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Comparative Effectiveness Review
Number 55

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

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Errata: Tables 2, 3, and 4 have been corrected.

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Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Structured Abstract

Objectives: Compare the benefits and harms of corticosteroids, oral and biologic disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis.

Data Sources: English-language articles from 1980 to February 2011 identified through PubMed, Embase, Cochrane Library, and International Pharmaceutical Abstracts; unpublished literature including dossiers from pharmaceutical companies.

Methods: Two people independently selected relevant head-to-head trials of any sample size, prospective cohort studies with at least 100 participants, and relevant good- or fair-quality meta-analyses that compared benefits or harms of 14 drug therapies. Retrospective cohort studies were also included for harms. For biologic DMARDs, placebo-controlled, double-blind RCTs were also included. We required trials and cohort studies to have a study duration of at least 12 weeks. Literature was synthesized qualitatively within and between the two main drug classes (oral and biologic DMARDs). Network meta-analysis also was performed to examine the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo controlled trials.

Results: Head-to-head trials showed no clinically important differences in efficacy among oral DMARD comparisons (methotrexate, sulfasalazine, leflunomide). The only head-to-head trial comparing biologic DMARDs (abatacept vs. infliximab) found no clinically important differences. Combination therapy of biologic DMARDs plus methotrexate improved clinical response rates and functional capacity more than monotherapy with methotrexate. Network meta-analyses found higher odds of reaching ACR 50 response for etanercept compared with most other biologic DMARDs (abatacept, adalimumab, anakinra, infliximab, rituximab, tocilizumab) for methotrexate-resistant patients with active rheumatoid arthritis. Similar overall tolerability profiles were found among oral and biologic DMARDs, but short-term adverse events were more common with biologic DMARDs. Adjusted indirect comparisons of biologic DMARDs found that certolizumab had the most favorable overall withdrawal profile, followed by etanercept and rituximab. Certolizumab had lower relative withdrawal rates due to lack of efficacy than adalimumab, anakinra, and infliximab. Certolizumab and infliximab had more, while etanercept had fewer withdrawals due to adverse events than most other drugs. Evidence was insufficient to assess comparative risk of serious adverse events among biologic DMARDs. Combinations of biologic DMARDs have higher rates of serious adverse events than biologic DMARD monotherapy. Limited data existed for subgroups.

Conclusions: Limited head-to-head comparative evidence does not support one therapy over another for adults with rheumatoid arthritis. Network meta-analyses from placebo-controlled trials of biologics suggest some differences, including higher odds of reaching ACR 50 response, but strength of evidence was low.

Executive Summary

Background

Rheumatoid arthritis (RA), which affects 1.3 million adult Americans, 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 with support from selected laboratory tests. Treatment of patients with RA aims to control pain and inflammation and, ultimately, the goal is remission or at least low disease activity for all patients. Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs or DMARDs (hydroxychloroquine, leflunomide, methotrexate [MTX], and sulfasalazine), and biologic DMARDs (five anti-tumor necrosis factor drugs [anti-TNF]: adalimumab, certolizumab, etanercept, golimumab, infliximab; and others including abatacept, anakinra, rituximab, and tocilizumab).

Treatment strategies for RA continue to evolve. Early use of DMARDs is considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with oral DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity or remission. Clinical experience supports the use of MTX as the oral DMARD of choice unless there are contraindications (e.g., liver impairment, alcohol abuse, pregnancy, lung disease). Experts have not arrived at consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare, for example, oral DMARDs with corticosteroids, oral DMARDs with biologic DMARDs, or a triple combination of corticosteroids, oral DMARDs, and biologic DMARDs. In addition, there is debate about how early in the disease process combination therapy should be initiated. 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.

Objectives

This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. This report updates a previous version published in 2007. The Key Questions (KQs) are as follows:

KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?

KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

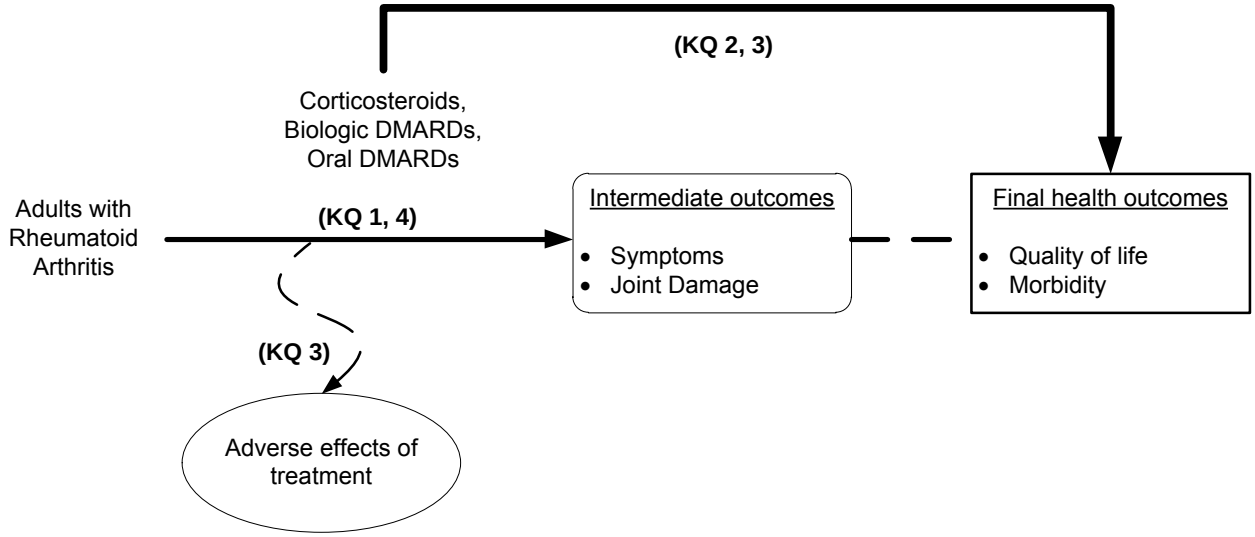
KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Analytic Framework

Figure A depicts the analytic framework for rheumatoid arthritis.

Figure A. Analytic framework for treatment for rheumatoid arthritis



Methods

A Technical Expert Panel was employed for the finalization of the KQs and review of the planned analysis strategy. Our KQs and protocol were posted on the Agency for Healthcare Research and Quality Web site for public review and comment. Individuals who were experts in rheumatology and various stakeholder and user communities performed an external peer review of the report. The report was also posted for public review. We compiled all comments and addressed each one individually, revising the text as appropriate.

We searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We limited the electronic searches to "human" and "English language." For this update, the searches went up to January 2011. Hand searches were conducted on the Center for Drug Evaluation and Research (CDER) database of the U.S. Food and Drug Administration and unpublished literature including dossiers from pharmaceutical companies.

Study eligibility (inclusion and exclusion) criteria were designed in respect to study design or duration, patient population, interventions, outcomes, and comparisons for each KQ. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug with another. For biologic DMARDs, we also included placebo-controlled, double-blind randomized controlled trials (RCTs). For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies. We included studies with sample sizes of at least 100 and duration of at

least 3 months. We only included studies that used doses within the recommended dosing range or that used doses that could be considered equivalent to recommended doses.

Two individuals independently reviewed abstracts identified by searches. If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles. Two individuals again independently reviewed the full text of all remaining articles to determine whether they should be included. We designed and used a structured data abstraction form to ensure consistency of appraisal for each included study. Trained reviewers abstracted data from each study. A senior evaluated the completeness of each data abstraction.

We rated the quality of individual studies using the predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[1] and the National Health Service Centre for Reviews and Dissemination.[2] Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. We graded the strength of evidence as high, moderate, low, or insufficient based on methods guidance for the Evidence-based Practice Program.[3,4] We graded strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., American College of Rheumatology [ACR] 20/50/70, Disease Activity Score [DAS]), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g., injection-site reactions, infections, malignancy). We generally synthesized the literature qualitatively, but we did conduct meta-analyses comparing the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo-controlled trials. To compare the relative efficacy of biologic DMARDs, we conducted a mixed treatment comparison (MTC) meta-analysis using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques. The primary efficacy outcome of our MTC meta-analysis was the ACR 50.

Results

We identified 3,868 citations from our searches. We included 258 published articles reporting on 211 studies: 31 head-to-head RCTs, 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. We identified 30 studies for quantitative synthesis for KQ1 and 42 studies for quantitative syntheses for KQ3. Most studies were of fair quality.

Our major findings are presented in this section by type of drug comparison for benefits and harms (Table A). Subpopulation analyses are described after Table A because the evidence is very limited.

Table A. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. **Low** No clinically significant difference for functional capacity. **Low** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. **Low**	No consistent differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Leflunomide vs. sulfasalazine	Mixed ACR response rates. **Insufficient** No differences in radiographic changes. **Low** Greater improvement in functional capacity for leflunomide **Low**	No differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes.[†] **Moderate** No differences for functional capacity.[†] **Moderate**	No differences in tolerability; more patients stayed on MTX long term. **Low** Mixed results for specific adverse events. **Insufficient**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. **Moderate** No differences in functional capacity. **Moderate**	Withdrawal rates attributable to adverse events higher with combination. **Low** Insufficient evidence for specific adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. **Insufficient** Less radiographic progression in patients on DMARD plus prednisone. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded. joints **Low** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. **Moderate** No difference in quality of life. **Low**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. **Moderate** No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications. **Low**
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **Low**	Discontinuation rates and severe adverse events higher with infliximab. **Low**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic vs. biologic *(Mixed treatment comparisons)*	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. **Low** Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. **Low**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **Low**
Biologic vs. biologic *(Mixed treatment comparisons)* (continued)	Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. **Low**	Risk for injection site reactions apparently highest with anakinra. **Low** Mixed results for specific adverse events. **Insufficient**
Biologic DMARDs vs. Oral DMARDs		
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. **Moderate** No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. **Low**; **Insufficient** Faster improvement in quality of life with etanercept than MTX. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. **Low**	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. **Moderate**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. **Moderate** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. **Low** In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (**Moderate**) and quality of life (**Low**) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No 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 **Insufficient**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. **High** for clinical response and functional capacity, **Moderate** for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis. **Low** Mixed evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Strategies in Early RA		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. **Low** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **Low**	No differences in discontinuation rates. **Moderate**
Three oral DMARDs plus prednisone vs. one oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low**	No differences in discontinuation rates. **Moderate**
Sequential monotherapy starting with MTX 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 and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. **Low**	No differences in serious adverse events between groups. **Low**

† at MTX doses ranging from 7.5-25 mg per week

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; MTC = mixed treatment comparisons; MTX = methotrexate; RA = rheumatoid arthritis; vs = versus

Subpopulations. Limited good or fair evidence for benefits or harms of subpopulations exists; therefore, the strength of evidence was low and results should be interpreted cautiously. Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity. For MTX, the odds for major clinical improvement dropped slightly as the age of clinical trial patients increased; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly. Those taking anakinra and concomitant diabetic, antihypertensive, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment. Those with high-risk comorbidities (cardiovascular events, diabetes, malignances, renal impairment) and taking anakinra did not experience an increase in serious adverse events or overall infectious events.

Discussion

Existing comparative evidence did not support the superiority of one oral DMARD over another. Limitations to these trials included the wide range of MTX dosing in the trials. Biologic DMARD comparisons are limited to mostly observational studies and findings from MTC meta-analyses. Our MTC meta-analyses, suggest some differences, such as etanercept having a higher probability of improvement in disease activity than most other biologic DMARDs, but are limited primarily to indirect evidence (low strength of evidence) and therefore should be interpreted with caution. The limited evidence precludes drawing firm conclusions about whether one combination strategy is better than another in early RA. Overall tolerability is similar among biologic and among oral DMARDs; however, several studies suggest that adverse events are more common with biologic DMARDs compared with oral DMARDs. Limited evidence does not suggest an increased risk of severe adverse events, including cardiovascular or cancer, with oral DMARDs. Most studies found no risk of cardiovascular events and malignancy with biologic DMARDs, except for cohort studies, which describe an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

Common problems for RA studies included the lack of effectiveness information, that is, 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 is also needed about the performance of these drugs in subgroups of patients defined by health status, sociodemographic, or other variables.

To address problems with current literature, future studies should include using designs of longer duration and followup, enrolling patients representing key subgroups (or reporting on them when they are enrolled), and ensuring that quality of life (or other patient-centered outcomes) is measured, in addition to clinician-centered measures such as joint erosion. Ideally, studies need to mimic clinical decisionmaking, where if a patient is not doing well after a specified time, the protocol gives them something different. Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) timing of initiation of therapies, and (3) applicability of combination strategies and biologic DMARD therapy in community practice. The results of the MTC meta-analyses suggested some differences. However, the strength of evidence was low for the MTC findings, and head-to-head

studies are needed to confirm or refute these results before any firm clinical recommendations can be made.

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. 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 helpful.

Abbreviations

ACR	American College of Rheumatology
Anti-TNF	Anti-tumor necrosis factor drugs
CDER	Center for Drug Evaluation and Research
DMARD	Disease-modifying antirheumatic drug
MCMC	Markov chain Monte Carlo techniques
MTC	Mixed-treatment comparisons
MTX	Methotrexate
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SF36	Short Form 36

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