons	Good
Haagsma et al., 1997[33]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	MTX (7.5 to 15 mg/week) + SSZ (2 to 3 g/day) vs. SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR or DAS responses	Fair
Mottonen et al., 1999;[43] Korpela et al., 2004[44] FIN-RACo study	RCT 199 24 months (5 year follow-up)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day) + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	Remission (defined by ACR preliminary criteria modified by authors) higher in combination group (37.9% vs. 18.4%; *P* = 0.011); ACR 50 higher in combination group (71% vs. 58%; *P* = 0.058); (5-year remission, NS, 28% vs. 22%; *P* = NS)	Fair
O'Dell et al., 2002[45]	RCT 171 2 years	Mean disease duration 5.8 to 7.9 years	1: MTX (7.5 titrated to 17.5 mg/week) + SSZ (2 g/day) + HCQ (400 mg/day) vs. 2: MTX + HCQ vs. 3: MTX + SSZ	ACR 20: 78%, 60%, 49% 1 vs. 2: *P* = 0.05 1 vs. 3: *P* = 0.002	Good

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
O'Dell et al., 1996[46]	RCT 102 2 years	Poor response to at least 1 DMARD; mean disease duration 6 to 10 years	1: MTX (7.5 to 17.5 mg/week) + SSZ (1 g/day) + HCQ (400 mg/day) vs. 2: MTX (7.5 to 17.5 mg/week) vs. 3: SSZ (1 g/day) + HCQ (400 mg/day)	50% improvement (defined by authors): 77%, 40%, 33% 1 vs. 3: $P < 0.001$ 1 vs. 2: $P = 0.003$	Good
Svensson et al., 2005[47]	Open-label trial 250 2 years	Population-based; active RA; duration 1 year or less	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	More patients in DMARD + PNL combination group achieve remission (DAS < 2.6) than DMARD-only group (55.5% vs. 43.8%; $P = 0.0005$)	Fair
Biologic DMARDs vs. Biologic DMARDs					
Clark et al., 2004[48]	Meta-analysis NR	Patients who have failed MTX treatment; mean disease duration varied	ANA vs. Anti-TNF as a class	Significantly lower ACR 20 response rates of anakinra than anti-TNF as a class. Risk difference: -0.21 (95% CI, -0.32-0.10)	Good
Gartlehner et al., 2006[49]	Meta-analysis 5,248	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ANA (100 mg/day), ETA (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in efficacy among anti-TNF drugs; greater efficacy of anti-TNF drugs than anakinra on ACR 20: RR, 0.61 (95% CI, 0.39-0.96)	Good
Geborek et al., 2002[50]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher)	Higher ACR 20 responses for ETA at 3 (data NR; $P < 0.02$) and 6 months (data NR; $P < 0.05$); no significant differences in ACR response rates at 12 months (data NR)	Fair
Hochberg et al., 2003[51]	Meta-analysis 1,053	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ETA (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in ACR 20 response rates among anti-TNF drugs	Fair
Kristensen et al., 2002[52]	Prospective cohort study 949 36 months	Inadequate response to at least 2 DMARDs	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher)	No difference in ACR 50 response at 36 months (data NR)	Fair
Wailoo et al., 2006[21]	Meta-analysis 6,694	Patients with RA; mean disease duration varied	INF, ETA, ANA, ADA	No difference in ACR 50 response rates among anti-TNF drugs	Fair
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Higher mACR 20 response rates for ETA than INF (41% vs. 26%; P = NR)	Fair

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Biologic DMARDs vs. Synthetic DMARDs					
Bathon et al., 2000;[54] Genovese et al., 2002;[55] Genovese et al., 2005[56] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for ETA 25 mg than for MTX (data NR; $P < 0.05$)	Fair
Breedveld et al., 2006 [57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Lower ACR 50 response rates for ADA than MTX (37% vs. 43%; P = NR)	Fair
Geborek et al., 2002[50]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETA (25 mg twice weekly) vs. INF (3 mg/kg or higher) vs. LEF (20 mg/day)	Higher ACR 20/50 responses for ETA and INF at 3 months (data NR; $P < 0.05$) and for ETA at 6 months (data NR; $P < 0.05$); results for 12 months: NR	Fair
Listing et al., 2006[58]	Prospective cohort study 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETA, INF; dose NR) vs. DMARDs as a class (dose NR)	Significantly higher chance of remission for biologics than DMARDs (OR, 1.95; 95% CI, 1.20-3.19)	Fair
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher) vs. MTX (10 to 15 mg/week)	Higher mACR 20 response rates for ETA than INF (41% vs. 26%; P = NR)	Fair
Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs					
Genovese et al., 2004[59]	RCT 242 24 weeks	Inadequate control of disease with MTX; mean disease duration 9.9 years	ETA (25 mg twice weekly) + AKA (100 mg/day) vs. ETA (25 mg/week)	Higher ACR 50 response rates for ETA monotherapy (31% vs. 41%; P = 0.914)	Fair
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs					
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	Significantly higher ACR 50 response rates for ADA + MTX than ADA (59% vs. 37%; $P < 0.001$)	Fair

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Combe et al., 2006[60]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETA (25 mg twice weekly)	Similar ACR 20 response rates between ETA + SSZ and ETA (74% vs. 74%; *P* = NR)	Fair
Edwards et al., 2004[61]	RCT 161 24 weeks	Active RA despite MTX treatment; mean disease duration 10.4 years	RIT (1,000 mg/days 1&15) + MTX (>10 mg/day) vs. RIT (1,000 mg/days 1&15) vs. MTX	Higher ACR 50 response rates for the RIT + MTX combination than for RIT monotherapy (43% vs. 33%; *P* = NR)	Fair
Hyrich et al., 2006[62]	Prospective cohort study 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly) + other DMARD (dose NR) vs. ETA (25 mg twice weekly) INF (3 mg/kg) + MTX (dose NR) vs. INF (3 mg/kg) + other DMARD (dose NR) vs. INF (3 mg/kg)	Significantly higher EULAR response rates for ETA + MTX than ETA (OR, 1.98; 1.45-2.71) Higher EULAR response rates for INF + MTX than INF (OR, 1.35; 0.92-2.00)	Good
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETA (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETA + MTX than ETA (18.3%-years vs. 14.7%-years; *P* < 0.0001) at 24 weeks	Fair
Van Riel et al., 2006[66]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETA (25 mg twice weekly) + MTX (>12.5 mg/week) vs. ETA (25 mg twice weekly)	Similar proportions of patients achieved an improvement of > 1.2 units of DAS 28 (75% vs. 73%; *P* = 0.66)	Fair
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Similar mACR 20 response rates for ETA + MTX and ETA (43% vs. 41%; *P* = NR)	Fair
Zink et al., 2005[67]	Retrospective cohort study 1,523 1 year	Patients with RA who had a change in treatment regimen	ETA + MTX vs. ETA (dosages NR) INF + MTX vs. INF, (dosages NR)	Discontinuation due to lack of efficacy: Greater in ETA monotherapy vs. combination (ETA + MTX: 16.9%; ETA: 19.9%; *P* = NR) Greater in INF monotherapy than combination (INF + MTX: 17.9%, INF: 45%)	Good

Table 10. Study characteristics, symptom response, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Biologic DMARDS + Synthetic DMARDs vs. Synthetic DMARDs					
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly higher ACR 50 response rates for ADA + MTX than MTX (59% vs. 43%; *P* < 0.001)	Fair
Combe et al., 2006[60]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. SSZ (2, 2.5, or 3 g/day)	Higher ACR 20 response rates between ETA + SSZ and SSZ (74% vs. 28%; *P* = NR)	Fair
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETA (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETA + MTX than MTX (18.3%-years vs. 12.2%-years; *P* < 0.0001) at 24 weeks	Fair
St Clair et al., 2004;[68] Smolen et al., 2006[69] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for INF 3 mg + MTX and INF 6 mg + MTX than MTX (38.9% vs. 46.7% vs. 26.4%; *P* < 0.001)	Fair

ACR-N, American College of Rheumatology percent improvement from baseline to endpoint; ADA, adalimumab; ANA, anakinra; BUD, budesonide; CI, confidence interval; Combo, combination therapy; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; ETA, etanercept; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquine; INF, infliximab; IQR, interquartile range; LEF, leflunomide; mACR, modified ACR; MACTAR, McMaster Toronto Arthritis Questionnaire; MTX, methotrexate; mg, milligram; NHS, National Health Service; NR, not reported; NS, not significant; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; SSZ, sulfasalazine; TNF, tumor necrosis factor; VAS, visual analog scale; vs., versus.

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Synthetic DMARDs vs. Synthetic DMARDs				
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference in total modified Sharp/van der Heijde score change (Data NR)

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Dougados et al., 1999[31]	RCT 209 (146) 52 weeks (5 years)	Yes	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Total modified Sharp/van der Heijde score change: 4.64 vs. 4.50 vs. 3.36; *P* = NS,NR; change at 5 years: 8.5 vs. 7.5; *P* = 0.7
Emery et al., 2000[32]	RCT 999 1 year with optional 2nd year	No	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Larsen score change at 1 year: 0.3 vs. 0.3; *P* = NS Larsen score change at 2 years: 1.27 vs. 1.31; *P* = NS, NR
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	No	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week) LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	No differences in total Sharp score change or Larsen score change
Smolen et al., 1999;[35] Larsen, et. al., 2001[36]	RCT 358 24 weeks (12 and 24 month followup)	No	LEF (20 mg/day) vs. SSZ (2 g/day)	Larsen score change at 24 weeks: 0.01 vs. 0.01; *P* = NS Larsen score change at 1 year: 0.02 vs. 0.02; *P* = NS Larsen score change at 2 years: -0.07 vs. -0.03; *P* = NR
Strand et al., 1999[37]	RCT 482 12 months (1 year continuation)	No	LEF (20 mg/day) vs. MTX (7.5 to 10 mg/week)	Total Sharp score change at 1 year: 0.53 vs. 0.88 (*P* = 0.05) Total Sharp score at 2 years: 1.6 vs. 1.2 (*P* = 0.659)
Synthetic DMARD Combinations vs. Monotherapy or Combinations, With or Without Corticosteroids				
Boers et al., 1997;[39] Landewe et al., 2002[40] COBRA study	RCT 155 (148) 56 weeks (5 year followup)	Yes	SSZ (2 g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Median modified Sharp/van der Heijde score change improved at 28 weeks (1 vs. 4; *P*< 0.0001), 56 weeks (2 vs. 6; *P* < 0.004) and 80 weeks (4 vs. 12; *P* < 0.01). [At 5 years mean modified Sharp/van der Heijde score change per year was lower for combo (5.6 vs. 8.6; *P*= 0.001)]
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference in total Sharp score (Data NR)

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Dougados et al., 1999;[31] Maillefert et al., 2003[41]	RCT 209 (146) 52 weeks (5 year followup)	Yes	SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	5-year mean modified Sharp/van der Heijde score change: 8.5 vs. 7.5; *P* = 0.7
Goekoop-Ruiterman, 2005[42] BeST study	RCT 508 12 months	Yes	1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d-7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	Median modified Sharp/van der Heijde score change: 2.0, 2.5, 1.0, 0.5; *P* = 0.003 for 1 vs. 3, *P* < 0.001 for 1 vs. 4*; P* = 0.007 for 2 vs. 3*; P*< 0.001 for 2 vs. 4
Mottonen et al., 1999; [43] Korpela et al., 2004[44] FIN-RACo study	RCT 199 24 months (5 years)	Yes	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day), + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	2-year Larsen score change: 2 vs. 10; *P* = 0.002 2-year erosion score change: 2 vs. 3; *P* = 0.006 5-year median Larsen score: 11 vs. 24; *P* =0.001
Svensson et al., 2005[47]	Open-label trial 250 2 years	Yes	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	Median modified Sharp/van der Heijde score change: 1.8 vs. 3.5; *P* = 0.019 Erosion score median change: 0.5 vs. 1.25; *P* = 0.007 Joint space narrowing score median change: 1.0 vs. 2.0; *P* = 0.08
Biologic DMARDs vs. Synthetic DMARDs				
Bathon et al., 2000;[54] Genovese et al., 2002[55] Genovese et al., 2005[56] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Yes; MTX-naive patients with early, aggressive RA	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	At 1 year: Total modified Sharp score change: 1.00 vs. 1.59; *P* = 0.11 Erosion score change: 0.47 vs. 1.03; *P* = 0.002 Joint space narrowing score change: NR At 2 years: Total modified Sharp score change: 1.3 vs. 3.2; *P* = 0.001 Erosion score change: 0.7 vs. 1.9; *P* = 0.001 Joint space narrowing score change: NR

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Total modified Sharp score change: 5.5 vs. 10.4; *P* < 0.001 Erosion score change: 3.0 vs. 6.4; *P* < 0.001 Joint space narrowing score change: 2.6 vs. 4.0; *P* < 0.001
Klareskog et al., 2004[63] van der Heijde et al., 2006[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	No	ETA (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	At 1 year: Total modified Sharp score change: 0.52 vs. 2.80; *P* = 0.047 Erosion score change: 0.21 vs. 1.68; *P* < 0.008 Joint space narrowing score change: 0.32 vs. 1.12; *P* = NR (NS)
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs				
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 5.5; *P* < 0.001 Erosion score change: 1.0 vs. 3.0; *P* < 0.001 Joint space narrowing score change: 0.9 vs. 2.6; *P* < 0.001
Klareskog et al., 2004[63] van der Heijde et al., 2006[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 52 weeks	No	ETA (25 mg twice weekly) + MTX (20 mg/week) vs. ETA (25 mg twice weekly)	At 1 year: Total modified Sharp score change: -0.54 vs. 0.52; *P* = 0.0006 Erosion score change: -0.30 vs. 0.21; *P* < 0.0001 Joint space narrowing score change: -0.23 vs. 0.32; *P* = 0.0007 At 2 years: Total modified Sharp score change: -0.56 vs. 1.10; *P* < 0.05 Erosion score change: -0.76 vs. 0.36; *P* < 0.05 Joint space narrowing score change: 0.20 vs. 0.74; *P* = NR (NS)
Biologic DMARDs + Synthetic DMARDs vs. Synthetic DMARDs				
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 10.4; *P* < 0.001 Erosion score change: 1.0 vs. 6.4; *P* < 0.001 Joint space narrowing score change: 0.9 vs. 4.0; *P* < 0.001

Table 11. Study characteristics and radiographic joint damage in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
St Clair et al., 2004; [68] Smolen et al., 2006[69] ASPIRE study	RCT 1,049 54 weeks	Yes; MTX-naive patients with early, aggressive RA	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Modified Sharp/van der Heijde score change: 0.4 vs. 0.5 vs. 3.7; $P < 0.001$ Erosion score change: 0.3 vs. 0.1 vs. 3.0; $P < 0.001$ Joint space narrowing score change: 0.1 vs. 0.2 vs. 0.6; $P < 0.001$

ADA, adalimumab; Combo, combination therapy; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; MTX, methotrexate; PNL, prednisolone; PRED, prednisone; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine.

Rheumatoid Arthritis: Overview

A total of 21 RCTs, one nonrandomized controlled trial, five observational studies, and five systematic reviews or meta-analyses compared symptom response, radiographic joint damage, and remission. Details are found in Evidence Tables 1 and 2, Appendix E. Table 10 provides information on comparisons made, symptom response, and quality ratings. Table 11 provides information on radiographic joint damage, indicating whether the study populations included patients with early RA. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs (also referred to simply as biologics), and various combined strategies.

Rheumatoid Arthritis: Key Points

Corticosteroids vs. corticosteroids. One head-to-head RCT found no significant differences between budesonide and prednisolone for outcomes assessed by the American College of Rheumatology (ACR) response criteria set for 20 percent improvement (ACR 20) or the disease activity score (DAS).[29] The strength of evidence is low.

Synthetic DMARDs vs. synthetic DMARDs. One systematic review and meta-analysis,[34] which included two RCTs, found methotrexate (MTX) resulted in higher ACR 20 responses at 1 year when compared with leflunomide (odds ratio [OR], 1.43; 95% CI, 1.15-1.77; $P = 0.001$), but statistical significance was lost at 2 years.[38] Radiographic changes were similar for both leflunomide and MTX. The results were limited by the few number of studies included for meta-analysis. The strength of the evidence is moderate.

Three RCTs found similar response rates for patients receiving sulfasalazine and for those receiving MTX on outcomes measured by ACR 20, DAS, and radiologic data.[30,31,33] The strength of evidence is moderate.

One RCT reported that leflunomide produced higher proportions of patients meeting ACR 20 and ACR 50 improvement criteria at 24 months than did sulfasalazine.[36] Radiographic changes were similar for leflunomide and sulfasalazine. The strength of the evidence is low.

No fair or good evidence exists for comparing hydroxychloroquine monotherapy with other synthetic DMARD monotherapy.

Synthetic DMARD combinations. Studies of several different types of combination strategies favored, overall, combination strategies using two or three drugs over fewer drugs.

Of three RCTs,[30,31,33] one supported combination therapy with sulfasalazine and MTX vs. monotherapy with either drug; the changes in DAS scores were greater for combination therapy (-1.26 for combination, -1.15 for sulfasalazine, and -0.87 for MTX) ($P = 0.019$).[31] The other two trials reported no differences but focused on patients with early RA. The strength of evidence is moderate. All RCTs were funded by the makers of synthetic DMARDs.

Two RCTs found that, at 2 years, the combination of MTX, sulfasalazine, and hydroxychloroquine had better ACR 20 response rates than one or two drugs.[45,46] The strength of evidence is moderate. Both RCTs were funded by the makers of synthetic DMARDs.

One open-label effectiveness trial suggested that combining one synthetic DMARD (MTX or sulfasalazine) with prednisolone delayed radiographic progression more than a synthetic DMARD alone (25.9 percent vs. 39.3 percent progressed based on modified Sharp/van der Heijde score; $P = 0.033$).[47] One RCT[39] with a 5-year follow-up cohort[40] reported that combination therapy, which included two synthetic DMARDs (MTX and sulfasalazine) plus a stepped-down prednisolone treatment, demonstrated less radiographic progression than sulfasalazine alone (5-year mean change in Sharp Scale score, 5.6 vs. 8.6; $P = 0.001$). Another RCT[43] with a 5-year follow-up cohort[44] suggested that the combination of three synthetic DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone had less radiographic change than one synthetic DMARD (5-year median Larsen Scale score, 11 vs. 24; $P = 0.001$). Although the data are limited to one study for each comparison, we judged the strength of evidence to be moderate for these combinations.

One complex effectiveness trial compared several strategies.[42] The authors reported that either (1) MTX, sulfasalazine, and tapered high-dose prednisone or (2) MTX and infliximab resulted in less radiographic change over 12 months than (3) sequential DMARD therapy or (4) step-up combination therapy. The median increases in modified Sharp/van der Heijde scores were, respectively, 2.0, 2.5, 1.0, and 0.5 ($P = 0.003$ for group 1 vs. group 3; $P < 0.001$ for group 1 vs. group 4; $P = 0.007$ for group 2 vs. group 3; $P < 0.001$ for group 2 vs. group 4). The data are limited to one trial. The strength of evidence is low.

Biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. Existing direct head-to-head evidence is limited to a nonrandomized, open-label effectiveness trial[50] and two prospective cohort studies;[52,53] all compared etanercept with infliximab. These studies reported a faster onset of response for etanercept during the first months of therapy but no differences in efficacy thereafter. The faster onset of etanercept might be attributable partly to necessary dose adjustments for patients treated with infliximab. One study, however, attributed differences to lower rates of adherence among patients on infliximab than among those on etanercept. Generally, because of methodological limitations, findings of these studies must be interpreted cautiously.

Adjusted indirect comparisons, based on placebo-controlled RCTs, do not suggest any differences in efficacy among adalimumab, etanercept, and infliximab.[21,48,49,51] This is consistent with results from the open-label effectiveness trial[50] and two observational studies[52,53] mentioned above.

Anakinra, however, appears to have lower efficacy than adalimumab, etanercept, and infliximab.[48,49] Although not all results reached statistical significance, anakinra had consistently lower response rates on ACR 20 (relative risk [RR], 1.64; 95% CI, 1.04-2.56) and ACR 50 (RR, 1.89; 95% CI, 0.98-3.57) than anti-tumor necrosis factor (anti-TNF) drugs as a class (i.e.,

adalimumab, etanercept, and infliximab as a class). Individual comparisons of anakinra with adalimumab, etanercept, and infliximab consistently presented lower response rates for anakinra, but the confidence intervals were wide and the findings did not reach statistical significance.

The strength of evidence for these comparisons is moderate. No evidence from adjusted indirect comparisons exists for abatacept and rituximab. The strength of the evidence for the comparative effectiveness of biologics is low.

Biologic DMARD combinations. One RCT did not detect any synergistic effects of a combination treatment of etanercept and anakinra compared with etanercept monotherapy.[59] The strength of evidence is low.

Four RCTs[57,61,63,66] and two prospective cohort studies[53,62] suggested that a combination of MTX with adalimumab,[57] etanercept,[63-66] infliximab,[53,62] or rituximab[61] led to statistically significantly greater improvements with biologic DMARDs than with monotherapy. A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy.[60] For most of these comparisons, however, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. Except for the PREMIER study on adalimumab,[57] none of these trials was conducted in patients with early RA. The strength of evidence is high for the comparison of etanercept with MTX and moderate for all the other comparisons. No evidence is available on abatacept, anakinra, rituximab, and combinations with synthetic DMARDs other than MTX and sulfasalazine.

Two studies found that a combination of adalimumab with MTX[57] and infliximab with MTX[68] in patients with early, aggressive (i.e., rapidly progressing) RA who were MTX-naive led to better clinical and radiographic outcomes than MTX monotherapy. Both RCTs were funded by the makers of the biologic DMARDs. The strength of the evidence supporting a greater efficacy of a combination treatment than monotherapy is moderate for the above comparisons.

The evidence on the comparative efficacy of biologic DMARDs and synthetic DMARDs is mixed. Population-based, observational evidence from prospective cohort studies indicated that biologic DMARDs as a class were more efficacious than synthetic DMARDs as a class. RCTs, however, did not indicate any substantial differences in clinical response between either adalimumab or etanercept and MTX.[54-57,63-65] Radiographic outcomes, however, were statistically significantly better in patients treated with biologic DMARDs than patients treated with MTX. How such intermediate outcomes translate to the long-term clinical progression of the disease remains unclear.

All RCTs were funded by the makers of the biologic DMARDs. No studies were available comparing biologics with either corticosteroids or with synthetic DMARDs other than MTX. The strength of the evidence for the available comparisons is moderate.

None of the RCTs can be considered an effectiveness study. Of four population-based prospective cohort studies, only one was conducted in the United States. The generalizability of results to the average primary care population, therefore, remains unclear. The strength of evidence regarding comparative effectiveness is low.

One small study, which did not meet eligibility criteria, reported a higher efficacy of infliximab compared with pulse methylprednisolone. No other evidence comparing biologic DMARDs with corticosteroids was available.

Rheumatoid Arthritis: Detailed Analysis

Corticosteroids vs. corticosteroids. We found one head-to-head RCT (N = 143) comparing two corticosteroids.[29] It examined the efficacy of low-dose budesonide (3 mg/day), high-dose

budesonide (9 mg/day), and prednisolone (7.5 mg/day) over 12 weeks. Mean disease duration of RA was 9 years. When comparing drugs, the percentage achieving ACR 20 response criteria for high-dose budesonide (9 mg) was significantly greater than that for lower dose budesonide (3 mg) (42 percent vs. 22 percent; $P < 0.001$), but the percentages for high-dose budesonide and prednisolone did not differ significantly (42 percent vs. 56 percent; $P = 0.11$). Similarly, high-dose budesonide and prednisolone did not differ significantly for tender joint count, swollen joint count, and the DAS.

Synthetic DMARDs vs. synthetic DMARDs. *Leflunomide vs. MTX.* We found two trials comparing leflunomide (20 mg/day) with MTX (studies ranging from 7.5 mg/week to 15 mg/week) and one systematic review with meta-analysis of leflunomide.[32,34,37] Given that the systematic review included only two trials comparing these two agents, we describe these two studies in detail here first. One trial randomized 482 patients to leflunomide (n = 182) or MTX (n = 182) over 12 months.[37] Mean disease duration of RA across these groups was 6.5 years to 7 years. The proportions of patients meeting ACR 20 response criteria at 12 months was higher for leflunomide than MTX but not statistically significantly so (52 percent vs. 46 percent; P = NR). Proportions meeting ACR 50 and ACR 70 criteria also did not differ significantly. Leflunomide had less disease progression by Sharp score than MTX (respectively, 0.53 vs. 0.88; $P = 0.05$).

A continuation study followed the same cohort for 2 years (leflunomide, n = 98; MTX, n = 101).[38] At 2 years, leflunomide was associated with higher proportions of patients meeting ACR 20 response criteria than MTX (79 percent vs. 67 percent; $P = 0.049$). The percentages of patients meeting either ACR 50 or ACR 70 criteria at 2 years did not differ significantly, and the change in total Sharp score also did not differ significantly at 2 years (1.6 vs. 1.2; $P = 0.659$).

These 2-year follow-up results are limited by the 45 percent attrition rate from the initial study.

The other trial comparing leflunomide to MTX examined 999 patients for 12 months with an optional second year (leflunomide, n = 501; MTX, n = 498).[32] Mean disease duration across the groups was 3.5 to 3.8 years. At 12 months, the proportion of patients meeting ACR 20 response criteria was lower for leflunomide than for MTX (50.5 percent vs. 64.8 percent; $P < 0.001$), but differences were not significant at 2 years (64.3 percent vs. 71.7 percent; P = NS, NR). Radiological outcomes at 12 months using Larsen Scale scores for joint narrowing were statistically equivalent (0.03 increase in both groups). After 2 years, no further increase in joint damage occurred in patients treated with leflunomide; patients taking MTX had a small improvement (data NR). The overall result was a small significant difference in Larsen Scale scores favoring MTX after 2 years (data NR).

In this systematic review including two trials comparing leflumonide with MTX (n = 1,481) there were significantly more responders on the ACR 20 at 12 months favoring MTX (OR, 1.43; 95% CI, 1.15-1.77; $P = 0.001$); however, by 2 years, the statistically significant difference favoring MTX disappears (OR, 1.28; 95% CI, 0.98-1.67; $P = 0.07$). ACR 50 and ACR 70 responses did not differ between leflunomide and MTX, and the two drugs also did not differ in delaying bone erosions or joint damage assessed by total Sharp score.[34] This systematic review was limited by the small number of studies that the authors could use for meta-analysis.

Leflunomide and sulfasalazine. One study[35] with a 2-year followup[36] compared leflunomide with sulfasalazine. In addition, one systematic review did a meta-analysis of leflunomide against sulfasalazine.[34] Given that the systematic review included only one trial with this comparison, we describe it in detail first.[35] This study was a 24-week, double-blind, multinational RCT of 358 patients on 20 mg/day leflunomide (n = 133) or 2 g/day sulfasalazine (n = 133).[35] Mean disease

duration across groups was 5.7 to 7.6 years. ACR 20 response at 24 weeks was similar for leflunomide and sulfasalazine (48 percent vs. 44 percent; *P* = NR). ACR 50 response rates were also similar (33 percent leflunomide, 30 percent sulfasalazine). Larsen Scale scores were also similar for leflunomide and sulfasalazine, and the Larsen Scale change score at endpoint was 0.01 for both drugs. In the follow-up study, patients who completed the first study could opt to continue on the 12- and 24-month double-blind extension.[36] At 12 months (leflunomide, n = 80; sulfasalazine, n = 76), ACR 20 response was similar for leflunomide and sulfasalazine (77 percent vs. 73 percent; *P* = NR). At 24 months (leflunomide, n = 28; sulfasalazine, n = 27), ACR 20 response was significantly greater for leflunomide (82 percent vs. 60 percent; *P* = 0.0085). Changes in Larsen Scale scores were also similar for leflunomide and sulfasalazine (mean change: 0.02 vs. 0.02 at 12 months, -0.07 vs. -0.03 at 24 months; *P* = NR). Changes in Sharp scores were also not significantly different (mean change: 0.97 vs. 1.38; *P* = 0.685). However, these long-term results are significantly limited by the attrition rates of 65 percent to 70 percent.

The systematic review with meta-analysis compared leflunomide (10 to 20 mg/day) with sulfasalazine (2 g/day).[34] The analysis included the study described above.[35,36] Response to the two drugs did not differ as measured by either ACR 20 or ACR 50 criteria at 6 months and 12 months. However, leflunomide was more efficacious at 24 months (ACR 20: OR, 0.35; 95% CI, 0.16-0.77; *P* = 0.009; ACR 50: OR, 0.32; 95% CI, 0.15-0.67; *P* = 0.003). The ACR 70 response was not different between groups at 6, 12, or 24 months. Leflunomide and SSZ also did not differ in delaying bone erosions or joint damage by Sharp score or Larsen Scale score at 6, 12, or 24 months. Again, these results are significantly limited because they include only the one study.[35]

Sulfasalazine and MTX. Three RCTs examined the efficacy of sulfasalazine and MTX.[30,31,33] Overall, findings from these studies showed similar response rates between sulfasalazine and MTX for ACR, DAS, and radiological outcomes. Two of the trials included patients with disease burden of less than 1 year and used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[31,33] These trials also included a combination therapy arm, which we describe below (in the section on *Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic DMARD monotherapy)*.

One trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine (n = 68), 7.5 mg/week to 15 mg/week MTX (n = 69), or a combination (n = 68) for 52 weeks.[31] Mean disease duration for the groups ranged from 2.3 months to 3.4 months. The ACR 20 responses did not differ statistically (59 percent sulfasalazine; 59 percent MTX; *P* = NR). The DAS change score favored sulfasalazine therapy (-1.15, sulfasalazine; -0.87, MTX; *P* = NR), but the statistical analysis examined only the comparison with combination therapy (reported under "*Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic DMARD monotherapy*"). Radiological scores at 5 years did not differ significantly; the mean total modified Sharp/van der Heijde scores were 8.5 for sulfasalazine and 7.5 for MTX (*P* = 0.7).

Another RCT, lasting 52 weeks (N = 105), also demonstrated similar ACR 20 and DAS results for sulfasalazine and MTX.[33] This trial compared 1 g/day to 3 g/day sulfasalazine (n = 34) with 7.5 mg/week to 15 mg/week MTX (n = 35) and with a combination (discussed later in this chapter); mean disease duration was 2.6 to 3.1 months. The mean change in DAS over 52 weeks was -1.6 in the sulfasalazine group and -1.7 in the MTX group (*P* = NS). ACR 20 response was 25 percent for sulfasalazine and 25 percent for MTX.

Finally, one trial included a population with a disease duration of up to 10 years.[30] The investigators gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS ≥ 2.4

were offered inclusion into a Phase II study and randomized to (1) sulfasalazine (n = 55), (2) MTX (n = 54) (maximum dose, 25 mg/week), and (3) sulfasalazine plus MTX (n = 56). At 18 months, the DAS change was similar for sulfasalazine and MTX alone (-0.30 vs. -0.26; *P* = 0.79). The ACR 20, 50, and 70 responses were also similar (ACR 20, 18 percent vs. 15 percent; ACR 50, 6 percent vs. 7 percent; ACR 70, 2 percent vs. 2 percent; *P* = NR). The modified Sharp/van der Heijde score, total erosions, and joint space narrowing also did not differ significantly (data NR). However, 18 months is a short period for observing radiological outcomes, and this study was not powered to detect radiological progression.

Synthetic DMARD combinations vs. synthetic DMARD combinations or synthetic DMARD monotherapy. *Sulfasalazine plus MTX vs. sulfasalazine or MTX.* Three RCTs compared the efficacy of sulfasalazine and MTX vs. that of either sulfasalazine or MTX alone.[30,31,33] Findings from two of these randomized trials consistently reported no significant differences in ACR, DAS, or radiological outcomes.[31,33] They included patients with disease duration of less than 1 year and again used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[31,33] The third trial included patients with RA duration of up to 10 years, and their DAS results favored the sulfasalazine-MTX combination therapy over monotherapy.[30]

One 52-week trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine and 7.5 mg/week to 15 mg/week MTX (n = 68), sulfasalazine (n = 68), or MTX (n = 69).[31] ACR 20 responses were numerically higher in the combination group, but the groups did not differ statistically (ACR: 65 percent combination; 59 percent sulfasalazine; 59 percent MTX; *P* = NS, NR). The DAS change favored combination therapy (DAS change: -1.26 combination; -1.15 sulfasalazine; -0.87 MTX; *P* = 0.019). In a 5-year prospective followup of this cohort, however, when comparing combination therapy vs. monotherapy, the differences in DAS change scores became nonsignificant at year 5.[41] Additionally, radiological scores did not differ at 5 years; the total modified Sharp/van der Heijde score was 7.5 for combination therapy and 8.5 for single therapy (*P* = 0.7). A 52-week RCT (N = 105) also reported no significant differences in ACR or DAS results between combination and single therapy in this population.[33]

Finally, another trial included a population with a disease duration of up to 10 years (mean, 1.6 to 1.8 years).[30] It gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS ≥ 2.4 were offered inclusion into a Phase II study and randomized to (1) sulfasalazine plus MTX (n = 56), (2) sulfasalazine (n = 55), and (3) MTX (n = 54) (maximum dose, 25 mg/week). At 18 months, the DAS was significantly better in the combination arm than in either the sulfasalazine or MTX arms (DAS change scores: -0.67, -0.30, -0.26; combination vs. sulfasalazine*; P* = 0.039; combination vs. MTX*; P* = 0.023). The ACR 20, 50, and 70 responses were all higher in the combination arm, but they were not statistically different across the three arms. Additionally, the total modified Sharp/van der Heijde score, total erosions, and joint space narrowing also did not differ significantly across arms (data NR). However, 18 months is a short period for radiological outcomes, and this study was not powered for radiological progression.

MTX plus hydroxychloroquine plus sulfasalazine vs. one or two synthetic DMARDs. Two RCTs examined the combination of MTX, sulfasalazine, and hydroxychloroquine against either one or two drugs.[45,46] Both studies found that the combination of the three DMARDs was more effective than either one or two DMARDs.

The more recent study randomized 171 patients over 2 years to (1) MTX 7.5 mg/week titrated to 17.5 mg/week plus sulfasalazine 2 g/day plus hydroxychloroquine 400 mg/day, (2) MTX plus hydroxychloroquine, or (3) MTX plus sulfasalazine.[45] Mean disease duration across

groups was 5.8 to 7.9 years. After 2 years, patients receiving triple therapy had an ACR 20 of 78 percent; the figures were 60 percent for those treated with MTX and hydroxychloroquine ($P = 0.05$) and 49 percent for those treated with MTX and sulfasalazine ($P = 0.002$).

Synthetic DMARDs plus corticosteroid combinations vs. synthetic DMARDs. *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* One open-label RCT compared a combination therapy involving a synthetic DMARD (either MTX or sulfasalazine) and a corticosteroid with a synthetic DMARD only (N = 250).[47] This study suggested that, for patients with early RA, combining a synthetic DMARD with prednisolone may help slow radiographic progression and extend remission. This 2-year, multicenter Swedish study compared prednisolone 7.5 mg/day added to a DMARD (n = 119) with a DMARD only (n = 131) in patients with early RA. Patients were eligible if they had been diagnosed with RA (1987 ACR criteria) in the past year and had been started by their treating rheumatologist on their first DMARD. The choice of DMARD had been left to the patient's primary rheumatologist and included MTX (mean dose 10 mg/week) or sulfasalazine (2 g/day). The combination group had significantly less radiographic progression than the monotherapy group (25.9 percent vs. 39.3 percent based on modified Sharp/van der Heijde score; $P = 0.033$). Additionally, remission was higher in the combination group (DAS 28 < 2.6, 55.5 percent vs. 43.8 percent; $P = 0.0005$). This study can be considered an effectiveness trial based on design criteria.[26] However, the results should be interpreted cautiously, given the open-label design and potential for measurement bias.

Two synthetic DMARDs plus corticosteroid vs. synthetic DMARD. One multicenter RCT, known as COBRA (Combinatietherapie Bij Reumatoide Artritis), assessed differences in efficacy between a combination of step-down prednisolone, MTX, and sulfasalazine and sulfasalazine only.[39] The investigators randomized 155 Dutch patients with early RA for 56 weeks. Patients with active RA were included if they had had symptoms for fewer than 2 years and had not used DMARDs in the past. Patients were then followed indefinitely in an open-label prospective cohort (5-year follow-up data reported).[40] Combination therapy included a stepped-down prednisolone treatment (60 mg/day tapered over 28 weeks), MTX (7.5 mg/week stopped after 40 weeks), and sulfasalazine (2 g/day). Mean duration of RA was 4 months. The authors applied a pooled index, which yielded a weighted change score of five disease activity measures: tender joint count, grip strength, erythrocyte sedimentation rate (ESR), assessor's global assessment by visual analog scale (VAS), and the McMaster Toronto arthritis questionnaire (MACTAR) (score range not given). At 28 weeks, patients on combination therapy had an improved change score in this index (mean change 1.4 vs. 0.8; $P < 0.0001$). At 52 weeks, however, the change results on the pooled index were no longer significant (mean change 1.1 vs. 0.9; $P = 0.20$). In terms of radiographic progression, patients on combination therapy had statistically significantly less progression than the monotherapy patients on the modified Sharp/van der Heijde score at 28 weeks (1 vs. 4; $P < 0.0001$), 56 weeks (2 vs. 6; $P < 0.004$), and 80 weeks (4 vs. 12; $P < 0.01$). Over 5 years, the modified Sharp/van der Heijde change score per year was lower for combination therapy than for monotherapy (5.6 vs. 8.6; $P = 0.001$).[40]

Three synthetic DMARDs plus corticosteroid vs. synthetic DMARDs. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a complex combination of prednisolone (5 to 10 mg/day), MTX (7.5 to 10 mg/week), sulfasalazine (2 g/day), and hydroxychloroquine (300 mg/day) against that of monotherapy with a DMARD with or without prednisolone.[43] The investigators randomized 199 patients with early RA to either combination therapy or monotherapy. Patients on monotherapy were initially started on sulfasalazine (2 to 3 g/day) but could be changed to MTX (7.5 to 15 mg/week), then changed to a

third DMARD if needed (azathioprine, auranofin, hydroxychloroquine, injectable gold, penicillamine, or podophyllotoxin). If patients reached remission in the first year, they could be tapered and prednisolone and MTX could be discontinued at 9 months and 18 months, respectively. Adding prednisolone (up to 10 mg/day) in the monotherapy group was left up to the treating physician and allowed in patients with continuously active disease. After 2 years, remission (judged by the authors using modified ACR 20) was higher in the combination group (37.9 percent vs. 18.4 percent; $P = 0.011$); the proportions achieving ACR 50 response criteria were higher but did not reach statistical significance (71 percent vs. 58 percent; $P = 0.058$). Larsen Scale radiographic scores had also improved at 2 years (Larsen Scale score increase 2 vs. 10; $P = 0.002$). Subsequently, patients in this trial were followed for 5 years.[44] Those in the monotherapy group were allowed to be treated with combinations of DMARDs if their response was insufficient. At 5 years, the median Larsen Scale score remained lower in the combination therapy group (11 vs. 24; $P = 0.001$). This trial can be considered an effectiveness trial given the flexibility of dosing in an effort to follow clinical practice.

Other complex combination strategies. One good-quality RCT examined four different treatment strategies over 12 months.[42] The BeSt Study (Dutch acronym for Behandel Strategieen, "treatment strategies") randomized 508 patients with early RA to one of four groups: (1) sequential DMARD, starting with MTX (15 mg/week), (2) step-up combination therapy with MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone, (3) initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone 60 mg/day to 7.5 mg/day in 7 weeks, and (4) initial combination therapy with MTX 25 to 30 mg/week and infliximab 3 mg/kg every 8 weeks (dose titrated up to 10 mg/kg dependent upon DAS44 > 2.4). This design called for frequent changes in treatment strategy; the DAS (i.e., DAS in 44 joints) was calculated every 3 months and if it was greater than 2.4, the therapeutic strategies were adjusted. At 12 months, more patients in group 3 (MTX, sulfasalazine, tapered high-dose prednisone) and in group 4 (MTX with infliximab) reached a DAS of 2.4 or less. Respectively, these proportions were 53 percent, 64 percent, 71 percent, and 74 percent ($P = 0.004$ for group 1 vs. group 3; $P = 0.001$ for group 1 vs. group 4; $P =$ NS for other comparisons). Additionally, the median change in modified Sharp/van der Heijde score was lower for groups 3 and 4 than for groups 1 and 2 (2.0, 2.5, 1.0, and 0.5, respectively; $P = 0.003$ for group 1 vs. group 3; $P < 0.001$ for group 1 vs. group 4; $P = 0.007$ for group 2 vs. group 3; $P < 0.001$ for group 2 vs. group 4).

Biologic DMARDs vs. biologic DMARDs. We did not identify any head-to-head RCTs. The head-to-head evidence was limited to one nonrandomized, open-label effectiveness trial[50] and two fair-quality prospective cohort studies;[52,53] all compared etanercept with infliximab. All three studies were primary care based with minimal exclusion criteria, enrolling patients who were starting treatments with biologic DMARDs. Mean disease durations ranged from 7.7 years to 14.7 years, indicating that most patients suffered from advanced RA; the proportion of patients with early RA in these studies remains unclear. One study was conducted in the United States;[53] the other two were carried out in Sweden.[50,52] In addition to these studies evaluating biologic monotherapies, an RCT compared etanercept monotherapy to a combination treatment of etanercept and anakinra.[59]

The nonrandomized, open-label effectiveness study (N = 369) assessed the effectiveness and safety of etanercept (25 mg twice weekly), infliximab (3 mg/kg or higher every 8 weeks), and leflunomide (20 mg/day).[50] Study duration was 12 months. Comparisons of etanercept and infliximab with the leflunomide arm are reported in the section below comparing synthetic

DMARDs with biologic DMARDs. Etanercept had significantly greater ACR 20 response rates at 3 months ($P < 0.02$; data NR) and 6 months ($P < 0.05$; data NR) and greater ACR 50 response rates at 3 months ($P < 0.005$; data NR) than infliximab. The authors attributed these differences partly to a high need of dose adjustments (57 percent) in the infliximab group during the first months of the study. No significant differences between the therapy groups could be detected after 6 months.

One prospective cohort study (N = 949) provided similar results. Etanercept treatments led to greater response rates than infliximab during the first months of treatment, but no differences were noted thereafter for up to 36 months.[52] The authors of this study created an index called the LUNDEX (an index of drug efficacy in clinical practice developed at Lund University in Sweden, calculated as the proportion of starters still on the drug at time T times the proportion responding at time T), which takes adherence and efficacy together into consideration. Patients on etanercept achieved higher LUNDEX scores than patients on infliximab, which reflected a significantly lower level of adherence of patients on infliximab compared with those on etanercept (data NR; $P < 0.001$).

Findings from the U.S. prospective cohort study, which was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program and funded by the maker of etanercept, reported similar results.[53] Etanercept-treated patients had greater response rates than infliximab-treated patients on the modified ACR 20 (mACR 20, which omits ESR and C-reactive protein [CRP] values because they are infrequently measured in clinical practice); percentage responses were 43 percent for etanercept plus MTX, 41 percent for etanercept monotherapy, 35 percent for infliximab plus MTX, and 26 percent for infliximab monotherapy (P = NR).

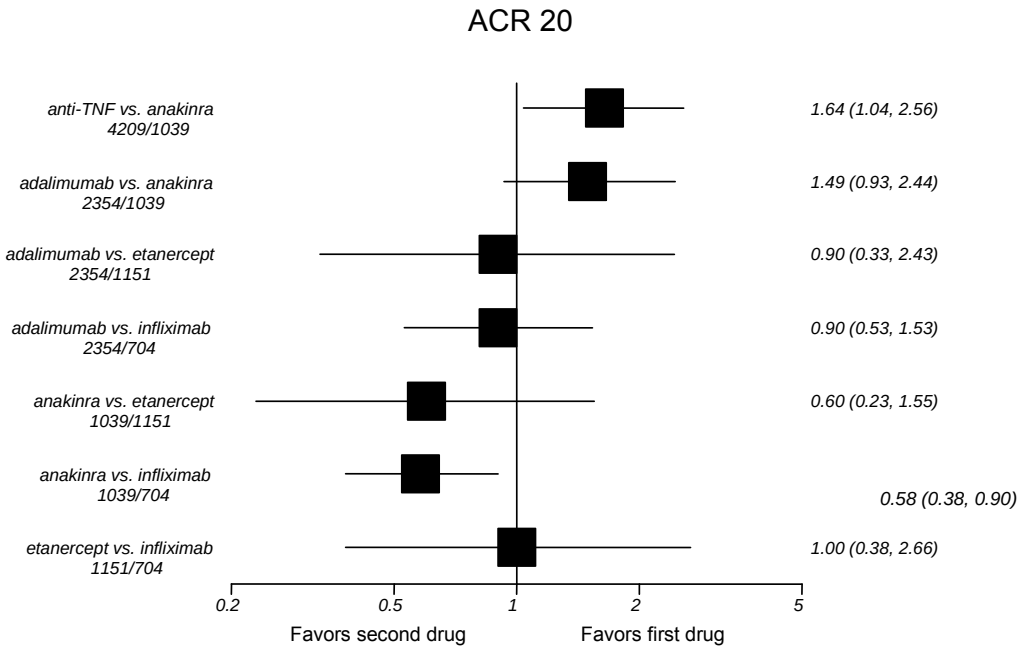
A well-conducted retrospective cohort study did not meet our eligibility criteria, but we present its findings here because it was the only study that examined radiographic progression for patients treated with etanercept or infliximab.[70] This population-based study determined erosion progression and joint space narrowing on 372 Swiss patients who were monitored through the Swiss Clinical Quality Management System. Combination therapies of infliximab and synthetic DMARDs or etanercept and synthetic DMARDs did not present statistically significant differences in progression of erosion (Ratingen score; data NR) after a mean followup of 1.7 years. The combination of infliximab and synthetic DMARDs led, however, to statistically significantly lower joint space narrowing than etanercept and synthetic DMARDs (data NR). This difference was not obvious when the analysis was limited to MTX as the concomitant DMARD. The combination of infliximab and MTX was statistically significantly more efficacious on all outcome measures than etanercept monotherapy (data NR).

Indirect head-to-head comparisons of biologic DMARDs. Multiple placebo-controlled RCTs and meta-analyses[20,71] provide evidence on the general efficacy of abatacept,[72-76] adalimumab,[77-83] anakinra,[48,84-89] etanercept,[63-65,90-97] infliximab,[90,98-107] and rituximab.[61,108] Most of these studies were conducted in patients who had failed synthetic DMARD treatment.

Using information from these placebo-controlled trials, four research groups did meta-analyses to produce adjusted indirect comparisons of biologic DMARDs.[21,48,49,51] The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[109] In the most recent analysis, findings suggested that efficacy does not differ substantially for adalimumab, etanercept, and infliximab (Figures 2 and 3).[49] However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty.

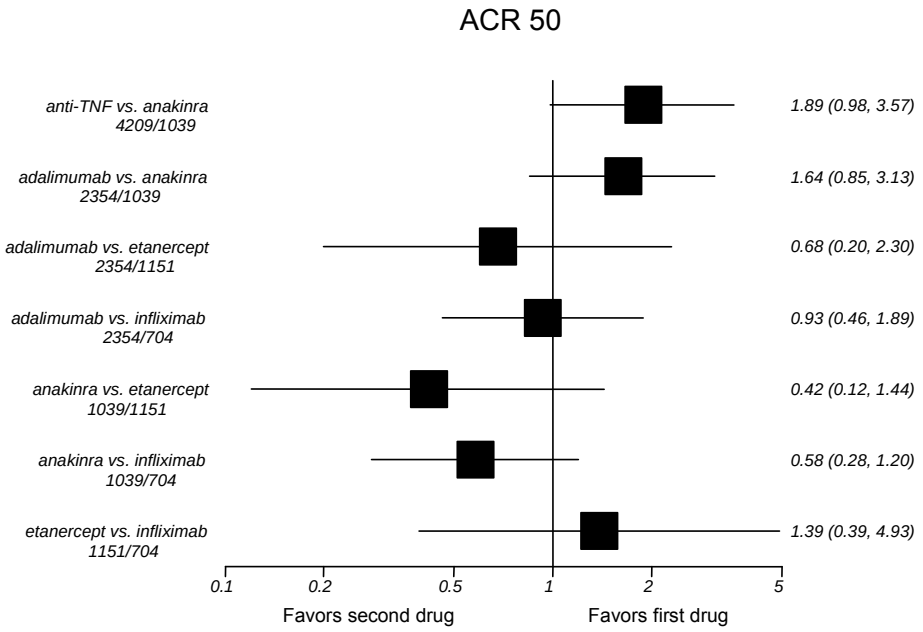
Compared with point estimates for anakinra, point estimates favored adalimumab, etanercept, and infliximab (Figures 2 and 3).[49] Not all differences reached statistical significance in adjusted indirect comparisons, which is likely attributable to a lack of power. Adjusted indirect comparisons of anti-TNF drugs as a class with anakinra showed a statistically significantly greater efficacy of the anti-TNF drugs on ACR 20 but not on ACR 50. Figures 2 and 3 summarize results of adjusted indirect comparisons of ACR 20 and ACR 50 responses.[49]

Figure 2. Adjusted indirect comparisons of biologic DMARDs for ACR 20 response rates



Adapted from Gartlehner et al., 2006[49]

Figure 3. Adjusted indirect comparisons of biologic DMARDs for ACR 50 response rates



Adapted from Gartlehner et al., 2006[49]

These findings are consistent with a good-quality German retrospective cohort study based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database, which reports higher discontinuation rates because of lack of efficacy for patients on anakinra than for patients on either etanercept or infliximab after 12 months of treatment (30 percent vs. 20 percent vs. 20 percent; P = NR).[67]

No indirect comparisons were available of abatacept and rituximab with other biologic DMARDs.

Biologic DMARDs vs. corticosteroids. One RCT, which did not meet our eligibility criteria because of its small sample size (N = 28), compared the efficacy of infliximab (3 mg/kg at weeks 0, 2, and 6) and pulse methylprednisolone (1 g/single infusion).[110] We briefly summarize its findings here because it was the only study comparing these two treatments. Significantly higher proportions of patients treated with infliximab than with pulse methylprednisolone met ACR 20 criteria (67 percent vs. 8 percent; $P < 0.05$) and ACR 50 criteria (44 percent vs. 0 percent; $P < 0.05$). No quality-of-life measure improved with pulse methylprednisolone treatment.

Biologic DMARDs vs. synthetic DMARDs. Three RCTs, a nonrandomized trial, and a prospective cohort study determined the comparative efficacy and safety of various biologic and synthetic DMARDs. The RCTs compared adalimumab[57] and etanercept[54,63] with MTX; the nonrandomized trial compared etanercept and infliximab with leflunomide;[50] and the cohort study assessed differences in class effects.[58] No evidence exists on abatacept, anakinra, and rituximab or on synthetic DMARDs other than MTX and leflunomide.

Biologic DMARDs as a class vs. synthetic DMARDs as a class. A prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n = 818) and DMARDs as a class (n = 265) in patients who had failed two previous DMARD treatments.[58] This study was population-based and part of RABBIT, a German long-term, prospective cohort study of RA patients who had

required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. In a multivariate logistic regression, adjusting for baseline confounders, the investigators determined that patients on biologics had a statistically significantly greater chance of remission (DAS < 2.6) after 12 months of treatment (OR, 1.95; 95% CI, 1.20-3.19). Likewise, patients treated with biologics had an almost four times higher likelihood of achieving functional independence than patients treated with synthetic DMARDs (OR, 3.88; 95% CI, 1.71-8.79). Nevertheless, both groups had a substantial risk of relapse during the treatment period. Approximately one-half of the patients who were in remission at 6 months achieved a sustained remission until 12 months (biologics, 55 percent; synthetic DMARDs, 58 percent).

Adalimumab vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[57] This multinational study randomized 799 patients with early RA to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). Two treatment arms of this 2-year study assessed differences in the efficacy of adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). After 2 years, the proportion of patients who met ACR 50 criteria was lower for those on adalimumab than for those on MTX monotherapy (37 percent vs. 43 percent; *P* = NR). Radiographic progression, by contrast, was statistically significantly lower in patients treated with adalimumab than with MTX (5.5 vs. 10.4 Sharp units; *P* < 0.001). No difference was apparent in clinical remission (DAS 28 < 2.6) between the two treatment groups (both 25 percent); discontinuation rates because of lack of efficacy were similar in the adalimumab and MTX groups (19.0 percent vs. 17.9 percent; *P* = NR). We report on results of the other comparisons of the PREMIER study in the respective sections (below) on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs.*

Etanercept vs. MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week) over 52 weeks.[54-56,63-65] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX naive.[54-56] The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial[63-65] randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week).[63-65] Patients had active RA and had failed at least one DMARD other than MTX. About 57 percent of the study population was MTX naive. Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study.

Both studies failed to show statistically significant differences between etanercept and MTX in clinical and health outcome measures (SF-36, the Health Assessment Questionnaire [HAQ], the Arthritis-Specific Health Index [ASHI]), and ACR 20/50/70 response rates at study endpoints (52 weeks). By contrast, radiographic outcomes were significantly better in patients on etanercept than in those on MTX. For example, in the ERA trial, 72 percent of patients on etanercept and 60 percent on MTX had no radiographic progression of disease (*P* = 0.007). Improved radiographic outcomes were maintained during an open-label extension of the ERA study to 2 years[55]and 5 years.[56]

Etanercept or infliximab vs. leflunomide. No RCT compared biologic DMARDs to leflunomide. The only head-to-head evidence came from a nonrandomized, open-label study (N = 369) that accessed the efficacy and safety of etanercept (25 mg twice weekly), infliximab (3

mg/kg or higher every 8 weeks), and leflunomide (20 mg/day).[50] This study has been described in greater detail in the section (above) on *Biologic DMARDs vs. biologic DMARDs*. At 3 months and 6 months, patients on etanercept had significantly higher ACR 20 and ACR 50 response rates than those on leflunomide (data NR; $P < 0.05$). Patients on infliximab achieved higher ACR 20 and ACR 50 response rates at 3 months (data NR; $P < 0.05$). The authors did not report 12-month data. Both etanercept and infliximab led to significant reductions in prednisolone dosage; by contrast, no reduction with leflunomide was seen. These findings must be viewed cautiously. Baseline characteristics of patients differed substantially between the leflunomide group and the biologic groups. Leflunomide patients were older and had significantly more joint damage than patients on etanercept or infliximab. Such differences can potentially confound results, introducing bias that would support differences in results among these treatment groups.

Biologic combination strategies: Biologic DMARD plus biologic DMARD vs. biologic DMARD. A 24-week RCT did not detect any synergistic effects of a combination treatment of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy.[59] Overall, 242 patients who were on stable doses of MTX treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8 percent for 50 mg etanercept plus anakinra, 4.9 percent for 25 mg etanercept plus anakinra, and 2.5 percent for etanercept only; P = NR). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6 percent vs. 7.4 percent; P = NR).

Biologic DMARD plus synthetic DMARD vs. biologic DMARD. The majority of trials assessed a combination of a biologic DMARD and MTX against a monotherapy of the respective biologic DMARD.[53,57,61-63,66] Only one trial used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD.[60] No evidence is available on combination treatments of abatacept or anakinra.

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[57] Details of this study are reported above in *Biologic DMARDs vs. synthetic DMARDs.* After 2 years, significantly more patients on the combination therapy exhibited responses on ACR 50 than patients on adalimumab monotherapy (59 percent vs. 37 percent; $P < 0.001$); in addition, they had statistically significantly less progression on a modified Sharp/van der Heijde score (1.9 vs. 5.5 Sharp units; $P < 0.001$). After 2 years of treatment, 49 percent of patients on the combination therapy and 23 percent on adalimumab monotherapy achieved remission (DAS 28 < 2.6; $P < 0.001$). Discontinuation rates because of lack of efficacy were lower in the combination group than in the monotherapy group (4.2 percent vs. 19.0 percent; P = NR). We report on results of the other comparisons of the PREMIER study in the respective sections on *Biologic DMARDs vs. synthetic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs*.

Etanercept plus MTX vs. etanercept. Two RCTs (in four publications)[63-66] and two prospective cohort studies[53,62] assessed differences in efficacy between an etanercept-MTX combination and etanercept monotherapy in patients with active, DMARD-resistant disease. Findings of these studies consistently supported greater efficacy for the combination therapy than for the etanercept monotherapy.

The TEMPO trial (described above in *Biologic DMARDs vs. synthetic DMARDs)* enrolled a mixed population of MTX-naive patients (about 57 percent) and patients who had been on prior

MTX treatment (about 43 percent). Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study. Results of the etanercept-MTX combination (25 mg twice weekly plus up to 20 mg/week) and the etanercept monotherapy (25 mg twice weekly) arms showed that the combination treatment was significantly more efficacious than etanercept alone. After 52 weeks, 69 percent in the combination group and 48 percent in the etanercept group achieved ACR 50 response criteria ($P < 0.0001$). Likewise, statistically significantly higher proportions of patients in the combination than in the monotherapy group met ACR 20 and ACR 70 response criteria. The proportion of patients achieving remission (DAS < 1.6) was 35 percent in the combination group and 16 percent in the monotherapy group ($P < 0.0001$). In addition, the combination regimen led to significantly better radiographic outcomes (changes in total Sharp score: -0.54 vs. 0.52; $P < 0.0001$) than the etanercept monotherapy.[64]

A German retrospective cohort study based on the RABBIT database did not find differences in discontinuation rates because of lack of efficacy between patients on etanercept monotherapy and those on an etanercept-MTX combination (20 percent vs. 17 percent; P = NR).[67]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of findings from efficacy RCTs.[65] ACR response rates, DAS remission rates, quality-of-life measures, and radiographic progression were statistically significantly better in the combination group than in the etanercept monotherapy group. Attrition was 39 percent after 2 years and could compromise the internal validity of the long-term results.

The other three studies included a 16-week, open-label RCT (N = 315),[66] a 12-month prospective cohort study,[53] and a 6-month prospective cohort study.[62] Their results were generally consistent with findings from the TEMPO trial. Both prospective cohort studies were population-based, one in the United States[53] and the other in the United Kingdom,[62] and both have a high generalizabilty.

The UK study also compared the effectiveness of the etanercept-MTX combination and a combination of etanercept and other DMARDs (leflunomide, azathioprine, sulfasalazine, hydroxychloroquine, cyclosporine A, penicillamine, gold, minocycline) as a class.[62] After adjusting for potential confounders, the investigators reported statistically significantly higher response rates for MTX as a cotherapy than for other DMARDs (OR, 1.66; 95% CI, 1.14-2.42).

Etanercept plus sulfasalazine vs. etanercept. A 24-week RCT assessed the comparative efficacy of etanercept and sulfasalazine combination therapy (respectively, 25 mg twice weekly plus 2, 2.5, or 3 g/day), etanercept monotherapy (25 mg twice weekly), and sulfasalazine monotherapy (2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[60] Because sulfasalazine monotherapy resembles a placebo treatment (patients had to have failed it to be eligible), we focus on results from the combination (n = 101) and etanercept monotherapy (n = 103) arms. After 24 weeks, both groups had similar clinical responses on multiple outcome measures (ACR 20/50/70, DAS 28). On ACR 20, the primary efficacy variable, 74 percent of patients in both groups met the relevant response criteria. Likewise, results on patient-reported measures of quality of life (HAQ, EuroQOL, general health VAS) were similar for patients on the combination and monotherapy interventions.

Infliximab plus MTX vs. infliximab. No RCT examined the comparative efficacy and effectiveness of a combination of infliximab and MTX against infliximab monotherapy in patients with RA. The only comparative evidence comprises one U.S. and one U.K. prospective cohort study (already described).[53,62] Both studies indicated that European League Against Rheumatism (EULAR) and modified ACR response rates were better for patients in the studies'

infliximab combination groups. Remission rates, however, were similar in both studies for the two regimens. At 6 months, U.K. patients in the combination group had higher EULAR response rates than those in the monotherapy group (OR, 1.35; 95% CI, 0.92-2.00).[62] At 12 months, mACR 20 responses were similar for U.S. patients in the combination and the monotherapy groups (OR, 0.96; 95% CI, 0.76-1.21; *P* = 0.72).[53]

A German retrospective cohort study assessing discontinuation rates in clinical practice reported findings similar to those noted above. Discontinuation rates because of lack of efficacy were higher among patients on an infliximab monotherapy than among with those on an infliximab-MTX combination regimen (45 percent vs. 18 percent; *P* = NR).[67] Overall discontinuation rates, however, were statistically significantly higher in the monotherapy than in the combination group (56 percent vs. 34 percent; hazard ratio, 1.9; 95% CI, 1.1-3.1).

Rituximab plus MTX vs. rituximab. One RCT enrolled patients with highly active, long-standing, DMARD-resistant RA to compare the efficacy of rituximab and MTX (1,000 mg on day 1 and day 15 plus MTX 10 mg or more/week), rituximab monotherapy (1,000 mg on day 1 and day 15), rituximab and cyclophosphamide, and MTX monotherapy.[61] Because cyclophosphamide is not a drug of interest for this report and because MTX monotherapy resembles a placebo treatment (patients had to have failed MTX treatment to be eligible), we focus on results of the rituximab-MTX combination (n = 40) and the rituximab monotherapy (n = 40) arms. After 24 weeks, patients on the combination intervention experienced changes in DAS outcomes similar to those for patients on rituximab monotherapy (-2.6 vs. -2.2; *P* = NR). Similar proportions of patients in both treatment groups achieved a good or moderate EULAR response (83 percent vs. 85 percent; *P* = NR). However, the proportions of patients meeting all three ACR response criteria were higher for patients treated with the rituximab combination treatment than for patients on rituximab monotherapy (ACR 20, 73 percent vs. 65 percent; ACR 50, 43 percent vs. 33 percent; ACR 70, 23 percent vs. 15 percent; *P* = NR). Higher ACR response rates for the combination treatment were maintained during a 48-week, double-blinded followup. After 48 weeks, 35 percent of patients on the combination regimen and 15 percent of patients on rituximab monotherapy had an ACR 50 response.

Biologic combination strategies: Biologic DMARD plus synthetic DMARD vs. synthetic DMARD. The evidence is limited to two studies comparing a combination regimen of adalimumab plus MTX[57]or a combination regimen of infliximab plus MTX[68] with MTX monotherapy. Both studies were conducted in patients with early, aggressive RA.

Adalimumab plus MTX vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA[57] (see *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs).* Two treatment arms of this 2-year study assessed differences in efficacy between a combination of adalimumab (40 mg every other week) and MTX (20 mg/week) and MTX monotherapy (20 mg/week).[57] After 2 years, statistically significantly more patients on the combination therapy met ACR 50 response criteria than patients on MTX monotherapy (59 percent vs. 43 percent; $P < 0.001$); in addition, they had statistically significantly less progression on the modified SHS score (changes in total Sharp score: 5.5 vs. 10.4; $P < 0.001$). After 2 years of treatment, 49 percent of patients on the combination therapy and 25 percent on MTX monotherapy achieved remission (DAS 28 < 2.6; $P < 0.001$). Discontinuation rates because of lack of efficacy were lower in the combination than in the MTX group (4.2 percent vs. 17.9 percent; *P* = NR).

Infliximab plus MTX vs. MTX. The ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial enrolled 1,049 patients

with early RA (disease duration < 3 years) who were MTX-naive.[68] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or of using two different combinations of MTX and infliximab (3 mg/kg or 6 mg/kg) over 54 weeks. At endpoint, patients in the combination groups had significantly higher ACR-N (ACR-N is the percentage of ACR improvement from baseline to endpoint) scores than patients on MTX monotherapy (38.9 percent [3 mg infliximab plus MTX] vs. 46.7 percent [6 mg infliximab plus MTX] vs. 26.4 percent [MTX]; $P < 0.001$); remission rates were 31 percent, 21 percent, and 15 percent, respectively. In addition, HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX group. Fewer patients in the combination groups than in the MTX monotherapy group withdrew because of lack of efficacy (1.9 percent vs. 3.3 percent vs. 9.6 percent; P = NR). More patients in the combination groups than in the placebo group had serious adverse events (14 percent vs. 11 percent; P = NR) and serious infections (5.6 percent [3 mg/kg infliximab] vs. 5.0 percent [6 mg/kg infliximab] vs. 2.1 percent [MTX]; $P = 0.02$ and $P = 0.04$). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone.[69]

Psoriatic Arthritis: Overview

Six RCTs and two systematic reviews examined symptom response, radiographic joint damage, and remission for psoriatic arthritis (PsA). Details are found in Evidence Tables 3 and 4 in Appendix E. Table 12 provides information on symptom response and quality ratings; Table 13 provides information on radiographic outcomes. The main drug classes examined include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 12. Study characteristics, symptom response, and quality ratings of studies in adults with psoriatic arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Synthetic DMARDs vs. Placebo					
Jones et al., 2000[111]	Systematic review and meta-analysis 1,022	Active PsA; concomitant MTX NR	MTX vs. placebo SSZ vs. placebo	Change in pooled index: MTX 0.65 units (95% CI, 0.00-1.30) SSZ 0.38 units (95% CI, 0.21-0.54)	Good
Kaltwasser et al., 2004[112,113]	RCT 190 24 weeks	Active PsA; failed at least one DMARD; concomitant MTX 0%	LEF (100 mg/day 3 days then 20 mg/day) vs. placebo	PsARC at week 24: LEF 58.9% vs. placebo 29.7% ($P < 0.0001$)	Fair
Biologic DMARDs vs. Placebo					
Mease et al., 2005 ADEPT Trial[114]	RCT 313 24 weeks	Active PsA; failed at least one DMARD; concomitant MTX 51%	ADA (40 mg every other week) vs. placebo	ACR 20 at week 24: ADA 57% vs. placebo 15% ($P < 0.001$)	Fair

Table 12. Study characteristics, symptom response, and quality ratings of studies in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Antoni et al., 2005 IMPACT Study[115,116]	RCT 104 50 weeks (16 blinded, 34 open-label)	Active PsA; failed at least one DMARD; concomitant MTX 56%	INF (5 mg/kg at weeks 0, 2, 6, 14 then every 8 weeks) vs. placebo 71% received a concomitant DMARD	ACR 20 at week 16: INF 65.4% vs. placebo 9.6% ($P < 0.001$)	Fair
Antoni et al., 2005 IMPACT 2 Study[117,118]	RCT 200 14 weeks (early escape at 16 weeks)	Active PsA; failed at least one DMARD; concomitant MTX 46%	INF (5 mg/kg at weeks 0, 2, 6, 14, 22) vs. placebo 46% received concomitant MTX	ACR 20 at week 14: INF 58% vs. placebo 11% ($P < 0.001$)	Fair
Mease et al., 2000[119]	RCT 60 12 weeks	Active PsA; failed at least one DMARD; concomitant MTX use 47%	ETA (25 mg twice a week) vs. placebo	PsARC at week 12: ETA 87% vs. placebo 23% ($P < 0.0001$)	Fair
Mease et al., 2004[120]	RCT 205 24 weeks (with additional 48 weeks open-label)	Active PsA; failed at least one DMARD; concomitant MTX 47%	ETA (25 mg twice a week) vs. placebo	ACR 20 at week 24: ETA 59% vs. placebo 15% ($P < 0.001$)	Fair
Woolacott et al., 2006[121]	Systematic review and meta-analysis 369	Adults with PsA; concomitant MTX 46% to 56%	ETA (25 mg twice a week) vs. placebo (two studies) INF (5 mg/kg) vs. placebo (one study)	ACR 20 at week 12: ETA 65% (RR, 4.19 [95% CI, 2.74-6.42] ACR 20 at week 16: INF 65% (RR, 6.80; 95% CI, 2.89-16.01)	Good

ACR 20, American College of Rheumatology 20 percent improvement from baseline to endpoint; ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NR, not reported; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Scale; RCT, randomized controlled trial; RR, relative risk; SSZ, sulfasalazine; vs., versus.

Table 13. Study characteristics and radiographic joint damage in adults with psoriatic arthritis

Study	Study Design N Duration	Population with Early PsA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Biologic DMARDs vs. Placebo				
Mease et al., 2005 ADEPT Trial[114]	RCT 313 24 weeks	No	ADA (40 mg every other week) vs. placebo	Mean change in the modified total Sharp score at week 24: ADA -0.1 vs. placebo 1.0 ($P < 0.001$) Erosion scores (mean change): ADA 0.0 vs. placebo 0.6 Joint space narrowing scores (mean change): ADA -0.2 vs. placebo 0.4 ($P < 0.001$ for both)

Table 13. Study characteristics and radiographic joint damage in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Population with Early PsA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Mease et al., 2004[122]	RCT 205 72 weeks (24 blinded, 48 open-label)	No	ETA (25 mg twice a week) vs. placebo	Mean annualized rate of change over 1 year of treatment in modified Sharp score: ETA -0.03 unit vs. placebo 1.00 unit (*P* = 0.0001)

ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; mg, milligram; PsA, psoriatic arthritis.

Psoriatic Arthritis: Key Points

We did not find any head-to-head comparison for any of the drugs used to treat PsA. One systematic review found that, compared with placebo, parenteral high-dose MTX and sulfasalazine improved patient outcomes.[111] The strength of evidence is low.

Leflunomide patients had higher response rates and quality-of-life outcomes than those in the placebo arm.[112,113] The strength of evidence is moderate.

The use of three biologics—adalimumab, etanercept, and infliximab—led to better outcomes than did placebo.[114-120,122] The strength of evidence is moderate.

Psoriatic Arthritis: Detailed Analysis

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of synthetic and biologic DMARDs in the treatment of PsA. This, however, does not provide evidence on the comparative efficacy and tolerability of treatments for PsA.

Corticosteroids. We did not identify any studies that examined the use of corticosteroids in the treatment of PsA.

Synthetic DMARDs. One systematic review examined the efficacy of synthetic DMARDs used in placebo-controlled trials.[111] The investigators used data from 13 RCTs that included 1,022 adults with PsA in a meta-analysis that focused on comparisons of sulfasalazine, auranofin, etretinate, fumaric acid, intramuscular injection of gold, azathioprine, efamol marine, and MTX with placebo. Two drugs (MTX and sulfasalazine) are of interest for our report. The primary outcome measure included individual component variables validated by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) to create a pooled index; components used include acute phase reactants, disability, pain, patient global assessment, physician global assessment, swollen joint count, tender joint count, and radiographic changes of joints in any trial of 1 year or longer. The primary outcome was change in a pooled disease index.

MTX. In a systematic review, one study compared MTX with placebo; parenteral high-dose MTX (weekly dose of 7.5 mg to 15 mg) showed an overall improvement in the OMERACT index of 0.65 units (95% CI, 0.00-1.30), although the sample for this study was small (N = 37).

Sulfasalazine. The investigators pooled six trials involving comparisons of sulfasalazine (average dose of 2 g/day to 3 g/day) with placebo (N = 564). Sulfasalazine showed an improvement in the pooled index of 0.38 units (95% CI, 0.21-0.54).[111]

Leflunomide. One trial (two publications) evaluated the efficacy of leflunomide against placebo in 190 patients over 24 weeks;[112,113] PsA was defined as having at least three swollen joints and three tender or painful joints and psoriasis over at least 3 percent of the body surface area. In this study, almost 50 percent of the patients were DMARD naive. Patients who were not DMARD naive were required to discontinue all synthetic DMARDs as well as biologic agents and investigational drugs 28 days before baseline.

The leflunomide group saw significantly greater response rates on a modified ACR 20 (36.3 percent) than the placebo group (20 percent; $P = 0.014$). The PsARC (Psoriatic Arthritis Response Criteria) is a composite measure requiring improvement in two factors (at least one being a joint score) and worsening in none among the following four factors: patient and physician global assessments (improvement defined as decrease by ≥ 1 unit; worsening defined as increase by ≥ 1 unit); and tender and swollen joint scores (the sums of all joints scored; improvement defined as decrease by ≥ 30 percent; worsening defined as increase by ≥ 30 percent). The PsARC was achieved in 58.9 percent of those on leflunomide and 29.7 percent of those on placebo ($P = 0.0001$). PASI 75 (Psoriasis Area and Severity Index) is a composite score (range 0 to 72) used to evaluate the severity of psoriatic lesions by assessing the extent of skin involvement, erythema, plaque thickness, and degree of scaling; the PASI 75 indicates a 75 percent improvement in psoriasis activity from baseline. In this study, 17.4 percent of the leflunomide group and 7.8 percent of the placebo group reached the PASI threshold ($P = 0.048$).

Biologic DMARDs. Five trials (eight articles) and one systematic review examined the efficacy of biologics against placebo in treating patients with PsA.[114-122] One trial was of adalimumab, two of etanercept, and two of infliximab. All trials used a synthetic DMARD, usually MTX, as a base treatment in all patients. The systematic review examined etanercept and infliximab vs. placebo.[121] All showed that the use of biologics led to significantly better outcomes than placebo.

Adalimumab. One trial examined the use of adalimumab (40 mg every other week) in 313 patients suffering from moderate to severe PsA (defined as having at least three swollen joints and three tender or painful joints) who had an inadequate response or intolerance to nonsteroidal anti-inflammatory drug (NSAID) therapy.[114] Patients were allowed to continue current MTX therapy as long as the dose had been stable for 4 weeks. The double-blinded phase of the study lasted 24 weeks, but patients who failed to achieve at least a 20 percent decrease in both swollen and tender joint counts on two consecutive visits could receive rescue therapy with corticosteroids or synthetic DMARDs. A significantly higher percentage of the adalimumab group met ACR 20/50/70 response criteria than the placebo group (all $P < 0.001$). According to the PsARC, 60 percent of the adalimumab group and 23 percent of the placebo group responded (P = NR). PASI 75 was achieved by 59 percent of the adalimumab group and 1 percent of the placebo group ($P < 0.001$). At 24 weeks, the changes in the modified Sharp score, erosion score, and joint space narrowing score were significantly less in adalimumab-treated than placebo-treated patients ($P = 0.001$).

Etanercept. Two studies examined the efficacy of etanercept (25 mg twice weekly by subcutaneous injections) in 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[119,120] In both studies, patients were allowed to continue MTX therapy as long as the dose had been stable for 4 weeks before entry into the study. One study

lasted 12 weeks (N = 60);[119] the other (N = 205) was double-blinded for 24 weeks.[120] In both studies, the proportions of patients on etanercept meeting ACR 20 response criteria were significantly higher than those for patients on placebo. In the 12-week study, 87 percent of patients on etanercept and 23 percent of those on placebo achieved a PsARC response ($P < 0.0001$).[119] The 24-week study had similar results at 12 weeks: 72 percent of patients on etanercept and 31 percent of those on placebo achieved a PsARC response (P = NR).[120] PASI 75 criteria were met by a greater proportion of patients in the etanercept groups than the placebo groups in both studies. In the 12-week study, 26 percent of patients on etanercept met PASI 75 criteria vs. zero patients on placebo ($P = 0.015$); in the longer study, the figures were 23 percent on etanercept vs. 3 percent on placebo ($P < 0.001$). The longer study assessed the radiographic progression of disease at 24 weeks in 205 patients; the mean annualized change in the modified Sharp score was significantly lower in etanercept-treated patients (decrease of -0.03) than in placebo-treated patients (increase of 1.0; $P = 0.0001$).[122]

A recent systematic review pooled the 12-week data from these two studies; the ACR 20 threshold for improvement was achieved by 65 percent of the etanercept groups, with a pooled relative risk of 4.19 (95% CI, 2.74-6.42).[121] The ACR 50 and ACR 70 criteria were achieved by 45 percent and 12 percent, respectively. In addition, the PsARC was reached by almost 85 percent, with a pooled relative risk of 2.6 (95% CI, 1.96-3.45).[121]

Infliximab. Two studies of infliximab compared with placebo included 304 patients with active PsA who had not adequately responded to conventional DMARD therapies.[115,117] In both studies, patients were allowed to continue MTX therapy as long as the dose had been stable for 4 weeks before study entry. The earlier study (N = 104) was double-blinded for 16 weeks.[115] The later trial was double-blinded for 24 weeks (N = 200 patients with cross-over allowed at week 16 for nonresponders); the primary outcomes were evaluated at 14 weeks and before any crossover.[117] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, and 14; the longer study had an additional injection at week 22. In both studies, the percentages meeting ACR 20 response criteria were significantly greater for infliximab than for placebo. In the earlier study, 86 percent of the patients on infliximab and 12 percent on placebo achieved a PsARC response ($P < 0.001$). The longer study had similar results in patients achieving a PsARC response at 14 weeks: 77 percent of the patients on infliximab and 27 percent on placebo ($P < 0.001$). PASI 75 was achieved by a greater proportion of patients in the infliximab groups than the placebo groups in both studies: for the 16-week study, 68 percent on infliximab vs. zero on placebo ($P < 0.01$) and, for the later study, 50 percent on infliximab vs. 1 percent on placebo ($P < 0.001$).

Key Question 2: Functional Capacity and Quality of Life

This question examined specifically the issue of whether, for patients with RA or PsA, drug therapies differed in their ability to improve functional capacity or quality of life. Findings are organized as for KQ 1: RA followed by PsA. Table 9 (above) lists the abbreviated and full names of all instruments and scales referred to in this section. Functional capacity, functional status, and functional ability are three concepts often used interchangeably to refer to similar capabilities. Quality of life is a far broader construct comprising physical health, mental or emotional health, a variety of symptom states (e.g., pain, fatigue), and coping, spiritual and other domains. For the purposes of this report we divided outcomes into functional capacity and health-related quality of life. We use the terms *functional capacity, functional status,* or *functional ability* to refer to

condition-specific measures, such as the Health Assessment Questionnaire (HAQ), developed to assess function in patients with RA or PsA. We use *health-related quality of life* when referring to generic measures, such as the Medical Outcomes Study Short Form 36 Health Survey (SF-36), that have been developed to assess quality of life in both healthy persons and those with different conditions. We also attempted to use terminology consistent with reporting from individual studies; if the authors used the term *functional ability* rather than *functional capacity,* we used the same term. Outcomes for functional capacity and health-related quality of life were sometimes secondary outcomes in these studies; that is, studies were not all designed to detect a difference between groups for these two types of outcomes.

Rheumatoid Arthritis: Overview

A total of 16 RCTS, two observational studies, and one systematic review compared functional capacity or quality-of-life outcomes between active drugs or between active drugs and placebo. Details are found in Evidence Tables 5 and 6 in Appendix E. Table 14 provides information on comparisons made, functional capacity, health-related quality of life, and quality ratings. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Corticosteroids vs. Corticosteroids						
Kirwan et al., 2004[29]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	Better improvement in mean HAQ scores for PNL PNL 0.393 units better than BUD 3 mg; *P* < 0.001 PNL 0.276 units better than BUD 9 mg; *P* < 0.01	Better improvement in SF-36 physical component for PNL than for BUD (mean change 5.4 units better than BUD 3 mg, *P* < 0.01; 3.7 units better than BUD 9 mg, *P* < 0.05)	Fair
Synthetic DMARDs vs. Synthetic DMARDs						
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference between groups in change from baseline HAQ (SSZ: -0.25; MTX: -0.19; *P* = 0.99)	NR	Fair
Dougados et al., 1999[31]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ -0.74 vs. MTX -0.73; *P* = NS)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Emery et al., 2000[32]	RCT 999 1 year with optional 2nd year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Change in HAQ at 12 months, minimal quantitative (data NR) but significant ($P < 0.05$); at 24 months, difference NS	NR	Fair
Haagsma et al., 1997[33]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks not significant (SSZ -0.32; 95% CI, -0.53 to -0.10, MTX -0.46; 95% CI, -0.68 to -0.25; P = NR)	NR	Fair
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week) LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	MHAQ scores improved significantly in LEF group compared with MTX at 6, 12, and 24 months; at both 12 and 24 months, no difference in improvement in HAQ At 6 and 24 months, LEF group had greater improvements in HAQ-DI than SSZ At one year there was no difference in work productivity in LEF vs. MTX weighted mean difference -2.3 points: 95% CI, 6.37-1.77	LEF showed better improvement than MTX in SF-36 physical component but not mental component	Good
Smolen et al., 1999[35] Scott et al., 2001[123]	RCT 358 (146) 24 weeks (12 and 24 month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Improvement in HAQ scores at 24 weeks greater in LEF than SSZ (-0.50 vs. -0.29; $P < 0.03$) and continued in 2-year followup group at 6 and 24 months (-0.50 vs. -0.29; -0.65 vs. -0.36; both $P < 0.01$)	NR	Fair
Strand, et al., 1999[37] Cohen, et al., 2001[38]	RCT 482 12 months (1 year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	Mean improvement in HAQ-DI greater in LEF than MTX at 12 months (-0.45 vs. -0.26; $P \leq 0.01$) and MHAQ (-0.29 vs. -0.15; $P < 0.01$)	Mean improvement in SF-36 physical greater in LEF than MTX at 12 months (7.6 vs. 4.6; $P < 0.01$) but not mental component (1.5 vs. 0.9; P = NS)	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Synthetic DMARD Combinations						
Boers et al., 1997;[39] Landewe et al., 2002[40] COBRA study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Mean change in HAQ: SSZ + MTX combination had greater improvements in functional capacity at 28 weeks (mean change in HAQ -1.1 vs. -0.6; $P <$ 0.0001) but difference not significant at 56 weeks (-0.8 vs. -0.6; $P <$ 0.06)	NR	Good
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	Change from baseline HAQ: no significant difference between groups (SSZ + MTX -0.50 vs. SSZ -0.25; P = 0.51), (SSZ + MTX -0.50 vs. MTX -0.19; P = 0.57)	NR	Fair
Dougados et al., 1999[31] Maillefert et al., 2003[41]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) plus MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ + MTX -0.70 vs. SSZ -0.74 vs. MTX -0.73; P= NS) or in mean HAQ at 5 years (combination 0.6 vs. either single therapy 0.6; P = 0.9)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Goekoop-Ruiterman et al., 2005 [42] BeSt study	RCT 508 12 months	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1 to 5), median duration of symptoms 23 weeks (IQR 14 to 53)	1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	Better functional ability after 12 months for patients treated with 3 or 4 than those treated with group (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.5, and 0.5, respectively; $P < 0.05$ for 1 vs. 3 and 4, NS for other comparisons)	NR	Good
Haagsma et al., 1997[33]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks NS (SSZ + MTX -0.51: 95% CI, -0.76 - -0.26 vs. SSZ -0.32: 95% CI, -0.53 - -0.10 vs. MTX -0.46: 95% CI, -0.68 - -0.25; P = NR)	NR	Fair
Mottonen et al., 1999;[43] Korpela et al., 2004;[44] Puolakka et al., 2004[124] FIN-RACo study	RCT 199 24 months (5 year followup)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day) + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL	Less work disability for combination group than monotherapy group (median 12.4 days per patient-observation year vs. 32.2; $P = 0.008$)	NR	Fair
Svensson et al., 2005[47]	Open-label trial 250 2 years	Population-based; active RA; duration 1 year or less	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	Greater improvement in DMARD + PNL group than DMARD-only group (from mean HAQ of 1.0 to 0.4 at 1 year and 0.5 at 2 years vs. 1.0, 0.6, and 0.7; P = NR) Mean SOFI index decreased from 8 at baseline to 4 at 1 year and 4 at 2 years vs. 9, 6, and 7 respectively; P = NR)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs vs. Biologic DMARDs						
Weaver et al., 2006[53]	Prospective cohort study 1,371 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETA (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Greater mean percentage improvements in HAQ at 12 months in ETA than INF (17% vs. 1%; *P* = NR)	NR	Fair
Biologic DMARDs vs. Synthetic DMARDs						
Bathon et al., 2000;[54] Genovese et al., 2002;[55] Genovese et al, 2005;[56] Kosinski et al., 2002[125] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETA (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Better improvement in HAQ early in treatment (first 12 weeks) for ETA than MTX (*P* < 0.0001). No significant difference in HAQ scores during weeks 16 to 52 Significantly greater percentage of patients with at least a 0.5 unit improvement in HAQ-DI at 24 months for ETA 25 mg than for either ETA 10 mg or MTX (55% vs. 43% vs. 37%; *P* = 0.021 and *P* < 0.001, respectively)	Better improvement in SF-36 physical summary and SF-36 arthritis-specific health index for ETA group than the MTX group during first 12 weeks (*P* < 0.0001) No significant difference in weeks 16 to 52	Fair
Breedveld et al., 2006 [57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	At 1 year, ADA and MTX monotherapy groups had similar improvement in HAQ-DI (-0.8 vs. -0.8; *P* = NR). Improvements remained similar after 2 years	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETA (25 mg twice weekly) vs. MTX (20 mg/week)	Similar improvement in mean HAQ scores for MTX and ETA (scores fell from 1.7 to 1.1 and 1.7 to 1.0; *P* = 0.3751)	NR	Good
Listing et al., 2006[58]	Prospective cohort study 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETA, INF; dose NR) vs. DMARDs as a class (dose NR)	Severely disabled patients (≤ 50% of full function) in biologic group more likely to achieve physical independence (≥ 67% of full function, Hanover Functional Status Questionnaire) than DMARD group (OR, 3.88; 95% CI, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in biologic group than in DMARD group (OR, 2.18; 95% CI, 1.04-4.6)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs + Synthetic DMARDs vs. Biologic DMARDs						
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	At 1 year, ADA + MTX group had greater improvements in HAQ-DI than ADA alone (mean, -1.1 units vs. -0.8; *P* = 0.002). After 2 years, there was no difference (-1.0 vs. -0.9; *P* = 0.058) After 2 years, more ADA + MTX patients had improvement of ≥ 0.22 in HAQ-DI than ADA patients (72% vs. 58%; *P* < 0.05); had a greater percentage with HAQ-DI scores of 0 (33% vs. 19%; *P* < 0.001)	NR	Fair
Combe et al., 2006[60]	RCT 260 24 weeks	Europe multicenter; active RA despite SSZ treatment; mean disease duration 6.6 years	ETA (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETA (25 mg twice weekly)	Mean percentage improvements in HAQ were similar for ETA + SSZ and ETA alone (40.2% vs. 35.3%, *P* = NS)	Mean percentage improvements in EuroQOL VAS were similar for ETA + SSZ and ETA alone (67.6% vs. 64.6%; *P* = NS)	Fair
Klareskog et al., 2004;[63] van der Heijde et al., 2006;[64] van der Heijde et al., 2006[65] TEMPO study	RCT 696 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETA (25 mg twice weekly) + MTX (20 mg/week) vs. ETA (25 mg twice weekly)	At 52 weeks ETA + MTX was more likely to attain HAQ-DI scores similar to population norms (< 0.5) than ETA alone (*P* < 0.05). Combination group had greater improvement in mean HAQ scores (mean fall from 1.8 to 0.8 vs. 1.7 to 1.0; *P* < 0.001; mean improvement from baseline HAQ 1.0 vs. 0.7; *P* < 0.01)	ETA + MTX patients reported better quality of life than ETA-only patients (mean EQ 5-D VAS 72.7 vs. 66.8; *P* < 0.05)	Good
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Patients treated with ETA + MTX had similar improvements in functional capacity to those treated with ETA only (mean percentage improvements in HAQ at 12 months: 17% vs. 17%; *P* = NR)	NR	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Biologic DMARDs + Synthetic DMARDs vs. Synthetic DMARDs						
Breedveld et al., 2006[57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week)	At 1 year, ADA + MTX had greater improvements in HAQ-DI than MTX alone (mean -1.1 units vs. -0.8; $P < 0.001$). After 2 years, ADA + MTX remained statistically greater (-1.0 vs. -0.9; $P < 0.058$) After 2 years, more ADA + MTX patients had improvement of ≥ 0.22 in HAQ-DI than MTX patients (72% vs. 63%; $P < 0.05$). Had greater percentage with HAQ-DI scores of 0 (33% vs. 19%; $P < 0.001$)	NR	Fair
St Clair et al., 2004;[68] Smolen et al., 2006[69] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Greater mean decrease in HAQ from weeks 30 to 54 for combination groups than MTX group (INF 3 mg + MTX and INF 6 mg + MTX vs. MTX: 0.80 and 0.88 vs. 0.68; $P = 0.03$; $P < 0.001$). Combination therapy was more effective for improving HAQ by at least 0.22 units (76.0% and 75.5% vs. 65.2%; $P = 0.003$; $P = 0.004$) Patients on combination treatment had a higher probability of improvement in employability than those on MTX alone ($P < 0.001$)	Significantly greater improvement in SF-36 physical component summary scores for INF 6 mg + MTX vs. MTX (13.2 vs. 10.1; $P = 0.003$) but not for INF 3 mg + MTX vs. MTX (11.7 vs. 10.1; $P = 0.10$)	Fair

Table 14. Interventions, functional capacity, health-related quality of life, and quality ratings of studies in adults with rheumatoid arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Weaver et al., 2006[53]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETA (25 mg twice weekly) + MTX (dose NR) vs. ETA (25 mg twice weekly)	Greater mean percentage improvements in HAQ at 12 months for ETA + MTX than MTX (17% vs. 7%; $P < 0.01$) Similar mean percentage improvements in HAQ at 12 months for INF + MTX and MTX (3% vs. 7%; P = NS)	NR	Fair

BUD, budesonide; combo, combination therapy; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETA, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NHS, National Health Service; NR, not reported; NS, not significant; PNL, prednisolone; PRED, prednisone; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; SOFI, Signals of Functional Impairment Scale; SSZ, sulfasalazine.

Rheumatoid Arthritis: Key Points

Corticosteroids vs. corticosteroids. Only one head-to-head RCT compared two corticosteroids, budesonide and prednisolone.[29] Prednisolone produced greater improvement in functional capacity and health-related quality of life than budesonide. The results are limited to one study. The strength of evidence is low.

Synthetic DMARDs vs. synthetic DMARDs. Two RCTs[32,37] and one systematic review with meta-analysis[34] compared leflunomide and MTX. Some results indicated greater improvement with leflunomide (mean improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI) at 12 months and 24 months and in the SF-36 (Medical Outcomes Study Short Form 36 Health Survey) physical component at 12 months; others showed no differences in work productivity or the SF-36 mental component. The strength of the evidence is moderate.

One RCT[35] with a 2-year followup[123] compared leflunomide and sulfasalazine. Leflunomide yielded greater improvements in functional capacity measured by HAQ scores at 24 weeks, 6 months, and 24 months. The results were limited to one study. The strength of the evidence is low.

Three RCTs compared sulfasalazine and MTX.[30,31,33] Results, consistent across the trials, did not support a difference in functional capacity between the medications. The strength of the evidence is moderate.

No fair or good evidence exists for comparing hydroxychloroquine to monotherapy with another synthetic DMARD.

Synthetic DMARD combinations. Three RCTs compared a combination of two synthetic DMARDs (sulfasalazine plus MTX) to monotherapy with either drug alone.[30,31,33] Findings do not support a difference in functional capacity between combination therapy and monotherapy. The strength of the evidence is moderate.

Three RCTs compared various combination strategies using corticosteroids and one or more synthetic DMARDs with synthetic DMARD monotherapy.[39,43,47] One open-label RCT compared the combination of a synthetic DMARD and prednisolone with synthetic DMARD monotherapy and found greater improvement in functional capacity for the combination group.[47] The functional capacity outcomes were not statistically evaluated for the two groups, and the clinical relevance of these results is uncertain. In addition, the results should be interpreted cautiously, given the open-label design and potential for bias. Another RCT found that the combination of sulfasalazine, MTX, and prednisolone vs. sulfasalazine alone resulted in greater improvements in functional capacity at 28 weeks, but the difference was no longer statistically significant at 56 weeks.[39] The third RCT compared a combination of three synthetic DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone with synthetic DMARD monotherapy.[43] The combination therapy group had significantly less work disability than patients in the monotherapy group at 5-year followup.[124] Of note, the randomized treatments were carried out for 2 years and treatments were then at the discretion of the treating physician.

The data are limited to one study for each comparison. The strength of the evidence is low for each individual comparison. However, the strength of evidence is moderate favoring combination strategies using corticosteroids plus one or more synthetic DMARDs over synthetic DMARD monotherapy.

One RCT in patients with early RA found that patients treated with initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab and MTX had statistically significantly better functional ability than those treated with sequential DMARD therapy.[42] However, the magnitude of difference was small, and the clinical significance of this result is uncertain. The strength of the evidence is low.

Biologic DMARDs vs. biologic DMARDs. We did not find any head-to-head RCTs that compared one biologic DMARD with another. The evidence was limited to one prospective cohort study that compared etanercept with infliximab.[53] Patients treated with etanercept had better functional capacity at 12 months than did those treated with infliximab (mean percentage improvements in HAQ 17 percent vs. 1 percent; P = NR). However, direct statistical comparisons between etanercept and infliximab were not described. The strength of the evidence is low.

Biologic DMARDs vs. synthetic DMARDs. We found three RCTs[54,57,63] and one prospective cohort study[58] that included comparisons of monotherapy with a biologic DMARD to monotherapy with a synthetic DMARD. The evidence from these studies is mixed. Population-based, observational evidence from the cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.[58] Two of the RCTs, however, found no differences when comparing either adalimumab[57] or etanercept[63] with MTX. The third RCT [54] found that etanercept resulted in better improvement of function and quality of life during the first 12 weeks of treatment, but it found no difference from week 16 to week 52. The study also reported that a greater percentage of patients treated with etanercept had significant improvements in functional capacity (≥ 0.5 unit HAQ-DI) at 24 months. All RCTs were funded by the makers of the biologic DMARDs. The strength of the evidence is moderate for biologics as a class compared to synthetics as a class.

No evidence exists on abatacept, anakinra, infliximab, and rituximab. No studies were available comparing biologics with synthetic DMARDs other than MTX.

Biologic DMARDS vs. corticosteroids. No studies meeting our quality criteria compared biologic DMARDs with corticosteroids.

Biologic DMARD combinations. Two RCTs suggested that a combination of adalimumab[57] or etanercept[63-65] with MTX led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with biologic DMARDs. One other RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.[60] One prospective cohort study found no differences in these outcomes when comparing etanercept plus MTX to etanercept alone or infliximab plus MTX to infliximab alone.[53] The strength of the evidence is low for all comparisons.

For most individual medications in these comparisons, however, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. No evidence (for biologic DMARD plus synthetic DMARD vs. biologic DMARD) was available on abatacept, anakinra, rituximab, and combinations with synthetic DMARDs other than MTX and sulfasalazine.

Two RCTs found that a combination of adalimumab plus MTX[57] or infliximab plus MTX[68] in MTX-naive patients with early, aggressive RA led to better functional capacity and quality of life than MTX monotherapy. Both RCTs were funded by the makers of the biologic DMARDs. One prospective cohort study found the etanercept-MTX combination to be greater than MTX monotherapy for functional capacity, but it found no difference between the infliximab-MTX combination and MTX alone.[53] The strength of the evidence supporting a greater efficacy of combination treatment with a biologic DMARD plus MTX than with MTX monotherapy is moderate for the above comparisons.

Rheumatoid Arthritis: Detailed Analysis

Corticosteroids. *Corticosteroid vs. corticosteroid.* One 12-week head-to-head RCT (N = 143) compared budesonide (3 mg/day or 9 mg/day; n = 37 and 36, respectively) and prednisolone (7.5 mg/day; n = 39).[29] Mean disease duration of RA was 9 years. Overall, prednisolone produced greater improvement in functional capacity and health-related quality of life than either dose of budesonide. At 12 weeks, those treated with prednisolone had better improvement in mean HAQ scores than budesonide (0.393 units better than budesonide 3 mg, $P < 0.001$; 0.276 units better than budesonide 9 mg, $P < 0.01$). A change of 0.22 units is generally considered the minimum clinically important difference.[126] Those treated with prednisolone also had better improvement in health-related quality of life as measured by the physical subscale of the SF-36 (difference in mean change of 5.4 units compared with budesonide 3 mg, $P < 0.01$; 3.7 compared with budesonide 9 mg, $P < 0.05$). Improvement on the mental subscale of the SF-36 was not statistically significantly different between groups. Of note, functional capacity and health-related quality of life were secondary outcome measures; the study had not been designed to compare differences in either the HAQ or the SF-36.

Synthetic DMARD vs. synthetic DMARD. *Leflunomide vs. methotrexate.* We found two RCTs[32,37] comparing leflunomide (20 mg/day) with MTX (7.5 mg/week to 15 mg/week)[32,37] and one good systematic review with a meta-analysis of leflunomide.[34] The systematic review included only two trials comparing leflunomide with MTX and only one study for all but one of the functional capacity and quality-of-life outcomes. We describe the individual studies first.

The first trial randomized 482 patients to leflunomide (n = 182) or MTX (n = 182) over 12 months.[37,127] It is described in more detail in the KQ 1 section entitled *Synthetic DMARDs vs. synthetic DMARDs.* Patients receiving leflunomide reported greater mean improvement in the HAQ-DI (-0.45 vs. -0.26; $P \leq 0.01$), MHAQ (-0.29 vs. -0.15; $P < 0.01$), and the SF-36 physical component (7.6 vs. 4.6; $P < 0.01$) than those receiving MTX at 12 months. At 12 months, the

two groups did not differ significantly in improvement in the SF-36 mental summary score (1.5 vs. 0.9; *P* = NS) or in work productivity. A 2-year followup of 235 patients (leflunomide, n = 98; MTX, n = 101) found greater mean improvement in the HAQ-DI (-0.60 vs. -0.37; *P* = 0.005) and MHAQ scores (-0.43 vs. -0.28; *P* ≤ 0.05) with leflunomide than with MTX.[38] The groups did not differ significantly in mean improvement in the SF-36 physical or mental summary scores at 24 months. These 2-year results are limited by the high attrition rate (45 percent) from the initial study.

One multinational trial comparing leflunomide and MTX was a 1-year RCT of 999 subjects with an optional second year.[32,128] Mean disease duration was 3.5 years to 3.8 years. At 12 months, a statistically significant but minimal quantitative difference (number not reported, shown in bar graph)[32] for change in the HAQ (*P* < 0.05) was reported between the two groups; at 24 months, however, the groups did not differ significantly.

The systematic review with meta-analysis included six trials (N = 2,044) comparing leflunomide (10 to 20 mg/day) with other synthetic DMARDs in patients with active RA.[34] It included two studies relevant to this section.[32,37] MHAQ scores improved significantly more in patients treated with leflunomide than in those treated with MTX at 6, 12, and 24 months. The leflunomide group and the MTX group did not differ in improvement on the HAQ index at either 12 months or 24 months. Work productivity did not improve significantly in the leflunomide group when compared with the MTX group (weighted mean difference [WMD], -2.3 points; 95% CI, -6.37-1.77). When comparing leflunomide with MTX, changes in SF-36 scores showed better improvement in the physical summary score (WMD, -3.0 points; 95% CI, -5.41 - -0.59) but not the mental summary score (WMD, -0.6 points; 95% CI, -3.01-1.81). This systematic review was limited by the number of studies included for meta-analysis; only one study was available for each individual functional capacity or quality-of-life outcome measure except for change in HAQ scores, for which there were two studies.

Leflunomide vs. sulfasalazine. One RCT[35] with a 2-year followup[123] compared leflunomide (20 mg/day) with sulfasalazine (2 g/day); one systematic review included a meta-analysis of leflunomide.[34] The RCT was a multinational, multicenter study of 358 patients (leflunomide, n = 133; sulfasalazine, n = 133).[35] Baseline HAQ scores were similar for all groups. The leflunomide group had significantly greater improvement in HAQ scores at 24 weeks than the sulfasalazine group (-0.50 vs. -0.29; *P* < 0.03). The 2-year followup found that the leflunomide group had significantly greater improvements in HAQ scores than the sulfasalazine group at 6 and 24 months (-0.50 vs. -0.29 and -0.65 vs. -0.36; both *P* < 0.01).[123] The study was limited by only including 146 (leflunomide, n = 60; sulfasalazine, n = 60) of the original 358 subjects and having a 21 percent attrition rate (116 completed the study).

One systematic review with meta-analysis compared leflunomide (10 to 20 mg/day) with other DMARDs in patients with active RA.[34] For comparing leflunomide and sulfasalazine, the meta-analysis included one study (N = 229) with changes in HAQ at 6, 12, and 24 months.[123] At 6 and 24 months, the leflunomide group had greater improvements in the HAQ-DI than the sulfasalazine group (WMD -0.25 point; 95% CI, -0.42 - -0.08; WMD -0.29 point; 95% CI, -0.57 - -0.01, respectively). This evidence is limited because the meta-analysis included only one study for this outcome; they did not pool data from multiple studies.

Sulfasalazine vs. MTX. Three RCTs compared sulfasalazine with MTX.[30,31,33] Their findings are consistent and do not support a difference in functional capacity between the groups receiving these two pharmaceuticals. A multinational 52-week RCT of 209 DMARD-naive subjects found no statistically significant difference in change in the HAQ from baseline to 1

year (sulfasalazine -0.74; MTX -0.73; *P* = NS).[31] A 52-week RCT of 105 DMARD-naive subjects in academic and peripheral clinics in the Netherlands reported a change in HAQ scores from baseline to 52 weeks of -0.32 (95% CI, -0.53 - -0.10) for sulfasalazine and a change of -0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[33] HAQ was a secondary outcome in this study; HAQ changes for the different groups were not compared statistically. An 18-month RCT of 165 subjects at eight sites in Scotland found no significant difference between the sulfasalazine and MTX groups on the HAQ between baseline and endpoint (-0.25 vs. -0.19; *P* = 0.99).[30]

Synthetic DMARD combinations. *MTX plus sulfasalazine vs. monotherapy with MTX or sulfasalazine.* Three RCTs (four publications) compared MTX plus sulfasalazine to either drug alone.[30,31,33,41] Two of the RCTs included patients with disease duration of less than 1 year;[31,33] the third included patients with RA of up to 10 years.[30] Findings of these studies do not support a difference in functional capacity between combination therapy and either monotherapy.

A multinational RCT of 209 DMARD-naive subjects compared sulfasalazine (2 g/day to 3 g/day; n = 68), MTX (7.5 mg/week to 15 mg/week; n = 69), and the sulfasalazine-MTX combination (n = 68) for 52 weeks. No statistically significant difference in changes in HAQ scores occurred from baseline to 1 year (combination -0.70; sulfasalazine -0.74; MTX -0.73; *P* = NS).[31] A long-term followup comparing the combination therapy to monotherapy (combining the two monotherapy groups) found no significant difference in mean HAQ scores at 5 years (combination 0.6; monotherapy 0.6; *P* = 0.9).[41]

A 52-week RCT of 105 DMARD-naive subjects in Dutch academic and peripheral clinics reported a change in HAQ scores between baseline and 52 weeks of -0.51 (95% CI, -0.76 - -0.26) for the MTX-sulfasalazine combination therapy, a change of -0.32 (95% CI, -0.53 - -0.10; *P* = NR) for sulfasalazine, and a change of -0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[33] The HAQ was a secondary outcome in this study; the authors did not attempt to explain these results or compare the values.

The third study was an 18-month RCT of 165 subjects at eight sites in Scotland. The investigators found no significant difference between the combination therapy and the monotherapy groups in changes from baseline HAQ scores (combination -0.50; sulfasalazine -0.25; MTX -0.19; combination vs. sulfasalazine, *P* = 0.51; combination vs. MTX, *P* = 0.57).[30]

Synthetic DMARD plus corticosteroid combinations vs. synthetic DMARDs. *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* The evidence is limited to one open-label RCT that compared synthetic DMARD use with and without prednisolone in patients with active RA for 1 year or less.[47] This 2-year study compared prednisolone (7.5 mg/day) added to an initial DMARD (chosen by the treating physician) with a synthetic DMARD only in patients with early RA; it is described in greater detail in the Key Question 1 section entitled *One synthetic DMARD plus corticosteroid vs. synthetic DMARD.* The authors reported greater improvement in functional capacity for the prednisolone group than the nonprednisolone group. The DMARD plus prednisolone group had a decrease in HAQ scores from a mean of 1.0 at baseline to 0.4 at 1 year and 0.5 at 2 years. The corresponding values for the DMARD-only group were 1.0, 0.6, and 0.7 (*P* = NR). The DMARD plus prednisolone group also had greater improvement in the mean Signals of Functional Impairment (SOFI) index (mean decrease from 8 at baseline to 4 at 1 year and 4 after 2 years compared to values of 9, 6, and 7, respectively; *P* = NR). Scores on the HAQ and the SOFI index were not statistically compared for the two groups; the clinical relevance of these results is uncertain. In addition, the results should be interpreted cautiously, given the open-label design and potential for bias.

Two synthetic DMARDs plus corticosteroid vs. synthetic DMARD. The COBRA (Combinatietherapie Bij Reumatoide Artritis) study assessed differences in efficacy between a combination of sulfasalazine, MTX, and prednisolone and sulfasalazine only.[39] This RCT evaluated 155 patients with early RA over 56 weeks. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week stopped after 40 weeks), and prednisolone treatment (60 mg/day tapered over 28 weeks). Compared with patients treated with sulfasalazine alone, patients treated with combination therapy had greater improvements in functional capacity at 28 weeks (mean change in HAQ of -1.1 vs. -0.6; $P < 0.0001$). The difference was no longer statistically significant at 56 weeks (mean change in HAQ, -0.8 vs. -0.6; $P < 0.06$).

Three synthetic DMARDs plus corticosteroid vs. synthetic DMARD. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a combination of MTX, sulfasalazine, hydroxychloroquine, and prednisolone against monotherapy with a DMARD with or without prednisolone.[43] This study randomized 199 patients with early RA to combination therapy or monotherapy. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week to 10 mg/week), hydroxychloroquine (300 mg/day), and prednisolone (5 mg/day to 10 mg/day). Patients on monotherapy were initially started on sulfasalazine (2 g/day to 3 g/day), but they could be changed to MTX (7.5 mg/week to 15 mg/week) or to a third DMARD if needed. The study is described further in the KQ 1 section entitled *Three synthetic DMARDs plus corticosteroid vs. synthetic DMARDs*. The initial publication reported no functional capacity or quality-of-life outcomes at 2 years. A 5-year follow-up trial reported that patients in the combination therapy group had significantly less work disability than patients in the monotherapy group (median 12.4 days per patient-observation year vs. 32.2 days; $P = 0.008$, sex- and age-adjusted $P = 0.009$).[124] After 2 years, the drug treatment strategy was no longer restricted.

Other combination strategies. The BeSt RCT (Dutch acronym for Behandel Strategieen, "treatment strategies") examined four different treatment strategies over 12 months.[42] Patients (N = 508) with early RA were randomized to one of four strategies: (1) sequential DMARD starting with MTX (15 mg/week); (2) step-up combination therapy of MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone; (3) initial combination therapy of MTX, and sulfasalazine with tapered high-dose prednisone (60 mg/day to 7.5 mg/day in 7 weeks); and (4) initial combination therapy with infliximab (3 mg/kg) and MTX (25 to 30 mg/week). Adjustments were made in each strategy when the DAS 44 (disease activity score in 44 joints) was greater than 2.4. All groups had similar D-HAQ (Dutch version of the HAQ) scores at baseline (1.4 ± 0.7 or 1.4 ± 0.6). Functional ability, measured by the D-HAQ, was a primary end point. After 12 months of treatment, patients treated with strategy 3 or 4 had statistically significantly better functional ability than those treated with strategy 1; (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.5, and 0.5, respectively; $P < 0.05$ for group 1 vs. groups 3 and 4, NS for other comparisons).

Biologic DMARD vs. biologic DMARD. We did not identify any head-to-head RCTs. The head-to-head evidence was limited to a prospective cohort study based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program that included etanercept and infliximab.[53]

Etanercept vs. infliximab. RADIUS was a primary care-based U.S. study that enrolled patients who were initiating any new DMARD at study entry. Mean disease duration was 9.3 years, indicating that most patients suffered from advanced RA. The percentage of patients with early RA was not reported. Patients treated with etanercept had greater mean percentage

improvements on the HAQ at 12 months than patients treated with infliximab (17 percent vs. 1 percent; *P* = NR). Among patients older than 65 years, after adjusting for baseline covariates, the authors reported that the etanercept-treated patients had greater mean percentage improvements in the HAQ at 12 months than infliximab-treated patients (22 percent vs. 4 percent; *P* = NR). However, direct statistical comparisons between etanercept and infliximab were not described. The study was designed to compare combinations of etanercept or infliximab with MTX to monotherapy with etanercept, infliximab, or MTX.

Biologic DMARDs vs. synthetic DMARDs. We found three RCTs and one prospective cohort study that included comparisons of biologic DMARD monotherapy with synthetic DMARD monotherapy. The RCTs compared etanercept with MTX[54,63] and adalimumab with MTX;[57] the cohort study assessed differences in class effects.[58] No head-to-head evidence exists on abatacept, anakinra, infliximab, and rituximab or on synthetic DMARDs other than MTX (although anakinra and infliximab were included in the prospective cohort study comparing biologics as a class to synthetic DMARDs as a class).

Biologic DMARDs as a class vs. synthetic DMARDs as a class. The prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n = 818) and synthetic DMARDs as a class (n = 265) in patients who had failed two previous DMARD treatments.[58] This study was population-based and part of the RABBIT study, a German long-term, prospective cohort study of RA patients who required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. Severely disabled patients receiving biologic therapies were more likely to achieve physical independence, defined as ≥ 67 percent of full function as measured by the Hanover Functional Status Questionnaire (FFbH, or Funktionsfragebogen Hannover), than controls on conventional synthetic DMARD therapy (OR, 3.88; 95% CI, 1.7-8.8). Functional remission (≥ 83 percent of full function) was more often achieved in patients receiving biologics than in controls (OR, 2.18; 95% CI, 1.04-4.6).

Adalimumab vs. MTX. The only data come from the PREMIER study, a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX.[57] Two treatment arms of this 2-year study were adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). Details of this study are reported in the KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs.* After 1 year, the adalimumab and MTX monotherapy groups had similar improvements in functional status measured using the HAQ-DI (mean: -0.8; -0.8; *P* = NR). Improvements remained similar after 2 years (-0.9; -0.9; *P* = NR). After 2 years, 19 percent of patients in both monotherapy groups had HAQ-DI scores of zero. We report on results of the other comparisons of the PREMIER study for functional status outcomes in the respective KQ 2 sections on *Biologic DMARDS plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs*.

Etanercept vs. MTX. Two trials (seven publications) compared etanercept with MTX (20 mg/week) over 52 weeks.[54-56,63-65,125] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX-naive.[54-56] The other study was the TEMPO trial (see KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs).*[63-65] Patients had active RA and had failed at least one DMARD other than MTX. About 60 percent of the study population was MTX-naive.

ERA was a 52-week multicenter RCT of 632 patients with early RA in the United States that compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week).[54-56,125] The

treatment groups were similar at baseline. Most patients were female, white, and rheumatoid factor positive and had had RA for fewer than 18 months. Patients treated with etanercept had better early responses for functional status and health-related quality of life. Compared with patients treated with MTX, patients treated with etanercept showed better improvement early in treatment (during the first 12 weeks) on the HAQ ($P < 0.0001$), the SF-36 physical subscale ($P < 0.0001$), and the SF-36 arthritis-specific health index (ASHI) ($P < 0.0001$). From weeks 16 to 52, these measures did not differ significantly; both groups showed similar improvement. These results may be attributed to an earlier response to etanercept than to MTX and the fact that patients were increased to the maximum MTX dose over 2 months. After 12 months, approximately 55 percent of patients in both the MTX and the 25-mg etanercept groups had at least a 0.5 unit improvement in the
HAQ-DI. At 24 months, 55 percent of the 25-mg etanercept group had this level of improvement, as did 37 percent of the MTX group ($P < 0.001$) and 43 percent of the 10-mg etanercept group ($P = 0.021$).

The 52-week TEMPO RCT of RA patients who had failed previous DMARD therapy compared patients treated with etanercept (25 mg twice weekly) with those treated with MTX (20 mg/week) and those given combination therapy with both drugs.[63] Baseline HAQ scores were similar for all three groups. At 52 weeks, improvement of functional status did not differ significantly between the MTX group and the etanercept group (mean HAQ scores fell from 1.7 to 1.1 and from 1.7 to 1.0, respectively; $P = 0.3751$). We report on comparisons of etanercept with the combination group in the KQ 2 section below on *Biologic DMARD plus synthetic DMARD vs. biologic DMARD*.

Biologic combination strategies: biologic DMARD plus synthetic DMARD vs. biologic DMARD. We found four studies, three RCTs[57,60,63] and one prospective cohort study,[53] comparing the combination of a biologic DMARD plus a synthetic DMARD with biologic DMARD monotherapy. The majority of these studies compared a combination of a biologic DMARD and MTX with monotherapy of the same biologic DMARD.[53,57,63] One trial used sulfasalazine as a synthetic DMARD in combination with a biologic DMARD.[60] We found no evidence on combination treatments of abatacept and anakinra.

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (< 3 years), aggressive RA.[57] This 2-year multinational study randomized 799 patients to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1 units) than the adalimumab group (-0.8; $P = 0.002$). After 2 years, the combination group (-1.0) and the adalimumab-only group (-0.9) did not differ significantly ($P = 0.058$) for improvements in the HAQ-DI. More patients in the combination group (72 percent) had achieved improvement of ≥ 0.22 (considered the clinically relevant threshold) in HAQ-DI than the adalimumab group (58 percent; $P < 0.05$). In addition, 33 percent of patients in the combination group and 19 percent of those in the adalimumab group had HAQ-DI scores of zero ($P < 0.001$). For functional capacity outcomes, we report on results of the other comparisons of the PREMIER study in the KQ 2 sections on *Biologic DMARDs vs. synthetic DMARDs* and *Biologic DMARDs plus synthetic DMARDs vs. synthetic DMARDs.*

Etanercept plus MTX vs. etanercept. One good-quality RCT (three publications)[63-65] and one prospective cohort study[53] assessed differences in efficacy between a combination of etanercept and MTX and etanercept monotherapy in patients with active, DMARD-resistant RA. The RCT

showed greater effectiveness for functional capacity and quality of life for combination therapy; the cohort study found no difference.

The 52-week TEMPO trial involved 696 patients with active RA who had failed previous DMARD therapy.[63-65,91] We focus here on results of the etanercept-MTX combination and the etanercept monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the etanercept monotherapy group. At 52 weeks, patients in the combination group were significantly more likely to attain HAQ-DI scores similar to population norms (< 0.5) than patients in the monotherapy group ($P < 0.05$). The combination group had greater improvement in functional capacity than the monotherapy group (mean HAQ changes from 1.8 to 0.8 vs. 1.7 to 1.0; $P < 0.001$; mean improvement from baseline HAQ 1.0 vs. 0.70; $P < 0.01$). In addition, those receiving combination therapy achieved better quality-of-life scores than etanercept monotherapy (mean European Quality of Life Health Status Visual Analogue Scale [EQ 5-D VAS] 72.7 vs. 66.8; $P < 0.05$).[64]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[65] Improvement in disability (based on HAQ) remained statistically significantly better in the combination group than in the etanercept monotherapy group ($P < 0.01$). However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

The prospective cohort study was based on the RADIUS program[53] (see *Biologic DMARD vs. biologic DMARD* above). Mean percentage improvements in HAQ at 12 months did not differ between patients treated with etanercept plus MTX and those treated with etanercept monotherapy (17 percent vs. 17 percent; P = NR).

Etanercept plus sulfasalazine vs. etanercept. A 24-week multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy (25 mg twice weekly), sulfasalazine monotherapy (2, 2.5, or 3 g/day), and an etanercept-sulfasalazine combination (25 mg twice weekly plus 2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[60] This study is described in greater detail in the corresponding section for KQ 1. We focus on results of the etanercept monotherapy (n = 103) and the combination (n = 101) arms. Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. The mean percentage improvement for HAQ was similar for the combination group (40.2 percent) and the etanercept group (35.3 percent; P = NS). The mean percentage improvement for health-related quality of life measured by the EuroQOL VAS was also similar (67.6 percent vs. 64.6 percent; P = NS).

Infliximab plus MTX vs. infliximab. No RCT compared the infliximab-MTX combination to infliximab monotherapy. The only comparative evidence comes from a cohort study from the RADIUS program (see *Etanercept plus MTX vs. etanercept*).[53] The mean percentage improvements in the HAQ at 12 months were similar for patients treated with the infliximab-MTX combination and those treated with infliximab monotherapy (3 percent vs. 1 percent; P = NR).

Biologic combination strategies: biologic DMARD plus synthetic DMARD vs. synthetic DMARD. We found two RCTs[57,68] and one prospective cohort study[53] comparing a combination regimen of adalimumab plus MTX,[57] infliximab plus MTX,[53,68] or etanercept plus MTX[53] with MTX monotherapy. Both RCTs were conducted in patients with early, aggressive RA. The RCTs found greater improvement in functional capacity and quality of life with combination therapies than with MTX monotherapy. The prospective cohort study found the etanercept-MTX combination improved in functional capacity more than MTX monotherapy, but the infliximab-MTX group did not differ from the MTX-only group.[53]

Adalimumab plus MTX vs. MTX. The PREMIER study was a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX; it compared adalimumab monotherapy, MTX monotherapy, and the combination of adalimumab plus MTX[57] (see KQ 1 section on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs*). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1) than the methotrexate group (-0.8; $P < 0.001$). After 2 years, the combination (-1.0) was superior to MTX (-0.9; $P < 0.05$). More patients in the combination group (72 percent) had achieved improvement of ≥0.22 (considered the clinically relevant threshold) in the HAQ-DI than the MTX group (63 percent; $P < 0.05$). In addition, 33 percent of patients in the combination group and 19 percent of those in the MTX group had HAQ-DI scores of zero ($P < 0.001$). We report on results of the other comparisons of the PREMIER study in the sections on *Biologic DMARDs plus synthetic DMARDs vs. biologic DMARDs* and *Biologic DMARDs vs. synthetic DMARDs.*

Infliximab plus MTX vs. MTX. The ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial enrolled 1,049 patients with early RA (disease duration < 3 years) who were MTX-naive.[68] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or with a combination of MTX and infliximab (3 mg/kg or 6 mg/kg) over 52 weeks. HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX-only group. The mean decrease from baseline HAQ score from week 30 to week 54 was greater for the combination groups (0.80 for 3 mg/kg group and 0.88 for the 6 mg/kg group) than for the MTX-only group (0.68; $P = 0.03$ and $P < 0.001$, respectively). In addition, more patients in the combination groups (76.0 percent and 75.5 percent, respectively) improved their HAQ scores by at least 0.22 units than in the MTX-only group (65.2 percent; $P = 0.003$ and $P = 0.004$, respectively). The mean increases in SF-36 physical component summary scores were 11.7 and 13.2 for the combination groups and 10.1 for the MTX-only group ($P = 0.10$ and $P = 0.003$, respectively). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone.[69]

One prospective cohort study from the RADIUS program in the United States (described above in the *Etanercept plus MTX vs. etanercept section)* involved patients who were initiating any new DMARD.[53] The mean percentage improvements in the HAQ at 12 months were not statistically significantly different between patients treated with the infliximab-MTX combination and those treated with MTX monotherapy (3 percent vs. 7 percent; P = NS).

Etanercept plus MTX vs. MTX. Another prospective cohort study from the RADIUS program showed that patients treated with the etanercept-MTX combination had greater mean percentage improvements in HAQ scores at 12 months than those treated with MTX alone (17 percent vs. 7 percent; $P < 0.01$).[53]

Abatacept plus synthetic DMARD vs. synthetic DMARD. One RCT,[129] ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders), that did not meet our inclusion criteria for KQ 2 deserves mention here because it provides some support that combination therapy with a biologic DMARD plus a synthetic DMARD may lead to greater improvement in quality of life and functional capacity than synthetic DMARD monotherapy. It was excluded for study design because all patients were on some background synthetic DMARD and were randomized to a biologic DMARD or placebo, rather than being randomized to abatacept plus a synthetic DMARD or placebo plus a synthetic DMARD. The study enrolled adults with RA for more than 1 year who had inadequate response to 3 months of anti-TNF therapy. Patients treated with abatacept had greater improvements in quality of life (mean change on SF-36 physical

component: 6.5 vs. 1.0; $P < 0.0001$; SF-36 mental component: 5.4 vs. 1.7, $P = 0.0025$) and functional capacity (mean change on HAQ-DI: -0.5 vs. -0.1; $P < 0.0001$) than patients treated with placebo.

Psoriatic Arthritis: Overview

A total of six RCTS examined functional capacity or quality of life in patients being treated for psoriatic arthritis. Details are found in Evidence Table 7 in Appendix E. Table 15 provides information on comparisons made, quality-of-life outcomes, and quality ratings. The main drug classes compared include corticosteroids, synthetic DMARDs, biologic DMARDs, and combined strategies.

Table 15. Interventions, functional capacity, health-related quality of life and quality ratings of studies in adults with psoriatic arthritis

Study	Study Design N Duration	Study Population	Comparison (dose)	QOL outcomes (HAQ, SF-36)	Quality Rating
Synthetic DMARD vs. Placebo					
Kaltwasser et al., 2004[112,113]	RCT 190 24 weeks	Active PsA; failed at least one DMARD	LEF (100 mg/day 3 days then 20 mg/day) vs. placebo	Change in HAQ LEF significantly greater than placebo (-0.19 vs. -0.05; $P = 0.0267$)	Fair
Biologic DMARDs vs. Placebo					
Antoni et al., 2005[115,116] IMPACT study	RCT 104 50 weeks (16 blinded, 34 open-label)	Active PsA; failed at least one DMARD	INF (5 mg/kg at weeks 0, 2, 6, 14 then every 8 weeks) vs. placebo 71% received a concomitant DMARD	HAQ INF significantly better than placebo (49.8 vs. -1.6 ; $P < 0.001$)	Fair
Antoni et al., 2005[117,118,130] IMPACT2 study	RCT 200 14 to 24 weeks	Active PsA; failed at least one DMARD	INF (5 mg/kg at weeks 0, 2, 6, 14, 22) vs. placebo 46% received concomitant MTX	INF significantly better than placebo in HAQ improvement, At week 14: -18.4% vs. 48.6% ($P < 0.001$) SF-36 change from baseline, at week 24: -19.4 vs. 46 ($P < 0.001$) SF-36 PCS; change from baseline: to week 14: vs. 9.1 ($P < 0.001$) to week 24: 1.3 vs. 7.7 ($P < 0.001$) SF36 MCS; change from baseline to week 14: -1.2 vs. 3.8 ($P = 0.001$) to week 24: 0.4 vs. 3.9 ($P = 0.047$) No significant difference in percentage of missed workdays in past 4 weeks at 14 weeks: 13% vs. 3.7% ($P = 0.138$)	Fair

Table 15. Interventions, functional capacity, health-related quality of life and quality ratings of studies in adults with psoriatic arthritis (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	QOL outcomes (HAQ, SF-36)	Quality Rating
Mease et al., 2005[39]	RCT 313 24 weeks	Active PsA; failed at least one DMARD	ADA (40 mg every other week) vs. placebo 51% received concomitant MTX	SF-36 PCS; change from baseline: to week 12 and week 24 ADA 9.3 vs. placebo 1.4 ($P < 0.001$) SF-36 MCS; change from baseline; to week 12: 1.2 vs. 1.6 (P = NS) to week 24: 0.6 vs. 1.8 (P = NS) HAQ-DI change from baseline; to week 12 and week 24 ADA -0.4 ± 0.5 vs. placebo -0.1 ± 0.4 ($P < 0.001$)	Fair
Mease et al., 2000[40]	RCT 60 12 weeks	Active PsA; failed at least one DMARD	ETA (25 mg twice a week) vs. placebo 51% received concomitant MTX	Improvement in HAQ from baseline ETA 83% vs. placebo 3% ($P <$ 0.0001)	Fair
Mease et al., 2004[41,47]	RCT 205 72 weeks (24 blinded, 48 open-label)	Active PsA; failed at least one DMARD	ETA (25 mg twice a week) vs. placebo 41% received concomitant MTX	Improvement in HAQ from baseline ETA 54% vs. placebo 6% ($P <$ 0.0001)	Fair

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HAQ, Health Assessment Questionnaire; INF, infliximab; LEF, leflunomide; MTX-methotrexate; PsA, psoriatic arthritis.

Psoriatic Arthritis: Key Points

Conclusions are limited because no head-to-head comparisons have been done for any of the drugs used to treat PsA. The available studies are all placebo-controlled studies. Leflunomide patients had better quality-of-life outcomes than those in the placebo arm. The strength of evidence about leflunomide is low. The use of biologics—adalimumab, etanercept, and infliximab—led to better outcomes than did placebo. The strength of evidence about these three biologic DMARDs is moderate.

Psoriatic Arthritis: Detailed Analysis

Leflunomide. One 24-week trial (two publications) evaluated the efficacy of leflunomide against placebo in PsA patients.[112,113] The study included 190 patients; PsA was defined as having at least three swollen joints and three tender or painful joints and psoriasis over at least 3 percent of the body surface area. Almost 50 percent of the patients were DMARD naive. Those who were not were required to discontinue all synthetic DMARDs, biologic agents, and

investigational drugs 28 days before baseline measures were done. At 24 weeks, quality of life was significantly improved in the leflunomide group as measured by the change in HAQ scores (-0.19 vs. -0.05; $P = 0.0267$).

Adalimumab. One adalimumab trial (40 mg every other week) included 313 patients suffering from moderate to severe PsA, which was defined as having at least three swollen joints and three tender or painful joints, who had had an inadequate response or intolerance to nonsteroidal anti-inflammatory drug (NSAID) therapy.[114] Patients were allowed to continue current MTX therapy as long as the dose had been stable for 4 weeks. The double-blinded phase of the study was 24 weeks, but patients who failed to achieve at least a 20 percent decrease in both swollen and tender joint counts on two consecutive visits could receive rescue therapy with corticosteroids or DMARDs. Quality of life was significantly improved as measured by the greater change in HAQ scores in patients who took adalimumab than in those who received placebo (-0.4 vs. -0.1; $P < 0.001$).

Etanercept. Two studies that examined the efficacy of etanercept included 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[119,120] In both studies patients were allowed to continue MTX therapy as long as it had been stable for 4 weeks prior to enrollment. One of these trials lasted 12 weeks (N = 60);[119] the other was double-blinded for 24 weeks (N = 205).[120] Both studies had the same dosing regimen of 25 mg of etanercept twice weekly by subcutaneous injections. Quality of life improved significantly as measured by the HAQ in both studies. Mean improvements were 83 percent in etanercept-treated patients and three percent in placebo-treated patients in the 12-week study ($P < 0.0001$). In the longer study, at 24 weeks the mean improvements were 54 percent in the etanercept group and 6 percent in the placebo group ($P < 0.0001$).

Infliximab. Two studies on the use of infliximab IMPACT involved 304 patients with active PsA who were not adequately responding to conventional DMARD therapies.[115,117] Both studies permitted patients to continue MTX therapy as long as it had been stable for 4 weeks before enrollment. One trial was double-blinded for 16 weeks (N = 104);[115] the other was double-blinded for 24 weeks (N = 200), with crossover allowed at week 16 for nonresponders on the primary outcomes measured at the 14-week evaluation (i.e., before crossover).[117] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, and 14; the longer study had an additional injection at week 22. Quality of life improved significantly as measured on the HAQ in both studies. Mean percentages of patients improving on the HAQ were 49.8 percent in infliximab and -1.6 percent in placebo-treated patients in the smaller study ($P < 0.001$). In the bigger study, at 14 weeks the mean percentages of patients improving were 48.6 percent in the infliximab group and -18.4 percent in the placebo group ($P < 0.001$). Additionally, the larger study found that, in the 4 weeks before week 14, 13 percent of the placebo group and 3.7 percent of the infliximab group missed work ($P = 0.138$).[130]

Key Question 3: Harms, Tolerability, Adverse Effects or Adherence

This key question examined overall harms for both diseases. Specifically, for patients with rheumatoid or psoriatic arthritis, do drug therapies differ in harms, tolerability, or adverse effects? We first address evidence on rheumatoid arthritis and then psoriatic arthritis. For each disease, we describe overall tolerability, then specific adverse events for each drug class,

followed by studies reporting on adherence for each disease. Evidence Tables 8 and 9 in Appendix E describe details about these studies, some of which were described for efficacy in KQ 1, above (i.e., Tables 10 and 11).

Rheumatoid Arthritis: Overview

A total of 28 randomized controlled trials (RCTs), one nonrandomized controlled trial, 48 observational studies, and four systematic reviews reported on tolerability, harms and adherence (see Evidence Tables 8 and 9 in Appendix E). Table 16 provides information on Food and Drug Administration (FDA) black box warnings and warnings in bold letters as well as toxicities requiring monitoring according to the American College of Rheumatology (ACR). A black box warning is a type of warning that the FDA requires on the labels of prescription drugs that may cause serious adverse effects, and it signifies that clinical studies have indicated that the drug carries a significant risk of serious or even life-threatening side effects. Its name comes from the black border that typically surrounds the text of the warning. A bold letter (or "bolded") warning is text prominently displayed on the main panel of the drug label that warns users about possible side effects and other cautions. Adding a bold-text warning is a lesser step than a black box warning, even if it does relate to the possibility of serious adverse effects.

Table 16. Drug toxicities and Food and Drug Administration warnings

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Corticosteroids	Hypertension, hyperglycemia, osteoporosis	No black box warnings[131-135]	Dosage requirements are variable and must be individualized on basis of disease under treatment and response of the patient[131-135]
Synthetic DMARDs			
Leflunomide	Diarrhea, alopecia, rash, headache, theoretical risk of immunosuppression infection	Pregnancy must be excluded before start of treatment; pregnancy must be avoided during treatment or prior to completion of treatment[136]	Hepatotoxicity; rare cases of severe liver injury, including cases with fatal outcome, have been reported[136]
Hydroxychloroquine	Macular damage	Physicians should be completely familiar with complete contents of package insert before prescribing[137]	No bold letter warnings[137]
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	Bone marrow, liver, lung, and kidney toxicities; hepatotoxicity, fibrosis and cirrhosis; chronic interstitial pneumonitis; diarrhea and ulcerative stomatitis; malignant lymphomas; severe to fatal skin reactions; fatal opportunistic infections; fetal death and/or congenital anomalies[138]	No bold letter warnings[138]
Sulfasalazine	Myelosuppression	No black box warning[139]	No bold letter warnings[139]

Table 16. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Biologics DMARDs			
Abatacept	No ACR recommendations about monitoring	No black box warning[142]	No bold letter warnings[142]
Adalimumab	No ACR recommendations about monitoring	Risk of infections (TB, invasive fungal infections, other opportunistic infections); some infections have been fatal; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment[143]	Should not be initiated in patients with active infections (chronic or localized); patients who develop new infections during treatment should be monitored closely; physicians should exercise caution when considering treating patients with history of recurrent infection or underlying conditions which may predispose them to infections; serious infections observed in clinical studies with concurrent use of anakinra; concurrent use of anakinra is not recommended[143]
Anakinra	No ACR recommendations about monitoring	No black box warning[144]	Increased incidence of serious infections; discontinue if patient develops serious infection; should not be initiated in patients with active infections; safety and efficacy in immunosuppressed patients or patients with chronic infections have not been evaluated; concurrent therapy with etanercept is not recommended[144]
Etanercept	None recognized by ACR guidelines	No black box warning[145]	Serious infections and sepsis, including fatalities; TB; should not be taken by patients with active infections; malignancies; neurologic events; should be discontinued if patient develops serious infection or sepsis; exercise caution when considering prescribing to patients with history of recurring infections or with underlying conditions which may predispose patient to infection, such as advanced or poorly controlled diabetes; concurrent therapy with anakinra is not recommended[145]

Table 16. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities[†]	Warnings Black Box	Warnings Bold Letter
Infliximab	None recognized by ACR guidelines[‡]	Increased risk for infections, including progression to serious infections leading to hospitalization or death; these infections include bacterial sepsis, TB, invasive fungal and other opportunistic infections; increased risk for TB; patients should be closely monitored for signs and symptoms of infection during and after treatment; patients should be evaluated for TB risk factors and tested for latent TB prior to treatment; fatal hepatosplenic T-cell lymphoma reported in adolescent and young adult patients with Crohn's disease[146]	Some serious infections resulted in patients on concomitant immunosuppressive therapy; some patients were hospitalized or had fatal outcome from infections while treated with infliximab alone; should not be given to patients with clinically important, active infection; new infections should be closely monitored; treatment should be discontinued if patient develops serious infection; TB, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other bacterial, mycobacterial and fungal infections observed; monitor patients for signs and symptoms of TB[146]
Rituximab	No ACR recommendations about monitoring	Fatal infusion reactions; these fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock; TLS—acute renal failure requiring dialysis; severe mucocutaneous reactions; PML—JC virus infection resulting in PML and death has been reported[147]	No bold label warnings[147]

[†]Toxicities requiring monitoring according to ACR guidelines, 2002.[140]
[‡]ACR issued a warning for hepatosplenic T-cell lymphoma with infliximab use.[141]
ACR: American College of Rheumatology; PML: progressive multifocal leukoencephalopathy; TB: tuberculosis; TLS: tumor lysis syndrome.

As with earlier KQs, the main drug classes examined are corticosteroids, synthetic DMARDs, and biologic DMARDs.

Most studies that examined the comparative efficacy of our drugs of interest also determined their harms. Methods of adverse events assessment, however, differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often, determining whether assessment methods were unbiased and adequate was difficult. Rarely were adverse events pre-specified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events.

Because few studies used the term *serious adverse events* as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,[148] we describe serious adverse events as the individual studies identified and reported them.

Rheumatoid Arthritis: Key Points

Tolerability and adverse events. *Corticosteroids.* Comparative tolerability and overall adverse events between corticosteroids were similar but data were limited to one 3-month trial.[29] The strength of evidence is low.

Corticosteroid use significantly predicted the risk of serious infections, as compared with methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide, and etanercept, in one long-term retrospective study (hazard ratio [HR] 1.56; 95% CI, 1.20-2.04).[149] The strength of evidence is low.

Synthetic DMARDs and combinations. Three efficacy trials and one meta-analysis indicated similar tolerability and discontinuation rates of leflunomide, MTX, and sulfasalazine in data up to 2 years.[32,34,35,37] The strength of evidence is moderate.

The proportion of patients who stayed on MTX was higher than the proportion remaining on sulfasalazine at 5 years in one meta-analysis of 71 RCTs and 88 observational studies (36 percent vs. 22 percent, P = NR).[150] The strength of evidence is moderate.

Five studies involving combinations of two or three DMARDs, including sulfasalazine, MTX, hydroxychloroquine, and etanercept (a biologic DMARD), vs. one or two DMARDs have similar withdrawal rates attributable to adverse events.[30,31,33,46,151] Although discontinuation rates were similar for these pharmaceuticals, the number of patients with adverse events (nausea, erythema, elevated transaminases) were higher in two studies of sulfasalazine plus MTX than in monotherapy with either drug.[31,33] The level of evidence is moderate.

Three studies of combinations including prednisone with one or more DMARDs indicated similar discontinuation rates between groups.[42,44,47] The level of evidence is moderate.

Hepatic events appeared to be similar among patients treated with MTX, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept in two retrospective studies over 2 years to 3 years.[152,153] Longer term evidence is lacking. The level of evidence is low.

In one 5-year retrospective cohort, interstitial lung disease appeared to be significantly higher with leflunomide use than with use of other DMARDs (RR, 1.9; 95% CI, 1.1-3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[154] The level of evidence is low.

In three cohort studies, infection risk was elevated in patients receiving prednisone and possibly MTX and leflunomide compared with the risk in patients receiving other DMARDs.[149,152,155] The level of evidence is low.

Estimates of cancer risk were limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine in a 30-year retrospective cohort.[156] Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR 1.28; P = 0.014).[157]

Biologic DMARDs. In efficacy studies, biologic DMARDs were generally well tolerated. Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (abatacept, infliximab, rituximab) were the two most commonly and consistently reported adverse events. Some infusion reactions appeared to be more serious than injection site reactions. Overall, 0.5 percent of patients treated with infliximab had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions.[158] Fatal infusion reactions have also occurred with rituximab.[147] The strength of evidence is moderate.

One nonrandomized, open-label 12-month trial directly compared the tolerability of two biologic DMARDs.[159] It did not report any differences in harms between etanercept and

infliximab. Evidence from placebo-controlled trials and observational studies is insufficient to draw conclusions about the comparative tolerability and safety of biologic DMARDs. The strength of the evidence is low.

In efficacy trials, injection site reactions were the most common reason for discontinuation because of adverse events.[49] Incidence rates appeared to be significantly higher with anakinra than with anti-TNF drugs.[49] In a large retrospective cohort study, anakinra led to statistically significantly higher discontinuation rates (41 percent) than etanercept (31 percent; $P = 0.004$) and infliximab (35 percent; $P = 0.03$).[67] A prospective cohort study indicated that etanercept had statistically significantly lower discontinuation rates than infliximab during 60 months of follow-up (data NR; $P < 0.001$).[52] The strength of the evidence is moderate.

Two trials indicated that a combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy.[59,160] The evidence, however, is limited to combinations of anakinra with etanercept and abatacept with anakinra, adalimumab, etanercept, or infliximab. The strength of the evidence is moderate.

Five long-term extension studies of adalimumab,[83] anakinra,[85] etanercept,[161] and infliximab[101,162] indicated that the rate of adverse events does not increase over time. The strength of the evidence is moderate. No evidence is available on the long-term tolerability of abatacept and rituximab.

The risk for long-term, rare but serious adverse events such as serious infections, malignancies, congestive heart failure, or autoimmunity is a cause of concern for all biologic DMARDs. We could not, however, reliably assess the *comparative* risk among biologic DMARDs for most serious adverse events because of insufficient evidence. One prospective cohort study suggested that risks do not differ for adalimumab, etanercept, and infliximab;[163] it showed that, compared with synthetic DMARDs as a class, anti-TNF drugs as a class did not lead to a higher overall risk for serious infections (incidence rate ratio [IRR], 1.03; 95% CI, 0.68-1.57). The strength of the evidence is low.

Two studies indicated that the general risk of biologic DMARDs for serious infections is dose dependent. The evidence, however, is limited to adalimumab[164] and infliximab.[107] The strength of the evidence is moderate.

Three observational studies indicated that infliximab might have a higher risk of granulomatous infections than etanercept.[165-167] The strength of the evidence is low.

Hepatotoxicity has been reported for infliximab but not for other biologic DMARDs. The strength of the evidence is low.[146]

Adherence. Few efficacy studies reported rates of adherence. Efficacy trials do not indicate any differences in adherence among drug therapies used to treat RA. However, the quality of reporting and assessment of adherence was limited.

Findings from highly controlled efficacy studies may have limited generalizability to "real world" practice, especially because of the overall short duration of these trials. The evidence is insufficient to draw any conclusions about adherence from effectiveness studies.

A review of a large, managed care database suggested that infliximab might have greater adherence than etanercept or MTX.[168] In contrast, however, an observational study that suggested that etanercept had a better response rate than infliximab attributable to greater adherence.[52] However, as noted below, measurements of adherence are different between these two studies. Strength of evidence is low for efficacy and effectiveness studies.

Detailed Analysis

Tables 17, 18, and 19 provide information on harms for the three main categories of drugs covered in this review. We cover overall tolerability, then specific adverse events. When sufficient data are available, we break out specific events by type (e.g., hepatic or infection).

Corticosteroids: overall tolerability. Corticosteroids are associated with several well-known side effects (noted already in Table 16). The prescription information for long-term use of corticosteroids highlights precautions including osteoporosis with secondary fractures, infection, glucose intolerance, peptic ulcer disease, gastrointestinal bleeding, cataracts and glaucoma.[131-135] Table 17 describes relevant studies for harms from corticosteroids.

Table 17. Comparative harms in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Corticosteroids Overall Tolerability					
Kirwan et al., 2004[29]	RCT 143 12 weeks	Active RA	BUD PNL	Similar in all groups	Fair
Corticosteroids Adverse Events					
Doran, et al., 2002[149]	Retrospective cohort 609 39 years	RA patients	Several synthetic DMARDs, corticosteroids	In patients hospitalized for infection, corticosteroid use increased risk (HR, 1.56; 95% CI, 1.20-2.04)	Fair
Saag et al., 1994[169]	Retrospective cohort 224 ≥ 1 year	RA patients on low-dose PRED (15 mg/day or less)	PRED No PRED	PRED 10 mg to 15 mg/day most related to development of AE (OR, 32.3; 95% CI, 4.6-220) PRED 5 mg to 10 mg/day (OR, 4.5; 95% CI, 2.1-9.6) No increase in AE for PRED < 5 mg/day Fracture: OR, 3.9 (95% CI, 0.8-18.1; *P* < 0.09) First infection: OR, 8.0 (95% CI, 1.0-64.0; *P* < 0.05) First GI event: OR, 3.3 (95% CI, 0.9-12.1; *P* < 0.07)	Fair

AE, adverse event; BUD, budesonide; CI, confidence interval; DMARD, disease-modifying antirheumatic drugs; GI, gastrointestinal; mg, milligram; HR, hazard ratio; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Comparatively, the tolerability for corticosteroids appears to be similar between groups, although the information is limited by short study duration and the fact that only one study is available. One head-to-head RCT, described more in detail for KQ 1, compared budesonide (3 mg/day), high-dose budesonide (9 mg/day), prednisolone (7.5 mg/day), and placebo over 12 weeks.[29] Overall rates of adverse events were similar among groups (89 percent, 3 mg/day budesonide; 94 percent, 9 mg/day budesonide; 85 percent, prednisone; 90 percent, placebo;

P = NR). Few adverse events caused patients to discontinue the drug; gastrointestinal symptoms, heart symptoms, and mood swings or insomnia were similar in all patient groups (*P* = NR).

Corticosteroids: specific adverse events. We found no comparative study of corticosteroids directly assessing specific serious adverse events. One study of a retrospective 39-year cohort of 609 RA patients in Rochester, Minnesota, examined the predictors of serious infections requiring hospitalization.[149] Corticosteroids (intravenous [IV] or intramuscular [IM]), various synthetic DMARDS including MTX, sulfasalazine, hydroxychloroquine, and leflunomide, and etanercept (a biologic DMARD) were among the predictors examined. Of those patients requiring hospitalization for infection, only the use of corticosteroids was associated with an increased risk (HR 1.56; 95% CI, 1.20-2.04). Cumulative dose or duration of corticosteroids did not provide additional information beyond a history of corticosteroid use.

One retrospective cohort study of 224 RA patients directly assessed the toxicity of low-dose, long-term corticosteroid therapy (mean 4.9 years).[169] In three outpatient rheumatology clinics, 112 patients on low-dose prednisone (< 15 mg/day) for more than 1 year were matched with 112 patients not using prednisone. Records were abstracted from the date of prednisone initiation to the date of a predetermined adverse event (fracture, avascular necrosis of bone, new onset diabetes or diabetes out of control, infection requiring hospital or surgical intervention, herpes zoster, myocardial infarction, cerebrovascular event, gastrointestinal (GI) bleeding or peptic ulcer disease, cataracts, glaucoma, and death). Low-dose and high-dose long-term prednisone use (>5 mg/day) was correlated with dose-dependent specific adverse events (adverse event at 10 to 15 mg/day: OR, 32.3; 95% CI, 4.6-220; *P* = 0.0004; adverse event at 5 to 10 mg/day: OR, 4.5; 95% CI, 2.1-9.6; *P* = 0.0001; and adverse event at 0 to 4 mg/day: OR, 1.9; 95% CI, 0.8-4.7; *P* = 0.15). Patients on long-term prednisone (any dose) were at higher risk for fracture (OR, 3.9; 95% CI, 0.8-18.1; *P* < 0.09), infection (OR, 8.0; 95% CI, 1.0-64; *P* < 0.09) and GI event (OR, 2.2; 95% CI, 0.9-12.1; *P* < 0.07).

Synthetic DMARDs: overall tolerability. MTX, sulfasalazine, hydroxychloroquine and leflunomide all can produce several well-known, and similar, reactions (Table 16). Frequently reported adverse reactions for these drugs found in package inserts include the following:

- MTX: ulcerative stomatitis, nausea and abdominal distress, fatigue, chills and fever, dizziness, leukopenia, and decreased resistance to infection;[138]
- Sulfasalazine: stomatitis, nausea, dyspepsia, rash, headache, abdominal pain or vomiting, fever, dizziness, pruritus, and abnormal liver function tests.[139]
- Hydroxychloroquine: dizziness, headache, abdominal pain/nausea/vomiting/diarrhea, pruritus, weight loss, hair bleaching, and alopecia;[137] and
- Leflunomide: diarrhea, rash, elevated liver enzymes, and alopecia.[136]

Table 18 describes studies providing information on tolerability and various adverse events. Three trials[32,35,37] and one meta-analysis with up to 2 years of data,[34] all described in more detail for KQ 1, indicated similar levels of general tolerability among leflunomide, MTX, and sulfasalazine, including similar discontinuation rates and frequency of serious adverse events. However, another meta-analysis of withdrawal rates from 71 RCTs and 88 observational studies, which included data up to 5 years, found that patients with RA stayed on MTX significantly longer than on either sulfasalazine or hydroxychloroquine.[150] At 5 years, 36 percent of patients had remained on MTX to continue their treatment; 22 percent had remained on sulfasalazine. Patients on sulphasalazine were more likely to have withdrawn from medication than those on

MTX (RR, 1.68; $P < 0.0001$). Withdrawal rates did not differ between observational studies and RCTs.

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Synthetic DMARDs Overall Tolerability					
Cannon, et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	AE rates in LEF, LEF + MTX were lower than or similar to AE rates for MTX and other DMARDS	Fair
Emery et al., 2000[32]	RCT 999 1 year with optional 2nd year	RA 4 months to 10 years	LEF, MTX	Frequency of SAEs similar between groups	Fair
Maetzel, et al., 2000[150]	Meta-analysis (RCT and observational) 159 studies MTX = 2,875 SSZ = 1,418 5 years	RA pt studies including withdrawal information	MTX SSZ HCQ (and gold)	Withdrawals due to toxicity for 5 years: MTX 35%, SSZ 52% Pts treated with SSZ were 1.68 times more likely to fail therapy due to toxicity than MTX (RR, 1.68; $P < 0.0001$)	Fair
Osiri et al., 2003[34]	Systematic review and meta-analysis 1,732 2 years	Active RA	LEF, MTX LEF, SSZ	Discontinuation rates from AEs were similar for LEF, MTX and SSZ	Good
Smolen et al., 1999[35]	RCT 358 24 weeks	Active RA	LEF, SSZ	Withdrawal due to AEs 14% vs. 19%	Fair
Strand, et al., 1999[37,38]	RCT 482 12 months (1 year continuation)	RA for at least 6 months, MTX-naive	LEF, MTX	AEs constant over time LEF and MTX 12 months: Higher discontinuation rate for LEF (22% vs. 10.4%, P = NR)	Fair
Synthetic DMARD Combinations Overall Tolerability					
Boer et al., 1997[39] COBRA study	RCT 155 56 weeks	Early RA, DMARD naive	PNL taper + MTZ + SSZ vs. SSZ	Lower withdrawal rate due to AEs (2.6% vs. 7.6%, P = NR)	Fair
Capell et al., 2007[30]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Active RA	SSZ + MTX vs. SSZ or MTX	Similar withdrawal rate due to AEs	Fair

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Dougados et al., 1999[31]	RCT 209 (146) 52 weeks (5 year followup)	DMARD naive, early RA	SSZ +MTX vs. SSZ or MTX	Discontinuation rate due to AEs similar among groups AEs higher in SSZ+MTX vs. SSZ vs. MTX (91% vs. 75% vs. 75%, *P* = 0.025)	Fair
Goekoop-Ruiterman et al., 2005[42] BeSt study	RCT 508 12 months	Early RA	Sequential monotherapy (starting with MTX) vs. step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. combination (MTZ, SSZ, tapered high-dose PRED) vs. combination with INF (3 mg/kg – could be titrated to 10 mg/kg based on DAS)	No significant differences in serious AEs in all groups	Good
Haagsma et al., 1997[33]	RCT 105 52 weeks	DMARD naive, early RA	SSZ + MTX vs. SSZ or MTX	No significant difference in number of withdrawals due to AEs	Fair
Korpela et al., 1999[44] FIN-RACo study	RCT 199 24 months	Early RA	MTX + HCQ + SSZ + PNL vs. DMARD ± PNL	Frequency of serious AEs similar in both groups Discontinuation due to AEs similar in both groups	Fair
O'Dell et al., 2006[151]	Prospective cohort 119 48 weeks	Active RA, previous use of DMARDs	ETA +SSZ vs. ETA + HCQ	Similar discontinuation rates due to AEs	Fair
O'Dell et al., 2002[45]	RCT 171 2 years	RA pts not previously treated with combination drugs	MTX + SSZ + HCQ vs. MTX + HCQ vs. MTX + SSZ	Similar withdrawal rate due to AEs across groups	Good
O'Dell et al., 1996[46]	RCT 102 2 years	RA and poor response to at least 1 DMARD	MTX + SSZ+ HCQ vs. MTX vs. SSZ + HCQ	Similar withdrawal rate due to AEs across groups	Good
Svensson et al., 2005[47]	Open-label RCT 250 2 years	Early RA	DMARD + PNL vs. DMARD	Similar number of discontinuations between groups	Fair

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Svensson et al., 2003[170]	Open-label RCT 245 2 years	Early RA	MTX + PRED SSZ + PRED	Lower withdrawal rate due to AEs or inefficacy for PRED + MTX group vs. PRED + SSZ group (11.5% vs. 33.3%, *P* = 0.0005)	Fair
Synthetic DMARDs Adverse Events					
Hepatic Event					
Cannon et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Hepatic event: LEF 4.1/1,000PY, MTX 6.2/1,000PY, Other 4.2/1,000PY, LEF + MTX 4.6/1,000PY	Fair
Suissa et al., 2004[153]	2 retrospective cohorts (claims data) 41,885 3 years	RA diagnosis	LEF, biologics, traditional DMARDs, MTX	Serious hepatic events compared with MTX: LEF rate ratio: 0.9 (95% CI, 0.2-4.9), traditional DMARD: 2.3 (95% CI, 0.8-1.4), biologic DMARD: 5.5 (95% CI, 1.2-24.6)	Fair
Interstitial Lung Disease					
Suissa et al., 2006[154]	Retrospective cohort (claims data) 62,734 5 years	RA diagnosis, on DMARD	MTX, LEF, biologics, traditional DMARDs	Risk of interstitial lung disease in LEF compared to other DMARDs: OR, 1.9 (95% CI, 1.1-3.6). No elevation noted in LEF pts with no history of MTX or no history of interstitial lung disease	Fair
Infection					
Cannon et al., 2004[152]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Respiratory infection: LEF 20/1,000PY, MTX 38.9/1,000PY, Other 36.9/1,000PY	Fair
Doran et al., 2002[149]	Retrospective cohort 609 39 years	RA pts	Several synthetic DMARDs, corticosteroids	Use of corticosteroids increased risk of hospitalization for infection (HR 1.56; 95% CI, 1.20-2.04)	Fair
Wolfe et al., 2006[155]	Prospective cohort 16,788 3.5 years	RA diagnosis	PRED, LEF, SSZ, MTX, ETA, INF, ADA	Risk for hospitalization for pneumonia: PRED HR 1.7 (95% CI, 1.5-2.0), LEF HR 1.2 (95% CI, 1.0-1.5). No significant differences for SSZ, MTX	Fair

Table 18. Comparative harms in patients with rheumatoid arthritis treated with synthetic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Malignancies					
Baecklund et al., 2006[156]	Retrospective cohort 756 30 years	RA pts with diagnosis of lymphoma	MTX, SSZ	No significant risk for lymphoma for MTX or SSZ	Good
Chakravarty et al., 2005[157]	Retrospective cohort 15,789 (RA) 4 years	RA pts	PRED, LEF, MTX	PRED was associated with increased risk for non melanoma skin cancer PRED: HR 1.28 (95% CI, 1.05-1.55, *P* = 0.014)	Fair

3x, three times; ADA, adalimumab; AEs, adverse events; AERS, adverse events reporting system; AKA, anakinra; CHF, congestive heart failure; CI, confidence interval; DAS; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GI, gastrointestinal; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; LFT, liver function test; mg/kg, milligram/kilogram; MTX, methotrexate; N/A, not applicable; NR, not reported; OR, odds ratio; PNL, prednisolone; PRED, prednisone; Pts, patients PY, person years; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; SAEs, serious adverse events; SSZ, sulfasalazine; TB, tuberculosis; TNF, tumor necrosis factor; txt, treatment; vs., versus.

For combination therapies, five studies of DMARD combinations (one up to 5 years[31]) included MTX, sulfasalazine, hydroxychloroquine, and etanercept (described in detail under KQ 1). They had similar withdrawal rates attributed to adverse events.[30,31,33,45,46,151] Although discontinuation rates were similar, rates of adverse events were higher in two studies for sulfasalazine plus MTX vs. monotherapy (adverse events for combination therapy range from 53 percent to 91 percent; adverse events for monotherapy range from 50 percent to 75 percent).[31,33] Side effects included nausea, erythema, and elevated transaminases. Three RCTs of combination therapy including prednisone with one or more DMARDs (described in detail in KQ 1) showed similar discontinuation rates between groups.[42,44,47] One open-label RCT of 155 patients comparing a prednisolone taper plus MTX plus sulfasalazine actually had a lower withdrawal rate because of adverse events than sulfasalazine only (2.6 percent vs. 7.6 percent, *P* = NR).[39] Another open-label RCT of 245 patients found the withdrawal rate for adverse events to be lower in the prednisone plus MTX group than in the prednisone plus sulfasalazine group (11.5 percent vs. 33.3 percent, *P* = 0.0005).[170]

Synthetic DMARDS: specific adverse events. Synthetic DMARDs can produce several serious adverse events (Table 16). The package inserts for MTX give several warnings.[138] It has been reported to cause congenital abnormalities. Severe and sometimes fatal bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of MTX and NSAIDS. MTX-induced lung disease can occur in doses as low as 7.5 mg per week. Malignant lymphoma may also occur in patients on low-dose MTX. Severe, occasionally fatal skin reactions have also been reported.

Less common but severe adverse and potentially fatal events for sulfasalazine include blood dyscrasias, hypersensitivity reactions including Stevens-Johnson syndrome, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis.[139] The package insert for hydroxychloroquine describes irreversible retinal damage in some patients on long-term therapy or high dosage. Other serious reactions include blood dyscrasias, seizures, hypersensitivity reactions, and hepatotoxicity.[137] Potentially severe adverse

reactions for leflunomide include blood dyscrasias, hepatotoxicity, and hypersensitivity reactions including Stevens-Johnson syndrome.[136]

Hepatic events. Two retrospective cohorts examined hepatic events in patients with rheumatoid arthritis.[152,153] Both studies found similar hepatic event rates for leflunomide and MTX.

A 2-year retrospective cohort from a U.S. insurance claims database (N = 40,594) examined the incidence rates of serious hepatic events in patients treated with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[152] The hepatic event rate for leflunomide was similar to that for other DMARDs (leflunomide, 4.1/1,000 person-years [95% CI, 2.4-7.0], MTX, 6.2/1,000 person-years [95% CI, 5.1-9.3]; other DMARDs, 4.2/1,000 person-years [95% CI, 3.3, 5.3], *P* = NS, NR).

Another group examined data from claims databases for two retrospective cohorts of 41,885 patients over 3 years for serious hepatic events associated with treatment with leflunomide, MTX, traditional DMARDs (hydroxychloroquine, sulfasalazine, gold, minocycline, penicillamine, chlorambucil, cylcophosphamide and cyclosporine), or biologic DMARDs (infliximab, etanercept).[153] Using MTX as the reference, they observed no higher rates in serious hepatic events for leflunomide (rate ratio 0.9; 95% CI, 0.2-4.9) or for traditional DMARDs (rate ratio 2.3; 95% CI, 0.8-6.5), but they did report higher rates for biologic DMARDs (rate ratio 5.5; 95% CI, 1.2-24.6).

Infection. Prednisone and possibly MTX and leflunomide increase the risk of infection compared with risks from other DMARDs. Two prospective cohort studies and one 39-year retrospective cohort study examined the risk of hospitalization for pneumonia infection.[149,152,155] One study examined 16,788 patients from U.S. rheumatology practices and followed up semi-annually with questionnaires for 3.5 years.[155] Both prednisone and leflunomide use increased the risk of hospitalization for pneumonia compared with RA patients not on these drugs (HR 1.7; 95% CI, 1.5-2.1; HR 1.3; 95% CI, 1.0-1.5); MTX, hydroxychloroquine, sulfasalazine, infliximab, etanercept, or adalimumab did not increase risks.

The 2-year retrospective database study examined RA patients to determine the incidence rates of adverse events during treatment with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[152] Respiratory infection rates per person-year were highest in the MTX group (38.9/1,000 person-years), next highest in the other DMARD group (36.9/1,000 person-years), and lowest in the leflunomide group (20/1,000 person-years) ($P < 0.0001$).

The 39-year population-based study of the Rochester, Minnesota, cohort examined potential risk factors for hospitalization for infection in RA patients (N = 609).[149] Outcomes were assessed by reviewing inpatient and outpatient community medical records. The use of corticosteroids increased hospitalization for infection (HR 1.56; 95% CI, 1.20-2.04). Compared with corticosteroids, other DMARDs including MTX, hydroxychloroquine, sulfasalazine, leflunomide, or etanercept had no increased risk of infection-related hospitalizations.

Interstitial Lung Disease. One 5-year retrospective cohort examined claims data from 62,734 patients with RA given a DMARD 1 year prior to the date of diagnosis of interstitial lung disease.[154] Patients were divided into four categories: leflunomide, methotrexate, biologic agents (infliximab, etanercept, adalimumab, anakinra), and traditional DMARDs (antimalarials, sulfasalazine, gold salts, minocycline, penicillamine, azathioprine, cyclosporine, other cytotoxic agents). In patients diagnosed with interstitial lung disease, those prescribed leflunomide were at increased risk compared to patients prescribed other DMARDs (RR, 1.9; 95% CI, 1.1-3.6) but

not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[154]

Malignancies. One retrospective study examined 756 patients with RA to determine the risk of lymphoma over a 30-year period.[156] This was a matched case-control of consecutive Swedish RA patients in whom lymphoma was diagnosed. Controls were RA patients matched for sex, year of birth, year of RA diagnosis, and county of residence. The investigators found no association between lymphoma and use of DMARDs, including MTX (OR, 0.7; 95% CI, 0.3-1.6) or sulfasalazine (OR, 0.6; 95% CI, 0.3-1.1).

Another retrospective cohort study examined the risk of nonmelanoma skin cancer in 15,789 U.S. patients with RA who were participating in a registry and returned semi-annual questionnaires over a 4-year period in which they reported any current malignancies.[157] Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR 1.28; $P = 0.014$). They found no association between this neoplasm and leflunomide plus MTX.

Biologic DMARDs: overall tolerability. Table 19 describes studies providing information on tolerability and various adverse events. Table 16 presented the basic information about toxicities and FDA or other warnings. The prescription information for abatacept highlights precautions for hypersensitivity reactions,[142] and the prescription information of rituximab has a black box warning for fatal infusion reactions.[147]

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
		Biologic DMARDs Overall Tolerability			
Bathon et al., 2000[54-56] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive	ETA, MTX	Significantly more patients on MTX than on ETA had nausea (29% vs. 15%; $P < 0.05$) or mouth ulcers (14% vs. 5%; $P < 0.05$)	Fair
Breedveld et al., 2006 [57] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive	ADA, MTX, ADA + MTX	No statistically significant differences in adverse events	Fair
Combe et al., 2006[60]	RCT 260 24 weeks	Active RA despite SSZ treatment	ETA, SSZ, ETA+SSZ	Significantly more infections in ETA and ETA+SSZ than in SSZ group (47% vs. 31% vs. 13%; $P < 0.05$)	Fair
Edwards et al., 2004[61]	RCT 161 24 weeks	Active RA despite MTX treatment	RIT,MTX, RIT+MTX, RIT+CYP	No significant differences in adverse events	Fair
Feltelius et al., 2005[161]	Case series 1,073 2 years	Pts with RA initiating ETA therapy	ETA	Incidence of serious adverse events remained constant over time	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Fleischmann et al., 2003[171]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	AKA	Higher rates of injection site reactions with AKA than placebo. Otherwise no statistically significant differences in adverse events	Fair
Fleischmann et al., 2006[172]	Open-label extension of RCT 1,346 Up to 3 years	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant over time	Fair
Flendrie et al., 2003[173]	Retrospective cohort study 230 NR	Pts with RA initiating therapy with biologic DMARDs	ADA, ETA, INF	No significant differences in discontinuation rates among anti-TNF drugs	Fair
Furst et al., 2003[80] STAR study	RCT 636 6 months	Pts with active RA despite MTX treatment	ADA	No statistically significant differences in adverse events	Fair
Gartlehner et al., 2006[49]	Meta-analysis 5,248 NA	Patients who have failed MTX treatment; mean disease duration: varied	ADA, AKA, ETA,INF	Higher rates of injection site reactions for AKA than ADA and ETA (56% vs. 19% vs. 25%)	Good
Geborek et al., 2002[50]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs	ETA, LEF, INF	No statistically significant differences in adverse events	Fair
Genovese et al., 2002[55]	Open-label extension of RCT 632 2 years	Pts with early, aggressive RA; MTX-naive	ETA	Incidence of serious adverse events remained constant over time	Fair
Genovese et al., 2004[59]	RCT 242 24 weeks	Inadequate control of disease with MTX	ETA, ETA+AKA	Significantly higher rates of serious adverse events in combination group	Fair
Genovese et al., 2005[56]	Uncontrolled extension of RCT 369 5 years	Pts with early, aggressive RA; MTX-naive	ETA	Rates of serious adverse events did not increase with long-term exposure	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Klareskog et al., 2004 [63-65] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs	ETA, MTX, ETA+MTX	No statistically significant differences in adverse events	Good
Langer et al., 2003[174]	Post marketing surveillance 454 6 months	Pts with RA, initiating AKA treatment	AKA	Rate of adverse events was generally similar to those reported in efficacy trials; lower rates of injection site reactions than in clinical trials	Fair
Maini et al., 2004[101]	Open-label extension of RCT 259 2 years	Pts with active RA despite MTX treatment	INF	Incidence of serious adverse events remained constant over time	Fair
Moreland et al., 2006[162]	Open-label extension of clinical trials 714	Pts treated with ETA	ETA	Incidence of serious adverse events remained constant over time	Fair
Nuki et al., 2002[85]	Uncontrolled extension of RCT 309 19 months	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant over time	Fair
O'Dell et al., 2006[151]	Nonrandomized, open-label trial 119	Pts with active RA despite treatment with SSZ, HCQ, or gold	ETA + SSZ ETA + HCQ ETA + gold	No differences in adverse event rates among 3 treatment groups	Fair
Schaible et al., 2000[158]	Retrospective data analysis of clinical trials 913 12 weeks to 3 years	Pts with RA or Crohn's disease	INF	17% of pts on INF in clinical trials had acute infusion reactions	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Schiff et al., 2006[175]	Retrospective data analysis of clinical trials; post marketing surveillance 10,050 12,506 pt years	Pts treated with ADA	ADA	Incidence of serious adverse events remained constant over time	Fair
St. Clair et al., 2004 [68,69] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive	MTX, INF, INF+ MTX	Significantly more patients in the INF than in the MTX group had more than one serious infection (5.3 vs. 2.1%; $P < 0.05$)	Fair
Van Riel et al., 2006[66]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX	ETA, ETA+MTX	No statistically significant differences in adverse events	Fair
Wasserman et al., 2004 [176]	Prospective cohort study 113 15 months	Pts with RA starting INF treatment in a clinical care setting	INF	53% of pts on INF experienced at least one infusion reaction	Fair
Weinblatt et al., 2006 [160] ASSURE study	RCT 1,456 1 year	Pts with active RA despite background biologic or synthetic DMARD treatment	ABA	Higher incidence of serious adverse events in pts on ABA and a biologic background DMARD	Fair
Weinblatt et al., 2006[83]	Uncontrolled extension of RCT 162 3.4 years	Pts with active RA despite MTX treatment	ADA	Incidence of serious adverse events remained constant over time	Fair
Westhovens et al., 2006 [107] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF + MTX, MTX	Risk of serious infections was similar between placebo and 3 mg/kg infliximab. 10 mg/kg infliximab led to increased risk of serious infections	Good
Zink et al., 2005[67]	Retrospective cohort study 1,523 1 year	Pts with RA who had a change in treatment regimen	AKA, ETA, INF, LEF	Significantly higher overall discontinuation rates for AKA than ETA and INF after 12 months; no differences in discontinuation rates due to adverse events	Good

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Biologic DMARDs Adverse Events					
Infectious Diseases					
Askling et al., 2005[177]	Retrospective cohort study 62,321 467,770 person-years	Pts with RA in daily clinical care in Sweden	ETA, INF	4-fold increase of risk for TB for ETA and INF compared with conventional DMARDs	Good
Bergstrom et al., 2004[178]	Retrospective cohort study 985 3 years	Pts with inflammatory arthritis in daily clinical care, U.S.	ETA, INF	Pts treated with INF or ETA are more likely to develop symptomatic coccidioidmoycosis than pts on synthetic DMARDs	Fair
Bongartz et al., 2006[164]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of serious infections for ADA and INF compared with placebo (OR, 2.0; 95% CI, 1.3-3.1)	Fair
Dixon et al., 2006[163]	Prospective cohort study 8,973 11,220 pt-years	Pts with active RA despite MTX treatment	ADA, ETA, INF	No differences among anti-TNF drugs for risk of serious infections. Similar risk for serious infections between anti-TNF drugs and synthetic DMARDs	Fair
Gomez-Reino et al., 2003[179]	Retrospective cohort study 1,540 1.1 years	Pts with RA in daily clinical care in Spain	ETA, INF	Higher risk of TB for ETA and INF than synthetic DMARDs	Fair
Keane et al., 2001[180]	Database analysis 70 cases of TB NA, AERS data	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
Lee et al., 2002[166]	Database analysis 10 cases of histo-plasmosis NA, AERS data	Pts treated with ETA and INF	ETA, INF	Histoplasmosis infections may be a serious complication of treatment with anti-TNF agents; pts on INF had a higher rate of infections than pts on ETA	Fair
Listing et al., 2005[181]	Prospective cohort study 1,529 Up to 12 months	Pts with RA in daily clinical care in Germany	AKA, ETA, INF	Higher risk of infections for AKA, ETA, INF compared with DMARDs	Fair
Mohan et al., 2004[182]	Database analysis 25 cases of TB NA, AERS data	Pts treated with ETA	ETA	Median interval between first dose and diagnosis of TB was 11.5 months	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Salliot et al., 2006[183]	Case series 709 NR	Pts with different rheumatic diseases; primary care-based cohort	ADA, ETA, INF	Rates of serious infections in daily practice were higher than ones reported in efficacy trials	Fair
Slifman et al., 2003[167]	Database analysis 15 cases of listeria infection NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of infections than pts on ETA	Fair
Wallis et al., 2004[165]	Database analysis 649 cases of granulomatous infections NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of granulomatous infections than pts on ETA	Fair
Wolfe et al., 2004[184]	Prospective cohort study with historic control 17,242 3 years	Pts with RA in daily clinical care in U.S.	INF, synthetic DMARDs	TB was more common in pts treated with INF than with synthetic DMARDs	Fair
Wolfe et al., 2006[155]	Prospective cohort study 16,788 3.5 years	Pts with RA	ADA, ETA, INF	No increased risk for hospitalization for pneumonia for ADA, ETA, and INF compared to a historic control	Fair
Lymphoma and Other Malignancies					
Askling et al., 2005[185]	Retrospective cohort study 60,930 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, synthetic DMARDs	No increase in solid cancers for pts treated with anti-TNF drugs	Fair
Askling et al., 2005[186]	Retrospective cohort study 53,067 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, synthetic DMARDs	No increase in lymphoma for pts treated with anti-TNF drugs	Fair
Bongartz et al., 2006[164]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of malignancies for ADA and INF compared with placebo (OR, 3.3; 95% CI, 1.2-9.1)	Fair
Brown et al., 2002[187]	Database analysis AERS 26 cases of lymphoma NA, AERS data	RA or CD pts treated with ETA and INF	INF, ETA	Median interval between initiation of therapy and lymphoma 8 weeks; some spontaneous remissions after discontinuation of therapy reported	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Chakravarty et al., 2005[157]	Retrospective cohort study 15,789 NR	RA or osteoarthritis pts treated with ETA or INF	ETA, INF	Statistically significant association between anti-TNF (HR 1.97; 95% CI, NR; *P* = 0.001) and corticosteroid (HR 1.28; 95% CI, NR; P = 0.014) use and nonmelanoma skin cancer	Fair
Geborek et al., 2005[159]	Retrospective cohort study 1,557 5,551 pt-years	Pts with RA in daily clinical care in Sweden	ETA, INF	Higher risk of lymphoma for anti-TNF drugs than synthetic DMARDs	Fair
Lebwohl et al., 2005[188]	Post marketing database review 1,442 3.7 years	Pts with RA treated with ETA	ETA	No increase in the incidence of cutaneous squamous cell carcinoma for ETA-treated pts	Fair
Setoguchi et al., 2006[189]	Retrospective cohort study 8,458 33,240 pt-years	Pts with RA in daily clinical care in U.S. and Canada	ADA, ETA, INF	No increased risk of hematologic and overall malignancies for pts treated with anti-TNF drugs compared with those on synthetic DMARDs	Good
Wolfe et al., 2004[190]	Prospective cohort study with external control 18,572 Up to 3 years	Pts with RA in daily clinical care in U.S.	INF, ETA	Pts with RA treated with INF or ETA are more likely to develop lymphoma than the general population	Fair
Congestive Heart Failure					
Chung et al., 2003[191]	RCT 150 28 weeks	Pts with CHF	INF	INF (10 mg)-treated pts were more likely to die than placebo-treated pts	Fair
Jacobsson et al., 2005[192]	Retrospective cohort study 983 NR	Pts with RA in daily clinical care in Sweden	ETA, INF	Pts on anti-TNF treatment had a lower rate of cardiovascular events than pts on traditional RA therapy	Fair
Kwon et al., 2003[193]	Database analysis AERS 47 cases of CHF NA, AERS data	Pts on ETA or INF therapy	ETA, INF	Most pts with CHF did not have preexisting conditions	Fair

Table 19. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Wolfe et al., 2004[194]	Retrospective cohort study 13,171 2 years	Pts with RA in daily clinical care in U.S.	ADA, ETA, INF	Pts on anti-TNF treatment had a lower rate of CHF than pts on traditional RA therapy	Fair
Demyelination					
Mohan et al., 2001[195]	Database analysis AERS 19 cases of demye-lination NA, AERS data	Pts on anti-TNF therapy	ETA, INF	Discontinuation of therapy led to partial or complete resolution of all cases	Fair
Other Adverse Events					
De Bandt et al., 2005[196]	Case series 22 cases with lupus syndrome	Pts with RA in daily clinical care in France	ETA, INF	Similar incidence of lupus syndrome between ETA and INF	Fair
Flendrie et al., 2005[197]	Prospective cohort study with historic control 578 911 pt-years	Pts with RA starting anti-TNF therapy	ADA, ETA, INF	Higher rates of dermatological conditions in pts on anti-TNF drugs compared to DMARDs	Fair
Shin et al., 2006[198]	Database analysis AERS 15 cases of Guillain-Barre and Miller Fisher syndromes NA, AERS data	Pts on anti-TNF therapy	ADA, ETA, INF	Demyelination is a potential adverse event of anti-TNF therapy	Fair

ABA, abatacept; ADA, adalimumab; AERS, adverse events reporting system; AKA, anakinra; CD, cardiovascular disease; CHF, congestive heart failure; CI, confidence interval; CYP, cyclophosphmide; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; mg/kg, milligram/kilogram; MTX, methotrexate; N/A, not applicable; NR, not reported; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; RCT, randomized controlled trial; RIT, rituximab; SSZ, sulfasalazine; TB, tuberculosis; TNF, tumor necrosis factor; US, United States.

In efficacy trials of biologic DMARDs, overall tolerability profiles appeared to be similar among biologic and synthetic DMARDs, or combinations of biologic and synthetic DMARDs. An exception was the combination of two biologic DMARDs. A 24-week RCT, described in more detail for KQ 1, assessed a combination treatment of etanercept (25 mg or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy.[59] The frequency of serious adverse events was substantially higher in the combination groups than the etanercept-only group (14.8 percent for 50 mg etanercept plus anakinra; 4.9 percent for 25 mg etanercept plus anakinra; 2.5 percent for etanercept only; P = NR). Furthermore, a study determining the efficacy of abatacept combined with different background treatments found substantially higher rates of serious adverse events in patients on abatacept combined with a biologic background treatment (22.3 percent) than in those not on a combination of two biologic DMARDs (12.5 percent).[160]

One nonrandomized open-label trial determined the comparative harms among combinations of biologic DMARDs and synthetic DMARDs other than MTX.[151] No differences in adverse events could be detected between a combination of etanercept and either sulfasalazine or hydroxychloroquine.

The ERA (Early Rheumatoid Arthritis) study, described in more detail in KQ 1, had an open-label extension of up to 2 years,[55] and an uncontrolled extension with etanercept (25 mg twice weekly) of up to 5 years.[56] The rates of adverse events for etanercept did not rise during long-term treatment compared with rates reported from the short-term RCT. These results are consistent with findings from long-term extension studies of efficacy RCTs on adalimumab,[83] anakinra,[85,172] and infliximab.[101,162] Likewise, safety analyses of post marketing surveillance data showed that the incidence of adverse events did not rise over time in patients treated with adalimumab[175] and etanercept.[161]

In placebo-controlled efficacy trials of biologic DMARDs, injection site reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were commonly reported adverse events.[49] Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (abatacept, infliximab, rituximab) were the more commonly and consistently reported adverse events. Most infusion reactions were nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever.

In clinical trials of infliximab for the treatment of RA or Crohn's disease, 17 percent of patients experienced infusion reactions; 0.5 percent were severe and resembled acute anaphylactic conditions or led to convulsions.[158] In these trials, however, less than 2 percent of patients discontinued because of infusion reactions.[158] A prospective cohort study of infliximab in a Canadian clinical care setting reported substantially higher rates of events than did the clinical trials.[176] Specifically, in the community study (113 patients with 1,183 infusions), 53 percent of patients experienced at least one infusion reaction during the course of the therapy (mean 15 months).

Injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity, and they were the most common reason for discontinuation blamed on adverse events. A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1-27.9) for adalimumab, 22.4 percent (95% CI, 8.5-36.3) for etanercept, and 67.2 percent (95% CI, 38.7-95.7) for anakinra.[49] The substantially higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with rates reported in the respective package inserts.[143-145] A German retrospective study based on post marketing surveillance data, however, reported a lower incidence of injection site reaction for anakinra than clinical trials (20 percent).[174]

The evidence on comparative discontinuation rates is limited to observational studies.[52,67,173] A Swedish population-based, prospective cohort study reported statistically significantly higher rates of overall discontinuation (data NR; $P < 0.001$), discontinuation because of adverse events (data NR; $P < 0.001$), and discontinuation because of lack of efficacy (data NR; $P < 0.018$) for patients on infliximab than for those on etanercept over 60 months of followup.[52] These findings are consistent with those from a German retrospective, population-based cohort study, based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database. This study reported that overall discontinuation rates among biologics were significantly higher for anakinra-treated patients (41 percent) than for patients on etanercept (31 percent; $P = 0.004$ for anakinra vs. etanercept) or those on infliximab (35 percent; $P = 0.03$ for anakinra vs. infliximab).[67] Treatment discontinuations because of adverse events, after 12

months of treatment, were lowest for etanercept (13 percent for etanercept, 16 percent for anakinra, and 19 percent for infliximab; *P* = NR).

Four RCTs were designed to assess adverse events as primary outcomes.[80,107,160,171] Overall, adverse event rates were similar for abatacept,[160] adalimumab,[80] anakinra,[171] or infliximab[107] and placebo. All four studies, however, reported a trend toward higher rates of *severe* infections in patients treated with biologic DMARDs than in those receiving placebo. In general, these studies were too short and did not have enough power to detect such rare but severe adverse events.

Specific adverse events. Because the evidence on the comparative risk for rare but severe adverse events is lacking for biologic DMARDs, we summarize the evidence on the risk of individual drugs below.

Serious infections. Because of the immunosuppressive nature of biologic DMARDs, serious infections including tuberculosis, pneumonia, osteomyelitis, progressive multifocal leucoencephalopathy (PML), and sepsis are of special concern. The FDA has issued black box warnings about an increased risk of infections for adalimumab and infliximab. The package inserts of anakinra and etanercept also contain bold letter warnings. Recently, the FDA issued an alert for health care professionals highlighting the death of two patients from PML who had been treated with rituximab for systemic lupus erythematosus.[199] The available head-to-head evidence is insufficient to draw firm conclusions about the comparative risk of biologic DMARDs.

The best evidence stems from a prospective cohort study.[163] This study enrolled 8,973 patients with severe RA from the British Society for Rheumatology Biologics Register. Patients were treated with adalimumab (n = 1,190), etanercept (n = 3,596), infliximab (n = 2,878), or synthetic DMARDs (n = 1,354). The overall followup included 11,220 patient-years. Results indicated no differences in risks among anti-TNF drugs. Compared with synthetic DMARDs, anti-TNF drugs did not lead to a higher overall risk for serious infections (IRR, 1.03; 95% CI, 0.68-1.57). The frequency of serious skin infections, however, was fourfold higher in patients treated with anti-TNF drugs than with synthetic DMARDs (IRR, 4.28; 95% CI, 1.06-17.17). What proportion of patients treated with anti-TNF drugs were also on a background synthetic DMARD regimen remains unclear. Although the statistical analysis controlled for multiple confounding factors, residual confounding in such a study design is likely. Results, therefore, must be interpreted cautiously. Event rates of serious infections in efficacy trials comparing anti-TNF drugs with synthetic DMARDs were generally too low to draw meaningful conclusions.

The following paragraphs summarize the evidence on the general risk of biologic DMARDs for serious infections (i.e., the risk of biologic DMARDs compared with that of placebo treatment).

Most studies defined serious infections as those that required antibiotic treatment or led to hospitalization or death. In placebo-controlled safety RCTs, the incidence of serious infections was consistently higher in biologic-treated than in placebo-treated patients. Although clinically significant, these differences rarely reached statistical significance because of low power. For example, in one large safety RCT (N = 1,414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1 percent vs. 0.4 percent; *P* = 0.068).[171] The START (Trial for Rheumatoid Arthritis with Remicade) study, another safety RCT (N = 1,084) conducted to assess the risk of serious infections during infliximab treatment for RA, indicated a dose-dependent risk for patients on infliximab.[107] After 22 weeks of treatment, patients on 3 mg/kg infliximab had similar rates of serious infections as patients on placebo (1.7 percent vs. 1.7 percent; RR: 1.0; 95% CI, 0.3-3.1). Patients treated with 10 mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo

(5.0 percent vs. 1.7 percent; RR: 3.1; 95% CI, 1.2-7.9). A fair meta-analysis of efficacy studies confirmed this finding and reported a similar dose-dependent risk for a combined population of adalimumab- and infliximab-treated patients.[164]

The higher risk of biologic DMARDs for serious infections was confirmed by a fair meta-analysis that pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[164] The pooled odds ratio for serious infections was 2.0 (95% CI, 1.3-3.1) relative to placebo. The number needed to harm (NNH) was 59 (95% CI, 39-125) within a treatment period of 3 months to 12 months.

Most long-term observational studies support these findings.[158,181,183,185] A large, French case series of 709 patients with various rheumatic diseases treated with adalimumab, etanercept, or infliximab in daily clinical practice reported a substantially higher rate of serious infections (10.5 per 100 patient-years) than rates reported in phase 3 efficacy trials (3 to 4 per 100 patient-years).[183]

The most common serious infections were cases of tuberculosis.[180] In addition, observational studies reported infections with coccidiomycosis,[178] histoplasmosis,[166] pneumocystis carinii,[200] and listeriosis[167] and candida.[180]

Six retrospective cohort studies determined the risk of tuberculosis or granulomatous infections during treatment with infliximab or etanercept.[165,177,179,180,182,184] All studies report a significant increase of risk attributable to anti-TNF therapy relative to placebo.

No evidence exists on the general risks of abatacept, adalimumab, anakinra, and rituximab. The best available evidence stems from three studies based on Spanish, Swedish, and U.S. databases that collected data on patients treated with biologic DMARDs.[177,179,184] These data were collected systematically from participating physicians, regardless of the occurrence of adverse events. By contrast, the adverse events reporting system (AERS) database of the FDA includes post marketing adverse events spontaneously reported from U.S. sources, serious and unlabeled spontaneous reports from non-U.S. sources, and serious, unlabeled post marketing clinical trial reports from all sources. Therefore, the AERS lacks an adequate denominator to draw inferences about causation and the comparative risks of any drugs. In addition, underreporting is likely.[201]

The U.S. study, using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of tuberculosis in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs.[184] The analysis yielded rates of 6.2 cases per 100,000 patient-years in the control group and 52.5 cases per 100,000 patient-years in patients on infliximab. The other two studies were based on the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia)[179] and several Swedish databases.[177] Both studies analyzed data on infliximab and etanercept and indicated a substantially higher risk for tuberculosis in patients treated with etanercept or infliximab than in those on synthetic RA therapy. The Swedish study reported a fourfold increased risk of tuberculosis (RR, 4.0; 95% CI, 1.3-12) for patients on anti-TNF treatment compared with the risk for RA patients not exposed to etanercept or infliximab.[177] Three studies based on the AERS database provided similar results.[165,180,182]

One analysis of AERS data focused on granulomatous infections in general. It indicated a higher rate among patients treated with infliximab (239 cases per 100,000 patients) than with etanercept (74 cases per 100,000 patients).[165] The rate of tuberculosis in this study was 144 cases per 100,000 patients for infliximab and 35 cases per 100,000 patients for etanercept. However,

incidence rates must be compared cautiously because this study reported cases per treated patients and not per patient years.[165]

Lymphoma and other malignancies. The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA compared with the general population.[202] Data from controlled trials do not provide sufficient evidence concerning a further increase in their risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and synthetic DMARDs. Findings from retrospective observational studies are mixed.

A large prospective cohort study followed 18,572 RA patients in a registry for up to 3 years.[190] The risk of lymphomas was higher for patients on anti-TNF therapies than for those on synthetic DMARDs, although not statistically significantly so. Confidence intervals for treatment groups overlapped and the results were insufficient to establish a causal relationship between RA treatments and lymphoma or to delineate differences in risks among treatments. The standardized incidence rate (SIR) in the overall cohort was 1.9 cases per 100,000. The SIR for patients not receiving MTX or any biologic agents was 1.0. The SIRs for patients on specific drugs were as follows: MTX, 1.7 (95% CI, 0.9-3.2); infliximab, 2.6 (95% CI, 1.4-4.5); and etanercept, 3.8 (95% CI, 1.9-7.5).

Three community-based, retrospective cohort studies from Sweden, Canada, and the United States, however, did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on synthetic DMARDs.[159,186,189] The largest study included 4,160 patients treated with anti-TNF drugs.[186] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6-2.1) for anti-TNF patients relative to patients on synthetic DMARDs.

Results regarding an increased risk for overall malignancies in patients treated with biologic DMARDs relative to placebo are also mixed. The best evidence comes from a fair meta-analysis that pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[164] The pooled odds ratio for malignancies was 3.3 (95% CI, 1.2-9.1). The NNH was 154 (95% CI, 91-500) within a treatment period of 3 months to 12 months. Two large retrospective cohort studies, however, do not support such findings.[185,189] The larger of these two studies, based on data on more than 60,000 Swedish patients, found SIRs for solid cancers to be similar for RA patients treated with anti-TNF medications and those on conventional therapy using both a contemporary and a historic control group.

A clinical trial database review did not detect a higher incidence of squamous cell carcinoma in 1,442 RA patients (4,257 patient-years) treated with etanercept (crude rate: 2.8 cases/1,000 patients) than for those on placebo;[188] the median follow-up time was only 3.7 years. A larger retrospective cohort study (N = 15,789), however, reported a statistically significant association of a combination of anti-TNF and MTX treatment and nonmelanoma skin cancer (hazard ratio [HR]: 1.28; 95% CI, NR; $P = 0.014$).[157]

Congestive heart failure. No direct evidence on the comparative risk of biologic DMARDs for congestive heart failure (CHF) exists. The evidence on the risk of CHF with anti-TNF therapy is mixed. Two observational studies reported lower rates of CHF[194] and cardiovascular events[192]for RA patients on anti-TNF therapy than for those on conventional RA therapies. A good-quality Swedish retrospective cohort study (N = 983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events in patients treated with anti-TNF medications than in those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25-0.85; $P = 0.013$). A large retrospective cohort study (N = 13,171) reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5;

P = NR) for patients treated with anti-TNF therapy compared with those not treated with anti-TNF medications over a 2-year period.[194] Confounding by indication, however, cannot entirely be ruled out with such study designs.

By contrast, an analysis of AERS data reported that half of the patients who developed new onset CHF under etanercept or infliximab treatment did not have any identifiable risk factors.[193] Indirect evidence comes from three trials, two on etanercept[203] and one on infliximab,[191] that evaluated the efficacy of these drugs for the treatment of CHF. Study populations did not have any rheumatoid illnesses. One of the two etanercept trials was terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[191] The package insert of infliximab issues a contraindication regarding use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity. Reports based on data from the FDA's AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[175,195] Similar cases have been seen in regulatory trials of adalimumab.[143] All neurologic events partially or completely resolved after discontinuation of treatment.

Similarly, reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases.[146,158,196,204] Lupus-like syndromes have also been reported for adalimumab.[175] Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other anti-TNF-α drugs.[143,145] The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters.[146] Severe liver injury, including acute liver failure, has been reported. Owing to a lack of studies with the methodological strength to assess these rare events, conclusions should be drawn on other grounds, such as comorbidities, taking case reports into consideration.

A prospective cohort study (N = 578) indicated that patients on anti-TNF treatments developed dermatological conditions (skin infections, eczema, drug-related eruptions) statistically significantly more often than anti-TNF-naive patients over a median treatment time of 2.3 years (25 percent vs. 13 percent; $P < 0.0005$).[197]

Adherence. The published literature in this area frequently uses the terms *compliance* and *adherence* interchangeably. *Compliance* has traditionally been used to describe a patient's ability to take medications as prescribed. Some authors argue, however, that *adherence* better represents the more complex relationship among patients, providers, and medications; it is meant to reflect the fact that following a medication regimen is not necessarily a simple choice.[205] Given the lack of a clear definition, we use the term *adherence*. Table 20 summarizes included studies for adherence.

Table 20. Studies assessing adherence in patients with rheumatoid arthritis

Author, Year	Study Type and Interventions	N	Results
Boers et al., 1997[39]	RCT MTX + SSZ + prednisolone vs. SSZ	155	Compliance satisfactory in 85%
Emery et al., 2000[32]	RCT LEF vs. MTX	999	Reason for withdrawal: noncompliance in the 1st year: LEF 11 (2%) vs. MTX 14 (3%) noncompliance in the 2nd year: LEF 6 (2%) vs. MTX 6 (2%)
Fleischmann et al., 2003[171]	RCT AKA vs. Placebo	1,414	AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8% <70% adherent with use of study drug: 0.8% vs. 1.7% >40% missed no injections >90% received at least 90% of intended doses
Goekoop-Ruiterman et al., 2005[42]	RCT Four treatment strategies	508	24 (5%) were nonadherent
Haagsma et al., 1997[33]	RCT SSZ + MTX vs. SSZ or MTX	105	Percentage of tablets taken > 90% (pill count)
Harley et al., 2003[168]	Retrospective database analysis INF vs. ETA vs. MTX	2,662	INF more adherent than ETA or MTX ($P < 0.05$)
Hyearich et al., 2006[62]	Prospective observational study	2,711	Adherence at 6 months: ETA 80% vs. INF 79% ETA subgroups (22% monotherapy, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy, vs. 22% DMARD co-therapy)
Kremer et al., 2002[126]	RCT LEF + MTX vs. placebo + MTX	263	Overall, 98% adherent Adherence rates 80%-120% LEF, 87.7% placebo 90.2%
Kristensen et al., 2006[52]	Prospective observational study INF vs. ETA	949	ETA had better drug survival than INF ($P = 0.001$)
Strand et al., 1999[37]	RCT LEF vs. MTX vs. placebo	402	Nonadherence as the reason for withdrawal: LEF (1) MTX (1)

AKA, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.

The majority of RCTs that reported adherence stated a rate between 85 percent and 100 percent. Six published studies reported levels of adherence in RCTs.[32,33,39,42,126,171] Most, however, contained only minimal information, and many did not stratify by treatment. Furthermore, they provided little or no information on the methods of assessment. For example, one study reported that adherence was satisfactory in 85 percent of patients, but the investigators did not describe their method of determining adherence.[39] Only three of the six RCTs reported adherence rates for different treatment arms.[32,126,171] None of these studies noted a significant difference in adherence. To what extent results from these highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

A retrospective database analysis used a large U.S. health plan, which included commercial and Medicare insurance, to examine adherence levels in 2,662 patients being treated with infliximab, etanercept, or MTX from November 1999 to December 31, 2001.[168] The primary outcome measured was the number of drug administrations or prescriptions filled, divided by the expected number during a 365-day period. Their primary finding was that patients on infliximab were significantly more adherent than patients on etanercept or MTX. After controlling for baseline covariates (age, sex, baseline cost, insurance type, health plan region, history of therapy of RA, comorbidities, type of physician), 81 percent of the patients receiving infliximab were adherent at least 80 percent vs. 68 percent of the etanercept and 64 percent of the MTX patients ($P < 0.05$ for infliximab vs. both other drugs) over 1 year.

A 5-year observational study from March 1999 to January 2004 with 949 patients in Sweden prospectively evaluated the long-term efficacy and tolerability of treatment with infliximab and etanercept in adults with RA using the LUNDEX.[52] The LUNDEX, a new index combining the proportion of responders with the proportion of patients adhering to treatment, was designed to compare the efficacy of the different therapies based on continued adherence and continuation of treatment. The study found that the etanercept group had a greater LUNDEX value, attributable primarily to better treatment adherence or survival time in the active treatment group, than did the infliximab group (P = NR).

Psoriatic Arthritis: Overview

A total of six RCTS compared tolerability, harms, and adherence. Details are found in Evidence Table 10 in Appendix E. Table 14 provides information on common adverse events of included drugs and black box warnings. Table 21 provides information on studies primarily examining comparative efficacy and safety. The drugs examined in patients with active disease included one synthetic DMARD (leflunomide) and the three biologic DMARDs (adalimumab, etanercept, or infliximab), all in comparison with placebo.

Table 21. Studies assessing adverse events and discontinuation rates during blinded portion of studies of psoriatic arthritis

Study	Study Design Duration	Study Population	Drug	Results	Quality Rating
		Synthetic DMARDs			
Kaltwasser et al., 2004[112]	RCT 190 24 weeks	Patients with active PsA	LEF	Differences in rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in ALT (for all, P = NR)	Fair
		Biologic DMARDs			
Mease et al., 2005[114]	RCT 313 24 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	ADA	No statistically significant differences in adverse events except for ISRs. ADA 6.6% vs. placebo 3.1% (P = NR)	Fair
Mease et al., 2000[119]	RCT 60 12 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETA	No statistically significant differences in adverse events except for ISRs. ETA 20% vs. placebo 3% (P = NS)	Fair

Table 21. Studies assessing adverse events and discontinuation rates during blinded portion of studies of psoriatic arthritis (continued)

Study	Study Design, Duration	Study Population	Drug	Results	Quality Rating
Mease et al., 2006[122]	RCT 205 72 weeks (24 blinded, 48 open-label)	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETA	No statistically significant differences in adverse events except for ISRs. ETA 20% vs. placebo 9% ($P \leq 0.001$)	Fair
Antoni et al., 2005[115] IMPACT study	RCT 104 16 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	INF	No statistically significant differences in adverse events	Fair
Antoni et al., 2005[117] IMPACT2 study	RCT 200 24 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	INF	No statistically significant differences in adverse events	Fair

ADA, adalimumab; ALT, alanine aminotransferase; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; ISR, injection site reaction; LEF, leflunomide; NR, not reported; NS, not significant; PsA, psoriatic arthritis; RCT, randomized controlled trial.

Psoriatic Arthritis: Key Points

Very limited information is available for harms, tolerability, adverse events, and adherence for patients with psoriatic arthritis. The available studies include only placebo-controlled studies; there are no head-to-head studies. The strength of evidence is low.

Synthetic DMARDs. The use of leflunomide vs. placebo can increase the likelihood of diarrhea and clinically significant increases in alanine aminotransferase. The rates of adherence are similar for leflunomide and placebo. The strength of evidence is low.

Biologic DMARDs. Five placebo-controlled studies of biologics, including one in adalimumab and two each in etanercept and infliximab, provide indirect evidence on harms. When the individual drugs are compared with placebo, the authors reported no differences in the rate of adverse events with the exception of increased rates of injection site reactions with the use of adalimumab and etanercept. No study reported adherence rates. The strength of evidence is low.

Psoriatic Arthritis: Detailed Analysis

Synthetic DMARDs. *Overall tolerability.* One 24-week trial in 190 patients examined adverse events in the treatment of PsA using leflunomide vs. placebo. The overall rates of adverse events were the same in each group: 85.4 percent of both trial arms experienced an adverse event.[112]

Specific adverse events. This same trial showed some differences in specific adverse events, in particular diarrhea (leflunomide, 24 percent; placebo, 13 percent; P = NR) and increases in alanine aminotransferase (leflunomide, 13 percent; placebo, 13 percent; P = NR).[112]

Biologic DMARDs. *Overall tolerability.* In efficacy trials for patients with PsA, overall tolerability profiles appeared to be similar for biologic DMARDs (adalimumab, etanercept, infliximab) and placebo.[112,114,115,117,119,122] Injection site reactions, dizziness, headaches, and

upper respiratory tract infections were the most commonly reported individual adverse events. Of these, injection site reactions appear to occur more often in the active group than in the control group.

Specific adverse events. Adalimumab and etanercept used to treat PsA show some differences in injection-site reactions. In a 24-week RCT examining adalimumab vs. placebo, the adalimumab group experienced more injection site reactions (6.6 percent) than the placebo group (3.1 percent; *P* = NR).[114] Two other studies comparing etanercept to placebo also showed higher rates of injection site reactions in the active arms.[119,122] A 12-week RCT reported injection site reaction rates of 20 percent in the etanercept group and 3 percent in the placebo group; these results were not significant, probably owing to the small sample size (N = 60).[119] In an RCT with 205 patients, however, the difference between these two groups was statistically different.[122] In the 24-week blinded portion of this study, injection site reactions occurred in 36 percent of the etanercept patients and 9 percent of the placebo patients (*P* < 0.001).

Adherence. Only one study reported adherence in the treatment of PsA (Table 22).[112] This 24-week study found that treatment adherence of ≥ 80 percent to < 110 percent was reported by 85 percent of leflunomide patients and 78 percent of placebo patients and (*P* = NR). Additionally, one patient was withdrawn by the investigator from the placebo group because of poor adherence.

Table 22. Adherence in patients with psoriatic arthritis

Author, Year	Study Type and Interventions	N	Results
Kaltwasser et al., 2004[112]	RCT LEF vs. placebo	190	Compliance of ≥ 80% to <110%: LEF, 85%; placebo, 78%. One patient was withdrawn from placebo arm because of poor adherence

LEF, leflunomide; RCT, randomized controlled trial.

Key Question 4: Benefits and Harms for Selected Populations

This key question concerned two main topics. Specifically, what are the comparative benefits and harms of drug therapies for rheumatoid arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities? Stage of disease and history of prior therapy were addressed under KQ 1. We did not find any interventions that grouped subjects by early RA vs. more advanced RA, or those that compared MTX-naive RA groups with those with RA who were MTX-experienced.

We found no studies of adults with PsA that compared efficacy, effectiveness, or harms of drug therapies between subgroups and the general population. No studies conducted subgroup analyses or used subgroups as the study population.

Rheumatoid Arthritis: Overview

We did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups and the general population for treating RA patients. Our findings are limited to results from subgroup analyses, a weaker form of evidence. Overall, we included

11 studies in addressing this key question: one RCT, four subgroup analyses of multiple RCTs, one database analysis, four observational studies, and one systematic review.

We focused on groups defined by demographics (age, sex, race or ethnicity), concomitant therapies, comorbidities (any comorbidity, cardiovascular disease, osteoporosis, and renal disease) and pregnancy. Strength of evidence is low for comparative efficacy and effectiveness for age, concomitant therapies, comorbidities, and pregnancy.

We present key points and detailed analyses below for the population groups noted above. Details about included studies are presented by subgroup analysis in Tables 23 to 28 (listed alphabetically by drug comparison).

Key Points

Demographics. We found no studies that conducted comparisons by sex, race, or ethnicity, but we did include one trial that addressed age;[206] two other studies, both rated poor quality, also addressed age, and we discuss them here because of the sparseness of this part of the evidence base.[207,208] One study directly compared the efficacy of DMARDs in elderly RA patients (65 years of age or older) with younger RA patients (under 64 years of age and older than 18); however, the analysis was focused on outcomes within age groups, not the specific effects of age.[209] Comparisons were available for only two DMARDs: one synthetic (MTX) and one biologic (etanercept).

Table 23 presents the studies of adults with RA that conducted comparisons by age groups. One systematic review by the Rheumatoid Arthritis Clinical Trial Archive Group found an inverse relationship between age and major clinical improvement.[206] Of the three trials reviewed, the differences between the odds ratios was small.[206] Two meta-analyses (pooled analyses of original data), both rated poor quality, provided mixed evidence on differences in efficacy in the elderly compared with a younger population treated with MTX and etanercept.[207,208] In one, the investigators determined that patients in the elderly age groups had a lower response to treatment than those in the younger age groups,[207] but both meta-analyses reported no difference in efficacy or function.[207,208] Given that two of the studies are of poor quality, the level of evidence is low.

Table 23. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by age

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Bathon et al., 2006[207]	Subgroup analysis within 4 RCTs 1,353 12 months to 6 years	Adults with early DMARD resistance or late-stage RA Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA 25 mg twice weekly + MTX vs. ETA 25 mg twice weekly	No significant difference found for improved efficacy or function between groups; elderly subjects had similar or less treatment response than younger subjects	Poor

Table 23. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by age (continued)

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Fleischmann et al., 2003[208]	Pooled data from RCTs 1,128 Varies	Adults with RA taking ETA continuously for 1 year Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA twice weekly Dosage not reported	No significant difference between elderly and younger groups at 1 year	Poor
Rheumatoid Arthritis Clinical Trial Archive Group 1995[206]	Systematic review 496 ≥ 12 weeks	Adults with RA Subgroups: Under 60 years of age; 60 to 64 years; 65 to 69 years; and 70 years or above	MTX Dosages not reported	Adjusted analysis demonstrated that as age increases, the odds ratio for major clinical improvement decreases; no effect found on toxicity	Fair
Schiff et al., 2006[209]	Pooled data from RCTs 1,049 ≤4 years	Adults with RA Subgroups: elderly (≥ 65 years of age) and younger adults (< 65 years of age)	ETA (25 mg twice weekly)	No significant difference found between groups in functional status; both groups exhibited similar improvements	Fair

ETA, etanercept; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Concomitant Therapies. We found no evidence from head-to-head comparisons, placebo-controlled trials, or observational studies on other treatment therapies and the various RA treatments addressed in this report. An analysis of data from a placebo-controlled trial involving RA patients receiving anakinra determined that the safety profiles did not differ in subjects receiving antihypertensive, antidiabetic, or statin medication treatments.[210] The level of evidence is low.

Comorbidities. Table 24 presents the studies found that addressed outcomes of RA patients with comorbidities. For RA patients with various high-risk conditions, one large placebo-controlled RCT of anakinra reported that there was no difference in serious adverse events or infections between the treated and placebo groups.[211] Lower rates of either myocardial infarction[192] or CHF[194] in RA patients on anti-TNF therapy compared with those on other RA therapies were reported by two observational studies. Another retrospective cohort study of RA patients on anti-TNF medications found that half of those who developed new onset CHF had no identifiable risk factors for CHF.[193] A systematic review of 11 MTX trials of RA patients determined that greater renal impairment was associated with greater toxicity.[206] The level of evidence is low.

Table 24. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis and other conditions

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Schiff et al., 2004[211]	RCT 951 6 months	RA patients with high-risk comorbid conditions	AKA 100 mg vs. placebo	In patients with comorbid conditions, no differences were found between treatment groups in regard to incidence of serious adverse events or overall infectious events	Fair
Jacobsson et al., 2005[192]	Case and comparison cohort study 983 7 years	RA patients treated with TNF blockers in a Swedish Arthritis Treatment Register compared to a non-exposed anti-TNF RA population from the same geographic area	TNF inhibitors	Treatment group had significantly lower incidence and RR for development of first time cardiovascular events (myocardial infarctions) than the community cohort not treated with anti-TNFs.	Fair
Kwon et al., 2003[193]	Database analysis AERS 47 cases of CHF NA	RA or other rheumatoid illness patients treated with ETA or INF	ETA, INF	Half of the patients who developed new onset CHF did not have any identifiable risk factors	Poor
Wolfe et al., 2004[194]	Retrospective cohort study 13,171 2 years	Patients with RA in daily clinical care in U.S.	ADA, ETA, INF	Absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5; *P* = NR) for patients treated with anti-TNF medications compared with those not treated with anti-TNF medications over a 2-year period	Fair
Rheumatoid Arthritis Clinical Trial Archive Group, 1995[206]	Systematic review of 11 RCTs 496 NA	Adults with RA treated with MTX and having age and renal function data available	MTX	Severe toxicity (severe upper abdominal pain, renal failure, proteinurea, cytopenias and liver toxicity) and respiratory toxicity (cough, pneumonitis, dyspnea, wheezing) worse with greater renal impairment	Fair

ADA, adalimumab; AERS, adverse events reporting system; AKA, anakinra; CHF, congestive heart failure; ETA, etanercept; INF, infliximab; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Pregnancy. The effects of DMARDs on pregnancy or neonatal outcomes are mixed. Table 25 presents the studies found that addressed neonatal or pregnancy outcomes for women with RA. Two observational studies[212,213] are presented. We included one poor-quality study due to the sparseness of evidence on pregnancy outcomes for women with RA. The level of evidence is low.

Table 25. Study characteristics, outcomes, and quality ratings of studies of pregnant women

Study	Study Design N Duration	Study Population	Comparison and Dose (mg/day)	Outcomes	Quality Rating
Chakravarty et al., 2003[213]	Case reports from mailed survey 65 NA	Women of childbearing age seen by responding rheumatologists	MTX, LEF, ETA, INF (no dose specified)	Rate of congenital abnormalities in women on MTX was 10%	Poor
Katz et al., 2004[212]	Retrospective analysis of drug safety database 146 NA	Pregnant women who either before or after conception were treated with INF or whose partners were treated with INF before conception	INF: 1 to 9 infusions vs. General population	No statistical differences in live births, miscarriages, or therapeutic terminations relative to rates in U.S. population of pregnant women	Fair

ETA, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; US, United States.

Detailed Analysis

Demographics. We identified three studies analyzing etanercept use in the elderly and two of MTX. The Rheumatoid Arthritis Clinical Trial Archive Group 1995 review of 11 MTX trials for adults with RA evaluated the effects of age or renal impairment on adverse events or treatment efficacy.[206] Although the authors reported that the odds for major clinical improvement dropped slightly as age increases, among all clinical trial patients, age did not affect MTX efficacy or the rate of side effects. Using the group under age 60 as the referent, the odds of major clinical improvement for those 60 to 64 years of age was 1.4 (95% CI, 0.7-2.6), 1.0 (95% CI, 0.5-2.2) for those 65 to 69 years of age, and 0.7 (95% CI, 0.3-1.7) for those 70 years of age or older (P = NR). As renal functioning declines, the odds for toxicity increased as much as four fold. Baseline renal function was found to be a significant predictor of toxicity, with the lower creatinine clearances ending up with greater toxicity ($P = 0.027$).[206]

In a post-hoc analysis of three controlled and open-label extension studies of RA patients treated with etanercept; outcomes for elderly and younger adult age groups were compared for all those treated with etanercept for at least 4 years.[209] Though the elderly group exhibited greater mean HAQ-DI improvements than those in the younger group (0.39 to 0.92 vs. 0.57 to 1.00), at baseline the elderly group was more disabled than the younger adults. Also, the proportion of elderly in each study was much smaller than the younger adult group, usually about 20 percent vs. 80 percent.[209] Both groups demonstrated similar rapid improvements in disability and pain during the first few months of the controlled phase of the trials, then stabilized, and improvements were maintained through the open-label portions of the trials.[209]

Another post-hoc analysis (poor quality) of original data from four RCTs evaluated treatment comparisons of etanercept, both in combination with MTX and as a monotherapy in adults with early DMARD resistance or late-stage RA.[207] Within each of the four trials, subset analysis was conducted comparing elderly subjects to younger adults (under 65 years of age). Each trial and extension exhibited similar or lower ACR responses for the elderly in comparison to the younger adult group in regard to functioning and progression (P = NR).

Another pooled analysis (poor quality) of nine RCTs found similar or less etanercept treatment response in elderly subjects than younger adults, although the difference was not significant for function and improved efficacy.[208]

Concomitant Therapies. One placebo-controlled trial of 1,399 adults with active RA disease examined safety profiles of those treated with 100 mg/day anakinra. No differences were found in the adverse event profiles of the subjects taking or not taking concomitant antihypertensive, antidiabetic, or statin pharmacotherapies. Even when the analysis was done comparing those treated with anakinra with those on placebo, no differences emerged (P = NR).[210]

Comorbidities. *Any comorbidity***.** We did not identify any study specifically designed to assess the comparative efficacy and risk of biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, or rituximab) in RA patients with common comorbidities. A post-hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with various comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, central nervous system-related events).[211] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

*Cardiovascular morbidity***.** No direct evidence exists on the comparative risk of biologic DMARDs in patients with both RA and cardiovascular disease. The evidence on the risk of cardiovascular disease with anti-TNF therapy is mixed. A Swedish retrospective cohort study (N = 983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events for patients treated with anti-TNF medications than for those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25-0.85; P = 0.013).[192] A large retrospective cohort study (N = 13,171) based on the National Databank for Rheumatic Diseases reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5; P = NR) for patients treated with anti-TNF therapy relative to the risk for those not treated with anti-TNF medications over a 2-year period.[194]

A MedWatch analysis of data from the AERS found that half of the patients who developed new onset CHF while being treated with etanercept or infliximab for RA or other rheumatoid illnesses did not have any identifiable risk factors.[193] These findings support the possible association between new onset cardiovascular harms for RA patients treated with etanercept or infliximab. However, package inserts for infliximab, etanercept, and adalimumab warn about a contraindication for patients already diagnosed with CHF. For infliximab that package insert warns about a contraindication regarding its use in patients with CHF;[147] the package inserts of etanercept and adalimumab express precautions in use of these agents in patients with CHF.[143,145]

Renal function. A systematic review of 11 RCTs of MTX use in 496 adults with RA concluded that toxicity worsened with greater renal impairment. Patients with high renal impairment had a fourfold risk (OR, 4.5; 95% CI, 0.9-22.6) for severe toxicity (severe upper abdominal pain, renal failure, proteinurea, cytopenias, and liver toxicity) than those with no renal impairment. Slightly more (4 percent vs. 1 percent) had respiratory toxicity (cough, pneumonitis, dyspnea, wheezing). No effect was found between renal impairment and increased liver toxicity.[206]

Pregnancy. Two observational studies addressed pregnancy in women with RA.[212,213] A retrospective analysis of data from a U.S. and European drug safety database found no statistical differences in live births, miscarriages, or therapeutic terminations in the subpopulation studied. The focus was on pregnant RA patients who had been treated with between one to nine infliximab infusions either before or after conception and male patients treated with up to nine

infusions before their partners' conception. The authors also reported no increase in adverse events from infliximab exposure during pregnancy relative to the rate in the U.S. population of pregnant women.[212]

One poor-quality study, using case reports from survey responses from 175 rheumatologists, found 10.3 percent (4/39) of women exposed to MTX during their pregnancies resulted in congenital malformations.[213] This is a much higher rate than the 2 percent to 3 percent average reported in a California cohort of 1.6 million infants.[213] In all, 23 physicians (rheumatologists) reported on 65 pregnancies with their patients treated with DMARDs (MTX, 38 patients; leflunomide, 10; etanercept, 14; infliximab, 2; and MTX plus etanercept, 1). A majority of the survey respondents agreed that pregnancy was contraindicated for women being treated with DMARDs, especially with patients being treated with MTX (95 percent agreement) and leflunomide (92.7 percent agreement). For patients treated with etanercept, the percentage agreement dropped to 38.6 percent, and for infliximab to 46.5 percent. Two observational studies addressed pregnancy in women with RA.[212,213]

A retrospective cohort study using data from a U.S. and European drug safety database found no statistical differences in live births, miscarriages, or therapeutic terminations in the subpopulation studied. The focus was on pregnant RA patients who had been treated with between one to nine infliximab infusions either before or after conception and male patients treated with up to nine infusions before their partners' conception. The authors also reported no increase in adverse events from infliximab exposure during pregnancy vs. those in the U.S. population of pregnant women.[212]

Discussion

This report provides a comprehensive review of the comparative efficacy, effectiveness, and harms of members of three main classes of drugs used to treat adult patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA). These include corticosteroids, synthetic disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. The objective of our report was to evaluate the comparative efficacy, effectiveness, and harms of monotherapies, combination therapies, and different treatment strategies.

Table 26 and Table 27 (for RA and PsA, respectively) summarize our findings and the strength of evidence for the four key questions (KQs) addressed by this report. In brief, the KQs involved benefits of these drugs, alone or in combination, in terms of reducing patient-reported symptoms, slowing or limiting the progression of radiographic joint damage, and maintaining remission (KQ 1); improving functional capacity and quality of life (KQ 2); harms and risks of these drugs (KQ 3); and the benefits or harms in various patient subpopulations defined by sociodemographic characteristics or health states (KQ 4). Most of the evidence meeting inclusion criteria focuses on comparative efficacy. We highlight comparative effectiveness studies when available.

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Key Question 1: Comparative Efficacy and Effectiveness of Drug Therapies		
Corticosteroids vs. corticosteroids	**Comparative efficacy:** One RCT indicated no differences in efficacy between prednisolone and budesonide. No other head-to-head evidence was available.	Low
Synthetic DMARD vs. synthetic DMARD	**Comparative efficacy:** Two trials and a good-quality meta-analysis (of these two RCTs) reported no differences in efficacy at 2 years for leflunomide and MTX.	Moderate
	One RCT reported higher efficacy for leflunomide than for sulfasalazine at 2 years.	Low
	Six trials and one meta-analysis found no differences in radiographic changes up to 2 years for MTX, leflunomide, and sulfasalazine.	Moderate
	No evidence exists for hydroxychloroquine.	NA
Synthetic DMARD combinations	**Comparative efficacy:** One RCT supported higher efficacy for sulfasalazine + MTX vs. monotherapy. Two studies reporting no difference focused on patients with early RA.	Low
	Two trials supported higher efficacy at 2 years for triple combination MTX + sulfasalazine + hydroxychloroquine than for 1 or 2 drugs.	Moderate
	Three trials including prednisone with 1, 2 or 3 synthetic DMARDs (respectively (MTX + sulfasalazine + hydroxychloroquine) showed less radiographic progression than 1 synthetic DMARD alone.	Moderate
	Comparative effectiveness: One fair trial of early RA patients found that combination therapy with MTX + sulfasalazine + tapered high-dose prednisone or infliximab + MTX showed less radiographic change than sequential DMARD or step-up combination therapy.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs vs. placebo	**Comparative efficacy:** Head-to-head trials are not available. Adjusted indirect comparisons indicated no differences in efficacy among adalimumab, etanercept, and infliximab. Anakinra appeared to be less efficacious than anti-TNF drugs. No adjusted indirect comparisons are available on abatacept or rituximab.	Moderate
Biologic DMARD combinations vs. monotherapy	**Comparative efficacy:** Combination of biologic DMARDs did not yield additional treatment effects compared with monotherapy of the same drugs.	Low
	Comparative effectiveness: A nonrandomized effectiveness study and two prospective observational studies indicated a faster onset of response for etanercept than for infliximab during the first months of therapy but no differences in effectiveness thereafter.	Low
Biologic DMARDs vs. MTX (class effects)	**Comparative efficacy:** Three RCTs (two with early RA patients) indicated no significant differences in clinical outcomes between either adalimumab or etanercept and MTX. Adalimumab and etanercept led to statistically significantly better radiographic outcomes than MTX.	Moderate
Biologic DMARDs vs. synthetic DMARDs	**Comparative effectiveness:** One retrospective cohort study indicated significantly higher rates of remission for biologic DMARDs as a class than synthetic DMARDs.	Low
Biologic DMARDs + MTX vs. biologic DMARDs	**Comparative efficacy:** Multiple good (or fair) RCTs supported a higher efficacy of a combination treatment of adalimumab, etanercept, infliximab, or rituximab and MTX compared with a monotherapy of the respective biologic DMARD. Some comparisons are limited to single studies.	High for etanercept Moderate for adalimumab, infliximab, and rituximab
Biologic DMARDs + synthetic DMARD other than MTX vs. biologic DMARDs	**Comparative efficacy:** One RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.	Low
Biologic DMARD + MTX vs. MTX	**Comparative efficacy:** Two RCTs indicated a greater efficacy of combinations of adalimumab or infliximab and MTX compared with MTX monotherapy in patients with early RA.	Moderate
Key Question 2: Functional Capacity or Health-related Quality of Life		
Corticosteroids vs. corticosteroids	**Comparative efficacy:** In one head-to-head RCT, prednisolone improved functional capacity and health-related quality of life more than budesonide.	Low
Synthetic DMARDs vs. synthetic DMARDs	**Comparative efficacy:** Seven studies compared synthetic DMARDs head-to-head: leflunomide with MTX, leflunomide with sulfasalazine, and sulfasalazine with MTX. Three RCTs and one systematic review suggested that leflunomide led to greater improvement in functional status and/or health-related quality of life than either MTX or sulfasalazine.	Moderate
	Three RCTs did not support a difference in functional capacity between sulfasalazine and MTX.	Moderate
Two synthetic DMARDs vs. synthetic DMARD monotherapy	**Comparative efficacy:** Three RCTs compared a combination of MTX and sulfasalazine to monotherapy with either drug alone. These studies did not support a difference in functional capacity between combination therapy and monotherapy.	Moderate
Synthetic DMARD combinations vs. synthetic DMARD monotherapy	**Comparative efficacy:** Three RCTs examined combination strategies with corticosteroids and one or more synthetic DMARDs compared to synthetic DMARD monotherapy. Some suggested better outcomes with the combination strategies.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs vs. biologic DMARDs	**Comparative effectiveness:** Head-to-head evidence was limited to a prospective cohort study that compared etanercept and infliximab. Etanercept patients had greater improvements in functional capacity, but the groups were not compared statistically.	Low
Biologic DMARDs vs. MTX	**Comparative efficacy:** Three RCTs (one good quality) found no difference in endpoint outcomes comparing either adalimumab or etanercept with MTX. Two of the RCTs found no difference between groups; one found greater improvement during the first 12 weeks in functional capacity and health-related quality of life with etanercept than with MTX but no difference from weeks 16 to 52.	Moderate
Biologic DMARDs vs. other synthetic DMARDs (as class effects)	**Comparative effectiveness:** No head-to-head evidence is available. One prospective cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.	NA
Biologic DMARDs + MTX vs. biologic DMARDs	**Comparative efficacy:** Evidence is mixed. Two RCTs found that a combination of adalimumab or etanercept with MTX led to statistically significantly greater improvements in functional capacity or health-related quality of life than monotherapy with the same biologic DMARDs. One prospective cohort study found no difference when comparing etanercept plus MTX with etanercept alone or infliximab plus MTX with infliximab alone. For most of these comparisons, the evidence is limited to a single study.	Low
Biologic DMARDs + synthetic DMARD other than MTX vs. biologic DMARDs	**Comparative efficacy:** One RCT found no difference between a combination of etanercept with sulfasalazine and etanercept monotherapy.	Low
Biologic DMARD + MTX vs. MTX	**Comparative efficacy:** Two RCTs found greater improvement in functional capacity and quality of life with combination therapies (adalimumab + MTX or infliximab + MTX) than with MTX alone. One prospective cohort study found, for functional capacity, the etanercept-MTX combination, but not the infliximab-MTX combination, to be better than MTX alone.	Moderate
Key Question 3: Comparative Tolerability and Safety of Drug Therapy		
General Tolerability		
Corticosteroids	Overall adverse events in one efficacy trial of prednisolone and budesonide were not different.	Low
Synthetic DMARDs	Three efficacy trials and one meta-analysis indicate no differences in tolerability for leflunomide, MTX, and sulfasalazine.	Moderate
Biologic DMARDs	**Overall adverse event profiles:** In efficacy trials, overall profiles did not differ among biologic DMARDs. Two fair RCTs suggested that the risk of serious adverse events is dose-dependent.	Moderate
	Injection site reactions: In efficacy trials, anakinra had substantially higher rates of injection site reactions than either adalimumab or etanercept.	Moderate
	Infusion reactions: The existing evidence is insufficient to draw conclusions about the comparative risk of abatacept, infliximab, and rituximab with respect to severe or fatal infusion reactions.	Low
Combination of two biologic DMARDs	Two RCTs indicated that the combination of two biologic DMARDs led to statistically significantly higher rates of serious adverse events than monotherapy.	Moderate

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Discontinuation Rates		
Synthetic DMARDs	Three trials and one meta-analysis indicate no differences in discontinuation rates for leflunomide, MTX, and sulfasalazine. However, one meta-analysis of studies up to 5 years indicated that the proportion of patients who discontinue MTX is lower than the proportion who discontinue sulfasalazine.	Moderate
Synthetic DMARD combinations	Five studies of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had no differences in withdrawal rates attributed to adverse events.	Moderate
	Three studies combining prednisone with one or more DMARDs reported no differences in discontinuation rates between groups.	
Biologic DMARDs	Two cohort studies indicated that infliximab has statistically significantly higher rates of discontinuation than etanercept.	Moderate
	One cohort study reported that anakinra had higher rates of discontinuation than etanercept and infliximab.	Low
Serious Infections		
Corticosteroids and synthetic DMARDs	Three cohort studies indicated elevated infection risk for prednisone and possibly MTX and leflunomide compared with other DMARDs.	Low
Biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of biologic DMARDs.	NA
Biologic DMARDs and synthetic DMARDs	One cohort study indicated that anti-TNF drugs as a class (adalimumab, etanercept, and infliximab) did not lead to a higher overall risk for serious infections compared with synthetic DMARDs as a class.	Low
Malignancies		
Synthetic DMARDs	The existing evidence is limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine.	Low
Biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of biologic DMARDs with respect to lymphoma or other malignancies.	NA
Combinations	One study of prednisone and a biologic DMARD-MTX combination was associated with nonmelanoma skin cancer.	Low
Other Serious Adverse Events		
Synthetic or biologic DMARDs	The existing evidence is insufficient to draw conclusions about the comparative risk of synthetic or biologic DMARDs with respect to serious adverse events such as demyelinations, drug-induced lupus, hepatotoxicity, interstitial lung disease, or congestive heart failure.	Low
Key Question 4: Differences by Subgroups		
Demographics: Age		
Various drug comparisons	The evidence base is sparse and mixed. One pooled analysis found similar responses in patients ages 65 years and older versus patients under 65 treated with a biologic (etanercept). Two poor-quality studies of one synthetic (MTX) and one biologic (etanercept) found no difference between these groups in adverse events, infections, or malignancies. A systematic review of MTX also found an inverse relationship between age and major clinical improvement, and no difference in toxicity.	Low

Table 26. Summary of findings with strength of evidence: rheumatoid arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Concomitant Therapies: Chronic Disease		
Various drug comparisons	No evidence is available from head-to-head comparisons, or observational studies for these concomitant treatment therapies. One subgroup analysis from a placebo-controlled trial involving anakinra found that safety profiles did not differ in subjects receiving antidiabetic, antihypertensive, or statin medication treatments.	NA
Comorbidities		
Various drug comparisons	**High-risk comorbidities:** One placebo-controlled RCT of anakinra found no difference between groups in serious adverse events or infections for adults with RA and various high-risk conditions.	Low
	Cardiovascular: Evidence is limited for subpopulations with cardiovascular disease. Two observational studies reported lower rates of either myocardial infarction or congestive heart failure on anti-TNF therapy than on other RA therapies. One database analysis found that only half of those with new onset congestive heart failure had no identifiable risk factors for congestive heart failure.	Low
	Renal impairment: One systematic review reported that greater renal impairment was associated with worse toxicity.	Low
Pregnancy and Neonatal Outcomes		
Various drug comparisons	**Fetal abnormalities:** Evidence is very limited and mixed. One poor-quality study using case reports calculated a higher incidence of congenital abnormalities in pregnancies of women taking DMARDs than in the general population, but a fair-quality database analysis found no statistical difference in live births, miscarriages, or therapeutic terminations in mothers or fathers treated with infliximab and the general population of pregnant women.	Low

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NA, not applicable; PSA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor; vs., versus.
* Studies are of fair quality (see Methods) unless otherwise noted.
† Strength of evidence assessed according to a modified GRADE approach.[27]

Table 27. Summary of findings with strength of evidence: psoriatic arthritis

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Key Question 1: Comparative Efficacy and Effectiveness of Drug Therapies		
Synthetic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, leflunomide produced greater response rates.	NA
Biologic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. The current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, and infliximab produced greater response rates.	NA
Key Question 2: Functional Capacity or Health-related Quality of Life		
Synthetic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one study, leflunomide provided better improvement in functional capacity and health-related quality of life.	NA

Table 27. Summary of findings with strength of evidence: psoriatic arthritis (continued)

Key Question and Drug Comparison	Findings*	Strength of Evidence†
Biologic DMARDs	**Comparative efficacy:** No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, and infliximab led to greater improvement in functional capacity and health-related quality of life.	NA
	Key Question 3: Comparative Tolerability and Safety of Drug Therapy	
Synthetic DMARDs	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo, leflunomide led to higher rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in alanine aminotransferase.	NA
Biologic DMARDs	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled efficacy trials. In these, overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. **Injection site reactions:** adalimumab and etanercept had more injection site reactions than placebo.	NA
	Key Question 4: Differences by Subgroups: No Evidence	

DMARD; disease-modifying antirheumatic drug; NA, not applicable.
* Findings are limited to placebo-controlled studies.
† No head-to-head studies that evaluated comparative effectiveness in psoriatic arthritis met the inclusion criteria.

Most of the trials were conducted in RA patients, and we can draw some conclusions regarding the comparative efficacy of drugs for RA. Data are quite limited for PsA patients, and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either synthetic or biologic DMARDs in this condition.

Key Findings

Rheumatoid Arthritis

Over the past few years, treatment strategies for RA have changed considerably. Early use of DMARDs is now considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity.

Existing comparative evidence permits us to draw some conclusions for monotherapies of synthetic and biologic DMARDs. Overall, the evidence supports similar efficacy and effectiveness for methotrexate (MTX) and sulfasalazine, but it is insufficient to draw conclusions about efficacy and effectiveness for sulfasalazine and leflunomide relative to each other.[30,31,33] All three drugs have similar discontinuation rates attributed to adverse events in short-term efficacy trials up to 2 years.[32,34,35,37]

Although the evidence is insufficient to draw firm conclusions on the comparative efficacy, effectiveness, and harms of biologic DMARDs, adjusted indirect comparisons of placebo-controlled studies suggest that no differences exist among the set of anti-tumor necrosis factor (anti-TNF) drugs (namely, etanercept, infliximab, and adalimumab).[21,48,49,51] Results of adjusted indirect comparisons indicate, however, that anakinra is less efficacious than anti-TNF drugs for

patients with RA.[48,49] Adjusted indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the similarity of study populations.

The evidence comparing monotherapy using a biologic DMARD with monotherapy using a synthetic DMARD is mixed. Monotherapies of adalimumab[57] and etanercept[54,63] generally did not reveal a benefit relative to MTX monotherapy; the exception was for radiographic outcomes, which were statistically significantly better in patients on biologic DMARDs than on MTX. Whether such differences are clinically relevant and can alter the long-term progression of the disease remains unclear. Other biologic DMARDs have not been directly compared with MTX.

By contrast, population-based, observational evidence suggests that biologic DMARDs as a class resulted in better functional capacity than synthetic DMARDs as a class.[58] No evidence exists on abatacept, anakinra, infliximab, and rituximab. No studies were available comparing biologics with synthetic DMARDs other than MTX. All randomized controlled trials (RCTs) were funded by the makers of the biologic DMARDs.

Although a substantial percentage of patients responds well to DMARD monotherapy,[34,54,57,63-65] some patients do not achieve an acceptable treatment response. As the BeSt study (Dutch acronym for Behandel Strategieen, "treatment strategies"), a Dutch effectiveness trial assessing different treatment strategies for RA, has indicated, tight disease control and an individualized treatment approach are paramount in achieving a satisfactory treatment response or remission.[42] Therefore, if dose escalation of a monotherapy does not achieve low levels of disease activity, combination therapies have to be taken into consideration. This is supported by multiple efficacy studies that indicate that combinations of biologic and synthetic DMARDs appear to be more efficacious than monotherapy of either drug.

The existing evidence supports combination strategies of up to three synthetic DMARDs, including corticosteroids, compared with strategies using one or two drugs. The data are limited, however, by the number of supporting studies for each drug combination. Moderate strength evidence from two efficacy trials reported higher proportions of patients meeting American College of Rheumatology (ACR) 20 criteria at 2 years for the combination of MTX plus sulfasalazine and hydroxychloroquine than for one or two drugs.[45,46]

Similarly, combination therapy of biologic DMARDs (adalimumab and etanercept) with MTX achieved better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs.[57,63-66] Whether these results can be extrapolated to combinations of biologic DMARDs with other synthetic DMARDs is uncertain. In clinical practice, patients often receive biologic DMARDs as an add-on therapy to an existing regimen of various synthetic DMARDs.

Combinations of two biologic DMARDs did not yield an additional treatment benefit but rather led to substantially higher rates of serious adverse events than monotherapies (14.8 percent vs. 2.5 percent; P = NR).[59,160] Current evidence also suggests improved functional capacity[39,43,47,124] and less radiographic progression[39,40,43,44,47] for combination strategies with corticosteroids and one or more synthetic DMARDs compared with synthetic DMARD monotherapy. For most of these comparisons, the evidence is limited to a single study.

The evidence is insufficient to draw firm conclusions about whether one combination strategy is better than another. Data are limited to one effectiveness trial for patients with early RA; it reported less radiographic progression over 12 months with either (1) MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy.[42] Of note, after the report was in peer review, the 2-

year followup was published.[214] Results of this study reinforced the conclusion that patients on initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with MTX and infliximab had less radiographic progression. However, all arms had similar functional ability by Health Assessment Questionnaire scores (HAQ), and similar disease activity by Disease Activity Score (DAS) values regardless of which initial therapy they received.

The therapeutic advantage of combination therapy compared with monotherapy does not seem to be outweighed by an increase in harms. Evidence of moderate strength suggests that combination studies of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had similar withdrawal rates attributable to adverse events. Combination studies including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Similarly, combinations of biologic and synthetic DMARDs had similar rates of adverse events than monotherapies of either drugs. However, because biologic DMARDs are relatively new medications, solid long-term data on safety are generally still missing. Especially rare but severe adverse events such as serious infections, lymphoma, autoimmunity, or congestive heart failure are of concern. The evidence is particularly sparse on abatacept and rituximab. Furthermore, the pharmaceutical industry funded a large percentage of these studies, and selective reporting is conceivable, although we had no way to account for missing information.

The most obvious differences among biologic DMARDs that might be clinically decisive for choosing a particular drug involve dosing and administration. Abatacept, infliximab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept once or twice per week. The route of administration is also the cause of the main differences in short-term tolerability. Anakinra appears to have a substantially higher rate of injection site reactions than anti-TNF drugs. Abatacept, infliximab, and rituximab carry the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously. Fatal infusion reactions have been reported for infliximab and rituximab.[146,147]

The existing evidence remains insufficient to draw firm conclusions on the best treatment regimen for patients with early RA. Studies conducted in patients with early RA suggested that an early start of a biologic DMARD can prevent joint erosions and beneficially influence the clinical course of the disease. Because the studies were of limited duration, however, they do not allow conclusions on whether early initiation of a biologic regimen can improve the long-term prognosis of RA. Currently, clinical practice guidelines recommend that clinicians start biologic DMARDs if patients have suboptimal response to synthetic DMARDs.[140,215]

A considerable limitation of our conclusions is that we have had to derive them primarily from efficacy trials. The direction and effect sizes of findings from effectiveness trials and observational studies were generally consistent with those from efficacy trials. Nonetheless, differences in the incidence of reported adverse events and discontinuation rates were obvious between clinical trials and population-based observational studies.

For example, clinical efficacy trials of infliximab reported infusion reaction in, on average, 17 percent of patients.[158] A prospective cohort study in a Canadian clinical care setting, however, reported substantially higher percentages.[176] In this study (113 patients with 1,183 infusions), 53

percent of patients experienced at least one infusion reaction during their therapy (mean, 15 months).

Patients who were enrolled in efficacy trials usually suffered from more severe disease than the average patient in clinical practice.[216] For example, a recent study found that only small proportions of consecutive patients with RA who were under the care of a private practice rheumatologist in Nashville, Tennessee, would have met eligibility criteria of the ERA (Early Rheumatoid Arthritis) trial;[54] only 31 percent of patients with early RA who had not taken MTX would have met the ERA criteria. The same pattern was true for the ATTRACT (anti-TNF trial in RA with concomitant therapy) study trials;[100,216] only 5 percent of patients in a long-term RA database would have been eligible for this trial. Therefore, the applicability of results from efficacy trials to the average patient in community practice appears to be limited.

Furthermore, with RA we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups and the general population. Several studies conducted subgroup analyses or used subgroups as the study population. Age subgroup analyses suggested no differences in adverse events, infections, or malignances in patients treated with MTX or etanercept.[207,208] For MTX, the odds for major clinical improvement dropped slightly as age increases in all clinical trial patients; age did not affect MTX efficacy or the rate of side effects.[206] The strength of this evidence is weak, and results have to be interpreted cautiously.

Psoriatic Arthritis

No head-to-head comparative evidence meeting inclusion criteria exists for any drugs in this review for treating patients with PsA. Parenteral high-dose MTX and sulfasalazine improved patient outcomes compared with placebo.[111] Additionally, patients taking leflunomide had higher response rates and quality of life outcomes than those taking placebo.[112,113]

Evidence supports the general efficacy of adalimumab, etanercept, and infliximab for the treatment of PsA.[114-122] However, evidence is insufficient to draw firm conclusions about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab for the treatment of PsA.

Information is insufficient for the harms, tolerability, adverse events, and adherence for patients with psoriatic arthritis. The available studies include only placebo-controlled studies; no head-to-head studies meeting inclusion criteria have been published.

Future Research

We have identified several areas needing further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for both RA and PsA.

Rheumatoid Arthritis

Important areas that will influence clinical decisionmaking include three critical topics: (1) timing of initiation of therapies, (2) applicability of combination strategies and biologic DMARD therapy in community practice, and (3) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs. Analyses involving subpopulations,

specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases.

Timing of initiation of therapies needs to be addressed, including whether aggressive early treatment in RA influences the course and prognosis beneficially. Adequately powered, long-term RCTs must examine different treatment strategies with and without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in this population. These trials should be conducted over multiple years to guarantee that results provide a relevant assessment of the long-term prognosis of RA under different treatment strategies. Such trials would also provide insight about whether the long-term benefits of any combination of drugs outweigh the adverse effects.

Given that available long-term data indicate high discontinuation rates for drugs used to treat RA, having backup regimens is crucial. Additional well-conducted research is needed to assess the comparative efficacy and safety of synthetic DMARDs in patients who currently do not qualify for a treatment with a biologic DMARD. Also still unclear is whether newer synthetic DMARDs such as leflunomide have a better, long-term adverse events profile than older synthetic DMARDs such as MTX. Additionally, although combination strategies with synthetic DMARDs with or without corticosteroids appear more effective, further research examining *which* combination strategy is more effective would be beneficial for medical treatment decisionmaking.

Moreover, head-to-head RCTs need to establish the comparative effectiveness and safety of biologic DMARDs. Currently, evidence from systematic reviews, placebo-controlled trials, and observational studies is insufficient to draw any firm conclusions. Biologic DMARDs differ substantially in the route and frequency of administration, which can influence the choice of a biologic agent by patients and physicians. Establishing the comparative effectiveness and safety of biologic DMARDs, therefore, is helpful for balanced, informed decisionmaking.

The risk of rare but serious adverse events such as malignancies, serious infections, demyelinations, severe infusion reactions, or congestive heart failure must be established in well-conducted observational studies, such as large cohort or case-control studies. The balance of risks and benefits of biologic DMARDs can be determined reliably only if good long-term data on such harms are available.

In general, all future studies have to ensure a high rate of applicability to patients seen in community practices. Future research has to establish the comparative effectiveness, health-related quality of life, and safety of all therapies, but especially biologic DMARDs, in settings that reflect daily clinical care and take into account factors such as varying adherence because of administration schedules, costs, and adverse events. The current evidence indicates that severity of disease and population characteristics may differ substantially between the highly selected populations enrolled in efficacy trials and those treated in daily clinical practice. Future trials must plan subgroup analyses in older patients or patients with comorbidities a priori.

Psoriatic Arthritis

For this condition, the available evidence is limited to placebo-controlled trials (six studies and two systematic reviews). The quality of studies on synthetic DMARDs is sparse and fraught with methodological issues.

Areas of future research are similar to the ones on RA outlined above. Head-to-head RCTs have to establish the comparative efficacy and safety of different treatment strategies with and

without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage.

Furthermore, head-to-head RCTs have to determine the comparative effectiveness and safety of biologic DMARDs for the treatment of PsA.

More generally, the issues of effectiveness, subgroups, and use in ordinary clinical settings highlighted for RA warrant attention for PsA as well.

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