Comparative Effectiveness Review
Number 54

Effective Health Care Program

Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report

Executive Summary

Background

Psoriatic arthritis (PsA) is among the most disabling forms of arthritis, even though it affects fewer people than other types of arthritis. PsA has a highly variable presentation, which generally involves pain and inflammation in joints and progressive joint involvement and damage. The condition is associated with the skin disease psoriasis, but not all people with psoriasis will develop PsA. Additionally, PsA may predate the development of skin disease, leading to some diagnostic uncertainty. Among people with psoriasis, the prevalence of arthritis varies from 6 percent to 42 percent. In the general population, the prevalence of PsA is estimated to be 0.3 percent to 1 percent. Based on estimates from the 2000 U.S. Census, 520,000 people ages 18 or older in the United States have PsA.

Treatment of patients with PsA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability. Available therapies for PsA include corticosteroids, oral disease-modifying antirheumatic drugs or DMARDs (hydroxychloroquine, leflunomide, methotrexate [MTX], and sulfasalazine), and biologic DMARDs. Five biologics (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) are also classified as antitumor necrosis factor (anti-TNF) drugs. The U.S. Food and Drug Administration (FDA) has approved adalimumab, etanercept, golimumab, and infliximab for use in

Effective Health Care Program

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patients with PsA. This report also reviews evidence for abatacept, anakinra, certolizumab, rituximab, and tocilizumab, which are approved for rheumatoid arthritis (RA).

Historically, few trials have been conducted with patients having PsA, with only minimal research before biologic agents were introduced; management options tended to be adapted from RA trial evidence. Similar to RA trials, 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.

Experts have not arrived at a consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs for treating PsA. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare. 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. 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 PsA. This report updates a previous version published in 2007. The Key Questions (KQs) are as follows:

KQ 1: For patients with PsA, 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?

KQ 2: For patients with PsA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

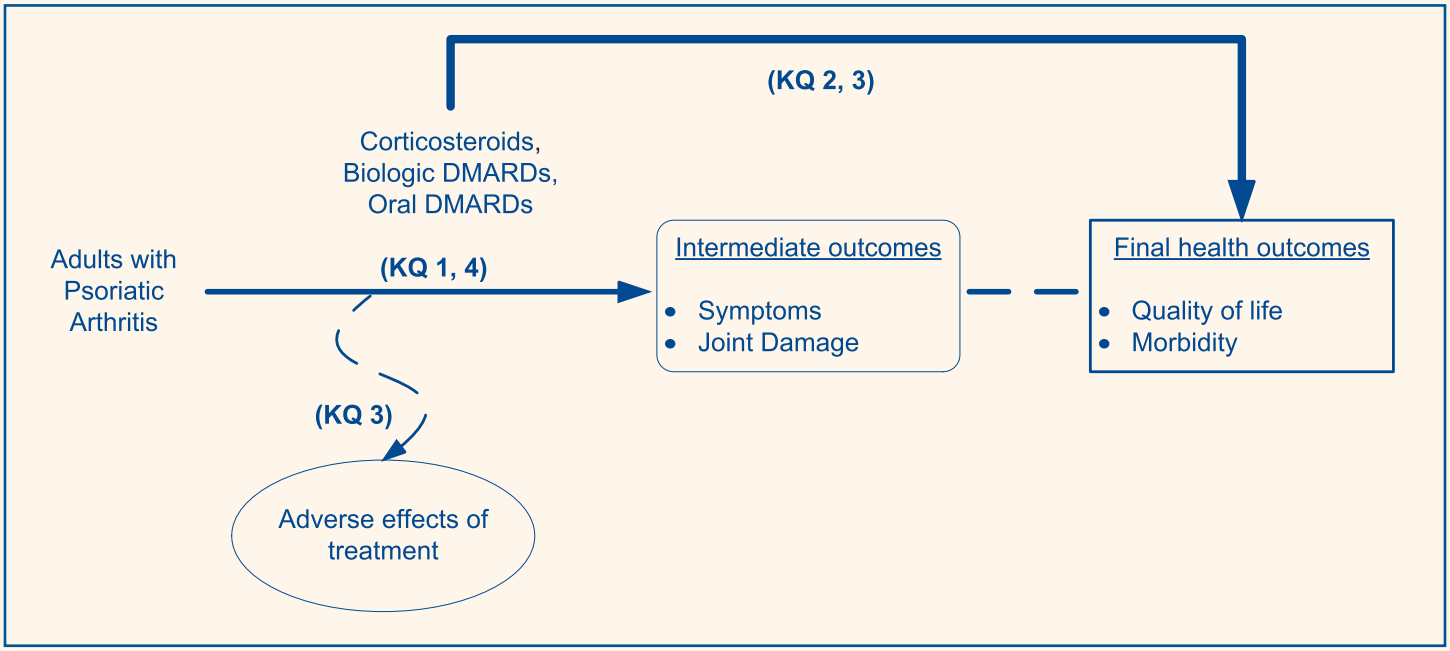
KQ 3: For patients with PsA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

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

Analytic Framework

Figure A lays out the analytic framework that guided the research.

Figure A. Analytic framework for treatment for psoriatic arthritis



DMARDS = disease-modifying antirheumatic drugs; KQ = Key Question

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 AHRQ Web site for public review and comment. Two reviewers performed an external peer review; one a leading expert in psoriatic arthritis and one a faculty member in clinical epidemiology and informatics as well the project director for the Oregon Health and Science University's Drug Effectiveness Review Project reports. 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 FDA and unpublished literature, including dossiers from pharmaceutical companies.

Study eligibility (inclusion and exclusion) criteria were designed with 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 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 included only 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 reviewer 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 synthesized the literature qualitatively. We graded the strength of evidence as high, moderate, low, or insufficient based on methods guidance for the EPC program.[3,4] We graded strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., ACR 20/50/70,* 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).

Results

We identified 3,868 citations from our searches. We included 24 published articles reporting on 16 studies: 0 head-to-head randomized controlled trials, 0 head-to-head nonrandomized controlled trials, 10 placebo-controlled trials, 3 meta-analyses or systematic reviews, and 3 observational studies. Our findings included studies rated good or fair for internal validity. Most studies were of fair quality.

Our major findings are presented in this section by type of drug comparison and important outcomes (both benefits and harms as described in KQ 1, KQ 2, and KQ 3) (Table A). No comparative evidence was identified for KQ 4.

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* American College of Rheumatology measure of disease activity: response scores based on 20, 50, or 70 percent criteria for improvement.

Table A. Summary of findings		
Key Comparisons	**Efficacy and Effectiveness Strength of Evidence Grade**	**Harms Strength of Evidence Grade**
Oral DMARDs		
Leflunomide	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. INSUFFICIENT Compared with placebo in one study, leflunomide produced better improvement in health-related quality of life and statistically significant, but not clinically significant, improvement in disease activity and functional capacity. LOW	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of leflunomide and other treatments. INSUFFICIENT Current evidence was 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. INSUFFICIENT
Methotrexate	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. INSUFFICIENT Current evidence was limited to placebo-controlled trials. Compared with placebo in one fair study, MTX resulted in greater improvement in physician assessment of disease activity than placebo. LOW	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of MTX and other treatments. INSUFFICIENT
Sulfasalazine	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. INSUFFICIENT Current evidence was limited to placebo-controlled trials. Compared with placebo in one good systematic review study, sulfasalazine reduced disease activity. MODERATE	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of sulfasalazine and other treatments. INSUFFICIENT
Biologic DMARDs		
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD	The current evidence was limited to two cohort studies. Compared to anti-TNF monotherapy (adalimumab, etanercept, or infliximab), MTX plus anti-TNF produced similar disease activity response rates. LOW One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. INSUFFICIENT	No head-to-head evidence met inclusion criteria; unable to draw conclusions on the comparative harms of biologic DMARD + oral DMARD and other treatments. INSUFFICIENT

Table A. Summary of findings (continued)		
Key Comparisons	**Efficacy and Effectiveness Strength of Evidence Grade**	**Harms Strength of Evidence Grade**
Biologic DMARDs (continued)		
Biologic	No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. INSUFFICIENT Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in disease activity, functional capacity[a] and health-related quality of life.[b] LOW to MODERATE[c]	Etanercept had a lower rate of withdrawals because of adverse events than infliximab in a prospective cohort study LOW Additional evidence was limited to placebo-controlled trials, where adverse events were not the primary outcome. Overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. However, compared with placebo, we noted the following: adalimumab and etanercept had more injection-site reactions and adalimumab had fewer events of aggravated psoriasis than placebo LOW Golimumab was associated with more malignancies than placebo in one RCT INSUFFICIENT

[a]Of seven studies reporting outcomes for the Health Assessment Questionnaire (HAQ), the magnitude of benefit in functional capacity compared with placebo reached the MCID (HAQ change of ≥ 0.22) for all but one study of adalimumab (which found a between-group difference of 0.2).[7] The magnitude of benefit for functional capacity (between-group difference for improvement in HAQ) ranged from 0.2 to 0.3 for adalimumab, 0.5 to 1.1 for etanercept, 0.34 to 0.4 for golimumab, and 0.4 to 0.6 for infliximab.

[b]The magnitude of benefit in quality of life reached the MCID for the SF-36 PCS for all five studies that reported the PCS and ranged from 2.9 to 7.9 for adalimumab, 8.6 for etanercept, 5.9 to 7.2 for golimumab, and 6.4 to 8 for infliximab.

[c]Low for golimumab and moderate for adalimumab, etanercept, and infliximab.

Abbreviations: ACR 20 = American College of Rheumatology 20 percent improvement from baseline to endpoint; ADA = adalimumab; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; INF = infliximab; LEF = leflunomide, MCID = minimal clinically important difference; MTX = methotrexate; PCS = physical component score; SF-36 = Medical Outcomes Study Short Form 36; SSZ = sulfasalazine; TNF = tumor necrosis factor.

Overall, the data are quite limited and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either oral or biologic DMARDs in this condition. Table B gives a range for effect sizes for commonly reported measures, including the American College of Rheumatology 20 percent improvement from baseline to endpoint (ACR 20), the Health Assessment Questionnaire (HAQ), and Medical Outcomes Study Short Form 36 Physical Component Score (SF-36 PCS). For the oral DMARDs, including sulfasalazine and methotrexate, sparse data are available.

Table B. Comparison of effect sizes* from placebo-controlled trials for ACR 20, HAQ, and SF-36 PCS by drug

Drug	Studies/ Participants	ACR 20 (% of Subjects Achieving)	HAQ (Mean Improvement)	SF-36 PCS (Mean Improvement)
Oral DMARDs				
Leflunomide	1 RCT/ 190	36	0.14	NR
Methotrexate	1 RCT/ 37	NR	NR	NR
Sulfasalazine	1 SER/ 1,022	NR	NR	NR
Biologic DMARDS				
Adalimumab	2 RCTs/ 415	39 to 57	0.2 to 0.3	2.9 to 7.9
Etanercept	3 RCTs/ 633	59 to 65	0.5 to 1.1	8.6
Golimumab	1 RCT/ 405	45 to 51	0.34 to 0.4	5.9 to 7.2
Infliximab	2RCTs,1SER/ 673	58 to 62	0.4 to 0.6	6.4 to 8

*Effect sizes represent the range of point estimates from individual studies for the absolute difference between drug and placebo. Minimally Clinically Important Differences (MCIDs): ACR 20 is 20% minimal improvement;ACR 50/70 considered more clinically significant; HAQ >=0.22 change, SF36 PCS>= 2 standard error of the mean (SEM).

Abbreviations: ACR 20 = American College of Rheumatology 20 percent improvement from baseline to endpoint; HAQ = Health Assessment Questionnaire; PCS = physical component score; SF-36 = Medical Outcomes Study Short Form 36; RCT = Randomized controlled trial; SER = systematic evidence review.

Discussion

No head-to-head controlled trials meeting inclusion criteria existed for any drugs in this review for treating patients with PsA. Two cohort studies with low strength of evidence indicated that the combination of an anti-tumor necrosis factor (TNF) (adalimumab, etanercept, or infliximab) with methotrexate (MTX) only was not different in treatment response[5,6] than treatment with anti-TNF only.

For the oral DMARDs, including sulfasalazine and methotrexate, the sparse data available involved placebo comparisons. For biologic DMARDs, evidence supported the efficacy of adalimumab, etanercept, golimumab, and infliximab for the treatment of PsA when compared to placebo.[7-17] Qualitatively, these biologic DMARDs appeared to achieve similar ACR 20, HAQ, and SF-36 PCS scores in these trials (Table B). However, findings should be interpreted cautiously given these were not head-to-head trials. Evidence was insufficient to draw firm conclusions about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of abatacept, adalimumab, anakinra, certolizumab, golimumab, etanercept, infliximab, rituximab, and tocilizumab for treating PsA.

Information generally was insufficient for the comparative harms, tolerability, adverse events, and adherence for patients with PsA. The available studies included two relatively small prospective cohort studies and placebo-controlled studies; no head-to-head studies meeting inclusion criteria have been published.

In terms of applicability to populations, the studies were generally multicenter involving adults with diagnosed PsA. Prior medications tried before these studies were variable, but in general patients had failed a DMARD prior to starting any of the biologic agents. It is also important to note that the diagnostic criteria for PsA before the 2006 publication of the ClASsification of Psoriatic Arthritis (CASPAR) criteria were not validated, which could lead to enrollment of patients that were not explicitly defined.

This report's findings did not reveal any differences with current standard of care. However the current available evidence for PsA was limited. Several areas need further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for PsA. For this condition, the available evidence was limited to two head-to-head cohort studies and placebo-controlled trials. Head-to-head randomized controlled trials are needed to establish the comparative efficacy and safety of different treatments with and without corticosteroids, oral DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage and optimize quality of life for people with PsA. Furthermore, head-to-head RCTs are needed to determine the comparative effectiveness and safety of biologic DMARDs for treating PsA. More generally, the issues of effectiveness, subgroups, and use in ordinary clinical settings warrant attention for PsA.

Abbreviations

ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
CASPAR	ClASsification of Psoriatic Arthritis
DMARD	disease-modifying antirheumatic drug
FDA	U.S. Food and Drug administration
HAQ	Health Assessment Questionnaire
MTX	methotrexate
PsA	psoriatic arthritis
RCT	randomized controlled trial
SF-36 PCS	Short Form 36 Physical Functioning Scale

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Full Report

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