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Draft Comparative Effectiveness Review
Number XX

Comparative Effectiveness of Drug Therapy for Psoriatic Arthritis in Adults

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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 (CERs) 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 strength 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 CERs 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 from 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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The information in this report is intended to help health care decision-makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf.

Comparative Effectiveness of Drug Therapy for Psoriatic Arthritis in Adults

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of rheumatoid arthritis and psoriatic arthritis in adults. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.
The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

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% to 42%. In the general population the prevalence of PsA is estimated to be 0.3% to 1%. Based on estimates from the 2000 US Census, 520,000 persons ages 18 and above have PsA in the US.

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 (i.e., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) are also classified as anti-tumor necrosis factor (anti-TNF) drugs. The US Food and Drug Administration (FDA) has approved adalimumab, etanercept, golimumab and infliximab for use in patients with PsA. This report also reviews evidence for abatacept, anakinra, certolizumab, rituximab, tocilizumab, which are approved for rheumatoid arthritis.

Experts have not arrived at 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—e.g., oral DMARDs with corticosteroids, oral DMARDs with biologic DMARDs, 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 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.

In patients with PsA, historically, few trials have been conducted, with only minimal research before biologic agents were introduced; management options tended to be adapted from rheumatoid arthritis (RA) trial evidence. Like in 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.

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. The key questions (KQs) were developed through a public process in conjunction with the Scientific Resource Center at the Oregon Health and Science University. This report updates a previous version published in 2007. The KQs are as follows:

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

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

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

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

We identified 3,487 citations from our searches. Working from 1040 articles retrieved for full review, we retrieved 219 for background and excluded 802 at this stage. We included 19 published articles reporting on 12 studies: 0 head-to-head randomized controlled trials (RCTs), 0 head-to-head nonrandomized controlled trials, 9 placebo-controlled trials, 2 meta-analyses or systematic reviews, and 1 observational study. Our findings include studies rated good or fair. Most studies were of fair quality; we designate in the text only those of good quality.

Conclusions

We present our major findings in this section by type of drug comparison and important outcomes (both benefits and harms). Table ES-1 summarizes the information for PsA for KQ 1 through KQ3. No comparative evidence was identified for KQ4.

Table ES-1. Summary of findings

Key Comparisons	Efficacy Strength of evidence grade	Harms Strength of evidence grade
Oral DMARDs		
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 is 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 SSZ and other treatments. INSUFFICIENT Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, sulfasalazine reduced disease activity MODERATE	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of SSZ and other treatments. INSUFFICIENT
Leflunomide	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of LEF and other treatments. INSUFFICIENT Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, leflunomide produced greater response rates, improvement in functional capacity and health-related quality of life. LOW	No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of LEF and other treatments. INSUFFICIENT 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. INSUFFICIENT
Biologic DMARDs		
Biologic DMARD + Oral DMARD	The current evidence is limited to one cohort study. Compared to anti-TNF monotherapy (ADA, ETN or INF), MTX plus anti-TNF monotherapy produced similar response rates. LOW	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

ACR, American College of Rheumatology; ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; HAQ-DI, Health Assessment Questionnaire Disability Index; INF, infliximab; LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36; SSZ, sulfasalazine; TNF, tumor necrosis factor.

Table ES-1. Summary of findings (continued)

Key Comparisons	Efficacy Strength of evidence grade	Harms Strength of evidence grade
Biologic	No head-to-head evidence met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. INSUFFICIENT	Etanercept had a lower rate of withdrawals due to adverse events than infliximab in a prospective cohort study. LOW
	Current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, golimumab and infliximab led to greater improvement in disease activity, functional capacity and health-related quality of life. INSUFFICIENT	Additional evidence is limited to placebo-controlled trials. 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; golimumab had more malignancies; and adalimumab had fewer events of aggravated psoriasis than placebo INSUFFICIENT

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.

Oral DMARDs

Parenteral high-dose MTX and sulfasalazine improved physician assessment of disease activity compared with placebo. Additionally, patients taking leflunomide had higher response rates and better quality of life outcomes than those taking placebo. Similarly, patients taking sulfasalazine had greater improvement in disease activity than placebo.

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

Biologic DMARDs

Evidence supports the general efficacy of adalimumab, etanercept, golimumab and infliximab for the treatment of PsA. Comparative data are limited to one cohort study, which found that compared to anti-TNF monotherapy (adalimumab, etanercept or infliximab), MTX plus anti-TNF produced similar response rates. Etanercept had a lower rate of withdrawals due to adverse events than infliximab in a prospective cohort. Adverse event profiles appear similar for biologic DMARDs and placebo. However, compared with placebo, adalimumab and etanercept had more injection site reactions; golimumab had more malignancies; and adalimumab had fewer events of aggravated psoriasis than placebo. However, evidence is insufficient to draw firm conclusions about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of adalimumab, golimumab, etanercept, infliximab for the treatment of PsA.

Information is insufficient for the harms, tolerability, adverse events, and adherence for patients with PsA. The available studies include only a relatively small prospective cohort study

and placebo-controlled studies; no head-to-head studies meeting inclusion criteria have been published.

Remaining Issues

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 is limited to one head-to-head cohort study (one study) and placebo-controlled trials (nine studies and two systematic reviews). Head-to-head RCTs are needed to establish the comparative efficacy and safety of different treatment strategies 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 the treatment of PsA. More generally, the issues of effectiveness, subgroups, and use in ordinary clinical settings warrant attention for PsA.

Evidence Report

Chapter 1. Introduction

Background

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults,[1] with more than 46 million Americans reporting doctor diagnosed arthritis.[2] 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 patients with arthritis the burden of disease is evidenced by decreased quality of life,[3-6] decreased employment rates,[7,8] and increased direct and indirect costs.[9-12] In 2003, arthritis and other rheumatic conditions (AORC) cost the United States $127.8 billion ($80.8 billion in medical care expenditures and $47.0 billion in lost earnings).[13]

Costs associated with PsA are not as well studied as in other arthritic conditions, although they are believed to be just slightly lower than those in RA.[11] Indirect costs are believed to increase over time since as the disease progresses so does the loss of function and inability to work. Based on 1997 estimates for psoriasis and PsA, annual direct costs are approximately $650 million.[14] Of these costs, hospitalizations accounted for $31 million, outpatient physician visits for $87 million, photochemotherapy for $27 million, dermatologic prescription drugs for $148 million, and over-the-counter medications for $357 million.[14,15] These estimates do not include indirect costs, and the specific direct costs of PsA are not known.

Causes and Diagnosis

Psoriasis, a skin disease, affects 2.2 percent of U.S. adults; approximately 6 percent to 42 percent of patients with psoriasis develop PsA.[16] Approximately 520,000 adults in the United States have PsA.[17] PsA can develop at any age but most often appears between 30 and 50 years of age. Unlike RA, PsA appears to affect men slightly more often than women.

Clinically PsA is a multifaceted disease and may have skin presentations to help with its diagnosis. 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.[18] Several classification systems have been proposed for the diagnosis of PsA,[19] but which one best represents true PsA remains unclear. Table 1 presents the CASPAR (ClASsification of Psoriatic ARthritis) as an example of one classification.[20]

Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf.

Table 1. 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.[20]

Treatment of Psoriatic Arthritis

Treatment of patients with 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 oral corticosteroids include methylprednisolone, prednisone, and prednisolone.

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. When used in PsA, corticosteroids are most often given as a joint injection rather than orally. Although they can be very effective in controlling joint inflammation, oral steroids are generally avoided in PsA, because a flare of skin disease has been described when steroids are tapered or withdrawn.

Oral disease-modifying antirheumatic drugs (DMARDs). Oral 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 oral 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.

Oral 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 oral DMARDs covered in this review can be given orally, although methotrexate can also be injected (SQ or IM).

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new category of DMARDs that differ from oral 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 eight additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), rituximab (2006), certolizumab pegol (2008), golimumab (2009), and tocilizumab (2010). Of the nine agents, all are currently FDA approved for treating RA, but only adalimumab, etanercept, golimumab and infliximab are approved for treating PsA. Even though anakinra, abatacept, certolixumab pegol, rituximab, and tocilizumab are not FDA-approved for PsA, this report reviews the evidence for all of these agents.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, certolizumab pegol, etanercept, golimumab, 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, infliximab and golimumab 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. Golimumab is also a human monoclonal antibody that binds to TNF alpha with high affinity. 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. Certolizumab pegol is a pegylated humanized antibody fragment of tumor necrosis factor monoclonal antibody. The drug binds to the TNF alpha-receptor and blocks TNF alpha actvity. It only possesses the Fab fragment and lacks the Fc region. Hence, it does not induce antibody-dependant cell mediated apoptosis or toxicity.

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.

IL-6 is a naturally occurring cytokine involved in the regulation of immune responses and inflammation. Tocilizumab is a monoclonal antibody that inhibits interleukin-6 (IL-6) receptors, blocking the action of IL-6, and leading to a reduction in cytokine and inflammatory response.

Table 2 and Table 3 provide detailed information on agents that may be used in the treatment of PsA that we have included in this review. Table 2 documents names, manufacturers, and available dosage forms. Table 3 shows routes of administration, labeled uses, and usual (recommended) adult doses and frequency.

Table 2. Pharmaceutical treatments for psoriatic arthritis

Class Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
Corticosteroids			
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, 15, and 20 mg/5 ml Tabs—5 and 15 mg
Oral 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, 20mg/0.4ml prefilled syringe
Anakinra†	Kineret®	Amgen	Injectable—100 mg/0.67 ml syringe
Certolizumab Pegol†	Cimzia®	UCB	Injectable – 200 mg powder for reconstitution; 200mg/ml solution
Golimumab	Simponi®	Centocor Ortho Biotech	Injectable – 50 mg/0.5 ml syringe
Etanercept	Enbrel®	Amgen Wyeth Immunex	Injectable—50 mg/ml in 25 mg or 50 mg single use prefilled syringe
Infliximab	Remicade®	Centocor	Injectable—100 mg in a 20 ml vial
Rituximab†	Rituxan®	Biogen Idec / Genentech	Injectable—100 mg/10 ml and 500 mg/50 ml vial
Tocilizumab†	Actemra®, RoActemra®	Genentech / Roche	Injectable—80mg/4ml, 200mg/10ml, 400mg/20ml vial

DMARD, disease-modifying antirheumatic drug.
*Listed trade names are limited to commonly prescribed U.S. products when multiple are available.
† Not approved by FDA for use in PsA.

Table 3. Route and usual dose of treatments for psoriatic arthritis

Class	Generic Name	Route	Usual Adult Dose
Corticosteroids			
	Methylprednisolone	Injectable / Oral	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	Oral—Use lowest effective dose (5-60 mg/day)
	Prednisolone	Oral	Oral—Use lowest effective dose (5 to 7.5 mg/day)
Oral DMARDs			
	Hydroxychloroquine‡	Oral	Oral—200 to 400† mg/day in 1 or 2 divided doses
	Leflunomide‡	Oral	Oral—Loading dose of 100mg/day for 3 days followed by 10 to 20 mg/day in a single dose
	Methotrexate‡	Oral	IM, SQ, oral—7.5 to 20 mg/week in a single dose
	Sulfasalazine‡	Oral	Oral—500 to 3,000 mg/day in 2 to 4 divided doses
Biologic DMARDs			
	Abatacept‡	Injectable	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	SQ—40 mg every other week
	Anakinra‡	Injectable	SQ—100 mg/day; dose should be decreased to 100 mg every other day in renal insufficiency
	Certolizumab Pegol‡	Injectable	Initial dose of 400 mg, repeat dose 2 and 4 weeks after initial dose; Maintainance dose is 200 mg every other week (May consider maintainace dose of 400 every 4 weeks)
	Golimumab	Injectable	SQ - 50 mg once per month
	Etanercept	Injectable	SQ—25 mg twice weekly or 50 mg once weekly
	Infliximab	Injectable	IV—5 mg/kg, with or without MTX, at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter
	Rituximab‡	Injectable	IV—1,000 mg on days 1 and 15 in combination with MTX
	Tocilizumab‡	Injectable	IV—4mg/kg followed by an increase to 8mg/kg based on clinical response; given every 4 weeks with or without MTX

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
‡ Dosed according to the RA dosing recommendations

Treatment Strategies

The first line of treatment of PsA is non-steroidal anti-inflammatory drugs (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 oral DMARDs (e.g., MTX).

Historically, few PsA trials have been conducted, and management has been adapted from RA trial data. Since the introduction of biologic therapy, however, dedicated PsA trials have demonstrated efficacy in this distinct disease. Detailed and comparative examination of the efficacy, effectiveness, and harms of treatments for PsA is needed.

Scope and Key Questions

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

- KQ1: For patients with psoriatic arthritis, do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission?
- KQ2: For patients with psoriatic arthritis, do drug therapies differ in their ability to improve patient reported symptoms, functional capacity or quality of life?
- KQ3: For patients with psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?
- KQ4: What are the comparative benefits and harms of drug therapies for 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 4. 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 (for PsA or RA) are not in our report.

Table 4. 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 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 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 PsA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100

KQ, key question; N, number; PsA, psoriatic arthritis; RCT, randomized controlled trial.

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 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 our title/abstract and full text review forms along with our abstraction form; Appendix D presents our full bibliography by database source; Appendix E contains excluded studies; Appendix F contains a list of studies included in the meta-analyses; Appendix G contains the evidence tables; Appendix H is our

quality rating forms; and Appendix I describes clinical assessment scales commonly used in arthritis trials.

Chapter 2. Methods

In this chapter, we document the procedures that the RTI International–University of North Carolina Evidence-based Practice Center (RTI–UNC EPC) used to develop this comparative effectiveness review (CER) on pharmacologic treatments for psoriatic arthritis. We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

This report is an update of a CER completed in 2007.[21] The topic of the original report and the 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-UNC EPC then refined the original questions, in consultation with AHRQ, the SRC, and the Technical Expert Panel (TEP) during multiple conference calls, into the key questions used for the original report. For this update, the key questions were again refined into the final set of key questions cited in the introduction. No substantive changes to the key questions were made for this update other than adding new medications that have been approved since the previous report. The protocol for the project was posted on the AHRQ website (http://www.effectivehealthcare.ahrq.gov/). The original report included both rheumatoid arthritis (RA) and psoriatic arthritis (PsA). When updating the material, the decision was made to divide into the material into two separate reports, one for RA and one for PsA. This report includes only the information related to patients with PsA. This report is intended to replace the original report; it includes the information from the original report as well as the new information we identified.

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 conducted this review at the same time as a review on rheumatoid arthritis; that is, we conducted the literature searches and review processes in parallel, shown 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 (psoriatic arthritis [PsA] and rheumatoid arthritis [RA]), drug interactions, and adverse events with a list of included medications. The medications we included were the following: corticosteroids (methylprednisolone, prednisone, and prednisolone), four oral disease-modifying antirheumatic drugs (DMARDs) (methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and nine biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab). We limited the electronic searches to

Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf.

"human" and "English language." For the original report, sources were searched from 1980 to September 2006. For this update, sources were searched from June 2006 to March 2010. We overlapped the update search with the original search to account for delays in indexing. We used the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We manually searched reference lists of pertinent review articles and letters to the editor to supplement searches for the original report. We used Scopus™ abstract and citation database to supplement searches for this update. We imported all citations into an electronic database (EndNote X.0.2). 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). The SRC also searched the following for potentially relevant unpublished and ongoing literature: FDA website, Health Canada, Authorized Medicines for EU, ClinicalTrial.gov, Current Controlled Trials, Clinical Study Results, WHO Clinical Trials, Conference Papers Index, Scopus, NIH RePORTER, HSRPROJ, Hayes, Inc. Health Technology Assessment, and the New York Academy of Medicine's Grey Literature Index.

Study Selection

We developed eligibility (inclusion and exclusion) criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons as described in Table 4 in the introduction. Two individuals 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.

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 were eligible for inclusion. For harms (i.e., evidence pertaining to tolerability, adverse effects, and adverse events), we examined data from both experimental and prospective and retrospective observational studies. We included RCTs (no sample size limit) and observational studies (with sample sizes ≥ 100 patients), lasting at least 3 months, and that reported an outcome of interest.

We reviewed studies that reported health outcomes for efficacy or effectiveness. For example, these included 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 systematic reviews and meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality. We did not abstract individual studies if they had been used in a systematic review or meta-analysis of good quality; studies in this group that met eligibility criteria are cited in Appendix F. However, we reviewed them to determine whether any other outcomes of interest were reported. Appendix E

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. A senior reviewer read each abstracted article and evaluated the completeness of the data abstraction.

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 4.0, Mobius Analytics™. Evidence tables containing all abstracted data of included studies are presented in Appendix G.

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)[22] and the National Health Service Centre for Reviews and Dissemination.[23] Elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, use of intention to treat (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 a low risk of bias and results are considered to be valid. A "fair" study is susceptible to some risk of 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 risk of bias (stemming from, e.g., serious errors in design, analysis reporting a large amount 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.[24] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis. To assess the quality of systematic reviews and meta-analyses, we assessed the following: whether the review was based on a clear question, clear reporting of inclusion criteria, methods used for identifying literature (the search strategy), whether two reviewers independently reviewed publications to determine eligibility, whether authors used a standard method of critical appraisal (or quality rating or validity assessment), assessment of heterogeneity, assessment of publication bias, and statistical analysis. Systematic reviews were categorized as good when all criteria were met.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. Appendix H 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. 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 risk of bias) in one or more categories were rated poor quality and excluded from our analyses. Poor-quality studies and reasons for that rating are presented in Appendix I.

Applicability Assessment

Using the parameters for evaluation on guidance provided by AHRQ's Methods Guide for Comparative Effectiveness Reviews,[25] we evaluated the applicability of the included studies. Applicability is similar to generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of follow-up, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out in Chapter 1, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of Evidence

We evaluated the strength of evidence based on methods guidance for the EPC program.[25,26] Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains: risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.[26] We judged good quality studies to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low degree of uncertainty. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.[26]

We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 5.

Table 5. Strength of evidence grades and their definitions

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

Throughout this CER we synthesized the literature qualitatively.

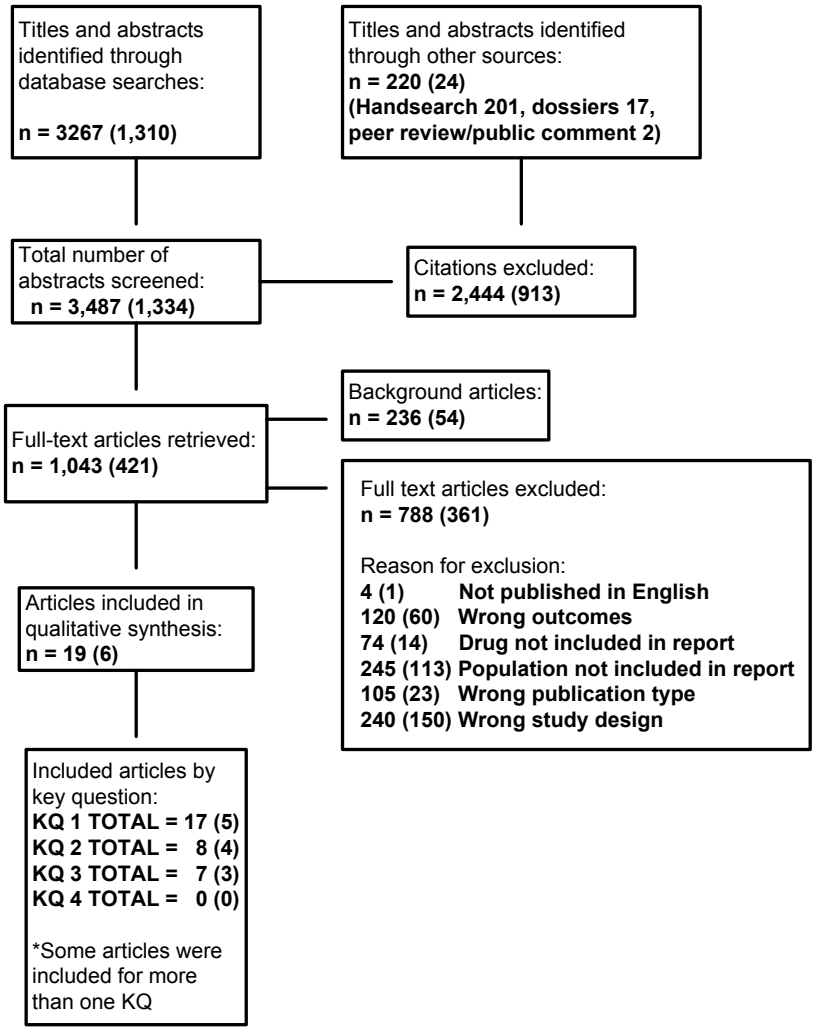
Peer Review

This CER underwent external peer review from individuals who were experts in rheumatology and from various stakeholder and user communities (listed in Appendix A [to be completed for final report]). The SRC oversaw the peer review process. 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 (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.

Chapter 3. Results

We identified 3,487 new citations from our searches (Appendix B). Figure 1 documents the results of the literature search. Working from 1,043 articles retrieved for full review, we retrieved 236 for background and excluded 788 at this stage (Appendix D). We included 19 published articles reporting on 12 studies: 0 head-to-head randomized controlled trials (RCTs), 0 head-to-head nonrandomized controlled trial, 9 placebo-controlled trials, 2 meta-analyses or systematic reviews, and 1 observational study. Our findings include studies rated good or fair for internal validity, unless a particular study rated poor provides some unique information that we judged to be of interest. 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 G.

Figure 1. Disposition of Articles (PRISMA figure)*



*The first number listed includes all references identified in both the original and update reports.
The number in parentheses indicates references identified in the update report only.

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

Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf.

We included articles based on eligibility criteria or methodological criteria (quality rating) as explained in Chapter 2.

Of the 12 included studies, 6 (50 percent) were supported by pharmaceutical companies; 4 (33 percent) were funded by governmental or independent funds; and 2 (17 percent) were supported by a combination of pharmaceutical and government funding.

This chapter is organized by key question. We then present findings in order by class of drugs and types of drugs as appropriate to the particular key question. Generally, the chapter is organized using the following categories: oral disease-modifying antirheumatic drug (DMARD) vs. placebo, biologic DMARD vs. placebo, oral DMARD vs. oral DMARD, biologic DMARD vs. biologic DMARD, biologic DMARD vs. oral DMARD, biologic DMARD + oral DMARD vs. biologic DMARD, and biologic DMARD + oral DMARD vs. oral DMARD.(see Table 3 in the introduction).

Across all key questions, we have included head-to-head studies, observational studies, and systematic reviews. When comparative evidence is available, we discuss it before presenting placebo-controlled trials.

Table 6 gives the numbers of trials or studies for drug class comparisons reported only from *head-to-head trials or studies;* when some groupings have important subcomparisons, we note these. We do not, however, offer an exhaustive list of all *possible* comparisons among corticosteroids, oral 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 6. Number of head-to-head studies by drug comparison for psoriatic arthritis*

Drug Comparison	Number of Trials or Studies; Quality Rating
Oral DMARDs vs. placebo	1good, 2 fair
Biologic DMARDs vs. placebo	2 good, 6 fair
Oral DMARDs vs. Oral DMARDs	0
Biologic DMARDs vs. biologic DMARDs	0
Biologic DMARDs vs. oral DMARDs	0
Biologic DMARDs + oral DMARDs vs. biologic DMARDs	1fair
Biologic DMARDs + oral DMARDs vs. oral DMARDs	0

DMARD, disease modifying anti-rheumatic drug; vs., versus.

Table 7 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 7. Disease activity, radiographic progression, functional capacity, and quality-of-life measures

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
DLQI	Dermatology Life Quality Index	0 to 30	Decrease
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase
EULAR response	European League Against Rheumatism response	N/A	N/A
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
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
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

* These key scales are defined in Appendix I.

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

This key question concerned three main topics. Specifically, "for patients with psoriatic arthritis, do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission?" Strength of evidence is presented in Table 8. Tables 9 and 10 provide selected study-specific information on outcomes, broken out by primary outcomes and by radiologic outcomes in Tables 11 and 12. Evidence Tables 1 (for head-to-head studies) and 2 (for systematic reviews and meta-analyses) in Appendix G* document details about all these studies.

Overview

A total of 9 RCTs, 0 nonrandomized controlled trials, 1 observational study, and 2 systematic reviews or meta-analyses examined symptom response, radiographic joint damage, and

* Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf.

Table 8. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. placebo						
Methotrexate vs. placebo 1 RCT; N = 37	Medium 1 RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement with physician assessment of disease activity than placebo	Low
Sulfasalazine vs. placebo 1 systematic review (including 6 RCTs); N = 564	Low 1 Systematic review/Good	Inconsistent	Direct	Precise	Greater improvement in disease activity with sulfasalazine than placebo	Moderate
Leflunomide vs. placebo 1 RCT; N = 190	Medium 1 RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in disease activity with leflunomide than placebo	Low
Biologic DMARD vs. placebo						
Adalimumab vs. placebo 2 RCTs; N =415	Medium 2 RCT/Fair	Consistent	Direct	Precise	Greater improvement in disease activity with adalimumab than placebo	Moderate
	Medium 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for adalimumab than placebo	Low
Etanercept vs. placebo 1 systematic review, 2 RCTs; N = 634	Low 1Systematic review/Good; 2 RCTs /Fair	Consistent	Direct	Precise	Greater improvement in disease activity with etanercept than placebo	Moderate
	Low 1RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for adalimumab than placebo	Low
Golimumab vs. placebo 1 RCT; N =405	Low 1 RCT/Good	Unknown, single study	Direct	Precise	Greater improvement in disease activity with golimumab than placebo	Low
Infliximab vs. placebo 1 systematic review, 2 RCTs; N =675	Low Systematic review/Good; 2 RCTs/Fair	Consistent	Direct	Precise	Greater improvement in disease activity with infliximab than placebo	Low
	Low 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for infliximab than placebo	Low
Oral DMARD vs. Oral DMARD						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs vs. Biologic DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; INF, infliximab; MTX, methotrexate; N, number; n/a, not applicable; RCT, randomized controlled trial; TNF, tumor necrosis factor; vs., versus.

Table 8. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence

Biologic DMARDs vs. Oral DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs						
Anti-TNF(ADA, ETN or INF) + MTX vs. Anti-TNF 1 cohort study; N = 261	Medium 1Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in disease activity	Low
Biologic DMARDs + Oral DMARDs vs. Oral DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient

Table 9. Disease activity of oral DMARDs vs. placebo

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Oral DMARDs vs. Placebo					
Jones et al., 2000[27]	Systematic review and meta-analysis 1,022	Active PsA; concomitant MTX NR	SSZ vs. placebo (6 RCTs)	Change in pooled index: SSZ 0.38 units (95% CI, 0.21-0.54)	Good
Willkens et al.,1984[28]	RCT 37 12 weeks	Active PsA; MTX naive	MTX (7.5mg-15mg/week vs. placebo	Median change in physician assessment of disease severity: MTX, 1 vs. placebo, 0 (P = 0.001)	Fair
Kaltwasser et al., 2004[29,30]	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

CI, confidence interval; DMARD, disease-modifying antirheumatic drug; LEF, leflunomide; mg, milligram; MTX, methotrexate; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Scale; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 10. Disease activity in biologic DMARD vs. placebo

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Adalimumab vs. Placebo					
*Genovese et al., 2007[31]	RCT 102 12 weeks	Active PsA; Failed at least one DMARD; concomitant MTX 46%	ADA (40mg every other week) vs. placebo	ACR 20 at week 12: ADA 39% vs. placebo 16% (*P* = 0.012)	Fair
Mease et al., 2005 ADEPT Trial[32]	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
Etanercept vs. Placebo					
Woolacott et al., 2006[33]	Systematic review and meta-analysis 369	Adults with PsA; concomitant MTX 46% to 56%	ETN (25 mg twice a week) vs. placebo (2 studies)	ACR 20 at week 12: ETN 65% vs. placebo NR (RR, 4.19 [95% CI, 2.74-6.42]	Good
Mease et al., 2000[34]	RCT 60 12 weeks	Active PsA; failed at least one DMARD; concomitant MTX use 47%	ETN (25 mg twice a week) vs. placebo	PsARC at week 12: ETN 87% vs. placebo 23% (*P* < 0.0001)	Fair
Mease et al., 2004[35]	RCT 205 24 weeks (with additional 48 weeks open-label)	Active PsA; failed at least one DMARD; concomitant MTX 47%	ETN (25 mg twice a week) vs. placebo	ACR 20 at week 24: ETN 59% vs. placebo 15% (*P* < 0.001)	Fair
Golimumab vs. Placebo					
*Kavanaugh., 2009[36]	RCT 405 14 weeks	Active PsA; failed at least one oral DMARD; concomitant MTX 35%	GOL (50mg every 4 weeks), GOL (100mg every 4 weeks) vs. placebo	ACR20 at week 14: GOL 50mg 51%, GOL 100mg 45%, placebo 9% (*P* < 0.001)	Good
Infliximab vs. Placebo					
Woolacott et al., 2006[33]	Systematic review and meta-analysis 369	Adults with PsA; concomitant MTX 46% to 56%	INF (5 mg/kg) vs. placebo (one study)	ACR 20 at week 14-16: INF 62% vs. placebo NR (RR, 5.75; 95% CI, 3.55-9.30)	Good
Antoni et al., 2005 IMPACT Study[37,38]	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[39,40]	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

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; ETN, Etanercept; GOL, golilumab; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, infliximab; kg, kilogram; mg, milligram; MTX, methotrexate; NR, not reported; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Scale; RCT, randomized controlled trial; RR, relative risk; vs., versus.

remission. Details are found in Evidence Tables 1 and 2, Appendix G. Tables 9 and 10 provide information on comparisons made, symptom response, and quality ratings. Tables 11 and 12 provide information on radiographic joint damage. The main drug classes compared include oral DMARDs, biologic DMARDs (also referred to simply as biologics), and combined strategies. Overall strength of evidence is listed in Table 8.

Table 11. Radiographic joint damage in biologic DMARD vs. placebo

Study	Study Design N Duration	Population with Early PsA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab vs. Placebo				
*Mease et al., 2005 ADEPT Trial[32]	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)
Infliximab vs. Placebo				
*Vander Heijde et al., 2007 IMPACT2 Trial[41]	RCT 200 24 weeks	No	INF 5mg/kg at 0,2,6 then every 8 weeks after	Mean change in Total Sharp/van der Heijde score at week 24: ADA -0.70 +/- 2.53 vs. placebo 0.82 +/- 2.62 (*P* < 0.001)
Etanercept vs. Placebo				
Mease et al., 2004[42]	RCT 205 72 weeks (24 blinded, 48 open-label)	No	ETN (25 mg twice a week) vs. placebo	Mean annualized rate of change over 1 year of treatment in modified Sharp score: ETN -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; ETN, Etanercept; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, infliximab; kg, kilogram; mg, milligram.

Table 12. Disease activity of Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results of Primary Outcome Measure	Quality Rating
Anti-TNF plus MTX vs. Anti-TNF					
*Kristensen et al., 2008[43]	Cohort 261 12 months	Active PsA; anti-TNF naïve; concomitant MTX 62%	ADA (40mg every other week) or ETN (25mg twice a week) or INF (3mg/kg at 0,2,6 then every 8th week) + MTX (median-15mg/week) vs. monotherapy with ADA or ETN or INF	No difference in ant-TNF + MTX vs. anti-TNF only (Data NR)	Fair

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; INF, infliximab; kg, kilogram; mg, milligram; MTX, methotrexate; NR, not reported; PsA, psoriatic arthritis; TNF, tumor necrosis factor; vs., versus.

Key Points

Oral DMARD vs. placebo. Evidence from one study found that parenteral high-dose MTX improves physician assessment of disease severity, compared with placebo. The strength of evidence is low.

One systematic review found that, compared with placebo, and sulfasalazine improved patient outcomes.[27,28] The strength of evidence is low.

Leflunomide patients had higher response rates and quality-of-life outcomes than those in the placebo arm.[29,30]

Biologic DMARD vs. placebo. The use of three biologics—adalimumab, etanercept, and infliximab—led to better outcomes than did placebo.[32,34,35,37-40,42]

Head to Head studies. We did not find any head-to-head controlled trials for any of the included drugs. One cohort study compared the combination of an anti-TNF (adalimumab, etanercept or infliximab) with MTX versus anti-TNF only and found no difference in treatment response.[43]The strength of evidence is low.

Psoriatic Arthritis: Detailed Analysis

Because of the paucity of head-to-head trials, we additionally reviewed placebo-controlled trials to summarize the general efficacy of oral and biologic DMARDs. This, however, does not provide evidence on the comparative efficacy and tolerability of treatments for PsA.

Oral DMARDs. We did not identify any studies meeting our inclusion/exclusion criteria that examined the use of corticosteroids in the treatment of PsA.

One systematic review examined the efficacy of oral DMARDs used in placebo-controlled trials.[27] 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. One multicenter 12-week RCT (N = 37),[28] included in the systematic review described above, compared MTX (weekly dose of 7.5 mg to 15 mg) with placebo. The study reported some improvement in psoriatic arthritis as measured by change in grip strength, morning stiffness, and patient assessment in the drug treatment group, but statistically significant improvement compared with placebo occurred only in physician assessment of disease severity ($P = 0.001$); there were no differences between groups in joint swelling or pain/tenderness. For psoriatic skin lesions showed no significant changes in scaling, induration, or erythema from entry appearance, but surface area involvement improved significantly compared with placebo ($P = 0.039$) in 14 of the MTX patients assessed (Table 9). The systematic review used this single study comparing MTX with placebo to calculate an overall improvement in the OMERACT index of 0.65 units (95% CI, 0.00-1.30).[27]

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).[27]

Leflunomide. One trial (two publications) evaluated the efficacy of leflunomide against placebo in 190 patients over 24 weeks;[29,30] 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 oral DMARDs as well as biologic agents and investigational drugs 28 days before baseline.

The leflunomide group had significantly greater improvements in measures of disease activity than the placebo group. These included response rates on a modified ACR 20 (36.3 vs. 20%; $P = 0.014$), the PsARC (achieved in 58.9% vs. 29.7%; $P = 0.0001$), and the PASI (17.4% vs. 7.8% reached threshold; $P = 0.048$).

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). 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.

Biologic DMARDs. Eight RCTs (eleven articles) and one systematic review examined the efficacy of biologics against placebo in treating patients with PsA.[31-35,37-40,42] Two trials were of adalimumab, two of etanercept, three of infliximab and one of golimumab. All trials allowed patients to continue an oral DMARD, usually MTX. The systematic review examined etanercept and infliximab vs. placebo.[33] All showed that the use of biologics led to significantly better outcomes than placebo.

Adalimumab. Two RCTs examined the use of adalimumab (40 mg every other week) in 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[32] or previous oral DMARD therapy.[31] Patients were allowed to continue current MTX therapy as long as the dose had been stable for 4 weeks. In the first study,[32] 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 oral 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 ($P = 0.001$). The second trial[31] randomized 102 patients for 12 weeks , and similarly found a higher percentage of patients meeting ACR 20 at week 12, than when compared to placebo (39% vs. 16%, $P = 0.012$).[31]

Etanercept. Two RCTs examined the efficacy of etanercept (25 mg twice weekly by subcutaneous injections) in a total of 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[34,35] 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);[34] the other (N = 205) was double-blinded for 24

weeks.[35] 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 ($P < 0.0001$).[34] The 24-week study 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).[35] 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; $P = 0.0001$).[42]

A 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 (placebo NR), with a pooled relative risk of 4.19 (95% CI, 2.74-6.42) compared to placebo.[33] The ACR 50 and ACR 70 criteria were achieved by 45 percent and 12 percent of those treated with etanercept, 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) compared to placebo (placebo NR).[33]

Golimumab. One 14 week RCT of 405 patients with active PsA compared golimumab (50mg ever 4week or 100mg every 4 weeks) with placebo.[36] At 14 weeks, all patients on either golimumab dose achieved a higher ACR 20 when compared with placebo (48% vs. 9%, $P < 0.001$). Significantly greater improvements were also noted for those treated with golimumab for 75% improvement in the PASI (40% in 50mg group, 58% in 100mg group and 3% in placebo; $P < 0.001$).

Infliximab. Two RCTs (3 articles) of infliximab compared with placebo included a total of 304 patients with active PsA who had not adequately responded to conventional DMARD therapies.[37,39,41] In both studies, patients were allowed to continue MTX therapy as long as the dose had been stable for 4 weeks before study entry. One RCT (N = 104) was double-blinded for 16 weeks.[37] The other RCT 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.[39] 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 subjects treated with infliximab than for those treated with placebo. In the shorter 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 ($P < 0.001$). Radiographic changes were also less at 24 weeks (sharp/van der Heijde (-0.70 +/- 2.53 vs. 0.82 +/-2.62, $P < 0.001$).[41]

A systematic review described above in the etanercept studies[33] pooled the 14 and 16-week data from these two infliximab studies;[37,39] the ACR 20 threshold for improvement was achieved by 62 percent of the etanercept groups (placebo NR), with a pooled relative risk of 5.75 (95% CI, 3.55-9.30) compared to placebo.[33] In addition, the PsARC was reached by almost 76 percent, with a pooled relative risk of 3.05 (95% CI, 2.29-4.08) compared to placebo (placebo NR).[33]

Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs. *Anti-TNF plus MTX vs. Anti-TNF.* One retrospective cohort (N = 261) of anti-TNF naive patients with active PsA in Sweden compared patients taking MTX concomitant with anti-TNF (adalimumab-40mg every other week, etanercept-25mg twice a week, or infliximab-3mg/kg at 0,2,6 and then every 8th week) versus anti-TNF alone.[43] Eligible patients had active PsA with high disease activity and/or unacceptably high steroid use. Over 12 months, there were no significant differences in EULAR good or EULAR overall between patients taking MTX with anti-TNF compared to anti-TNF only.

Key Question 2: Functional Capacity and Quality of Life

This question specifically examined the issue of whether, for patients with PsA, drug therapies differed in their ability to improve patient reported symptoms, functional capacity, or quality of life. Findings are organized as for KQ 1. Table 7 (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 PsA or other types of arthritis. 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 use health-related quality of life when referring to measures developed to assess quality of life for a specific condition or group of conditions, such as the Dermatology Life Quality Index (DLQI), a quality-of-life instrument for dermatologic diseases. We 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 often secondary outcomes in these studies; that is, studies were not all designed to detect a difference between groups for these types of outcomes.

Overview

A total of nine RCTS examined functional capacity or quality of life in patients being treated for psoriatic arthritis. Details are found in Evidence Table 3 and 4 in Appendix G. Table 13 provides information on comparisons made, quality-of-life outcomes, and quality ratings. We found no head-to-head studies. Evidence was limited to one study (two articles) comparing an oral DMARD with placebo[29,30] and eight studies comparing a biologic DMARD with placebo. Overall results and strength of evidence are described below in Key Points and in Table 13.

Table 13. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. placebo						
Leflunomide vs. placebo 1 RCT; N = 190	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with LEF than placebo	Low
Biologic DMARD vs. placebo						
Adalimumab vs. placebo 2 RCTs; N = 415	Medium RCTs/ 2 Fair	Consistent	Direct	Precise	Greater improvement in functional capacity with adalimumab	Moderate
		Inconsistent	Direct	Imprecise	For health-related quality of life, results tended to favor adalimumab	Low
Etanercept vs. placebo 2 RCTs; N = 265	Medium RCTs/2 Fair	Consistent	Direct	Precise	Greater improvement in functional capacity with etanercept	Moderate
Golimumab vs. placebo 1 RCT; N = 405	Low RCT/Good	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with golimumab	Low
Infliximab vs. placebo 2 RCTs; N = 304	Medium RCTs/2 Fair	Consistent	Direct	Precise	Greater improvement in functional capacity and quality of life with infliximab	Moderate
Oral DMARD vs. Oral DMARD						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs vs. Biologic DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs vs. Oral DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient
Biologic DMARDs + Oral DMARDs vs. Oral DMARDs						
No studies	n/a	n/a	n/a	n/a	n/a	Insufficient

Key Points

Conclusions are limited because no head-to-head studies were found for any of the included medications. The available studies are all placebo-controlled studies evaluating the efficacy of one oral DMARD or one biologic DMARD.

Oral DMARD vs. placebo. Evidence from one study provides a low strength of evidence that patients treated with leflunomide had better functional and quality-of-life outcomes than those treated with placebo.

Biologic DMARD vs. placebo. Evidence from seven studies comparing either adalimumab (2 studies), etanercept (2 studies), golimumab (1 study), or infliximab (2 studies) with placebo provides a low to moderate strength of evidence for the efficacy of each of these biologic DMARDs for improving functional capacity and quality of life.

Detailed Analysis

Oral DMARDs. We did not identify any studies that examined the use of corticosteroids in the treatment of PsA or any head-to-head studies of oral DMARDs reporting outcomes relevant for this section. One study met inclusion criteria for this section. It compared leflunomide with placebo (Table 14).[29,30]

Table 14. Oral DMARD vs. placebo studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Leflunomide vs. Placebo					
Kaltwasser et al., 2004[29,30]	RCT 190 24 weeks	Active PsA; failed at least 1 DMARD	LEF (100 mg/day 3 days then 20 mg/day) vs. placebo	Mean change in HAQ: -0.19 vs. -0.05; *P* = 0.0267 Mean change in Dermatology Life Quality Index (DLQI): -1.9 vs. -0.2; *P* = 0.0173	Fair

Leflunomide. One 24-week trial (two publications) evaluated the efficacy of leflunomide in PsA patients.[29,30] The study randomized 190 subjects to leflunomide or placebo; 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 DMARD naïve were required to discontinue all oral DMARDs, biologic DMARDs, and investigational drugs 28 days before baseline measures were done. At 24 weeks, subjects treated with leflunomide had greater improvement in functional capacity (mean change in HAQ scores: -0.19 vs. -0.05; $P = 0.0267$) and quality of life (mean change in DLQI: -1.9 vs. -0.2; $P = 0.0173$) than those treated with placebo.

Biologic DMARDs. We did not identify any head-to-head studies of biologic DMARDs reporting outcomes relevant for this section. Seven studies (12 articles) compared one biologic DMARD with placebo (Table 15).[31,32,34-40,42,44,45]

Table 15. Biologic DMARD vs. placebo studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab vs. Placebo					
*Genovese et al., 2007[31]	RCT 102 12 weeks	Active PsA; failed at least one DMARD	ADA (40 mg every other week) vs. placebo	Mean change in HAQ (12 wks): ADA -0.3 vs. placebo -0.1; *P* = 0.010 Mean change in SF-36 PCS (12 wks): ADA 5.7 vs. placebo 2.8, *P* = 0.082 Mean change in SF- 36 MCS (12 wks): ADA 1.1 vs. placebo -0.6, *P* = 0.242 Mean change in Dermatology Life Quality Index (DLQI) (12 wks): -3.4 vs. -1.7 (*P* = 0.171)	Fair
Mease et al., 2005;[32] Gladman et al., 2007[44] ADEPT	RCT 313 24 weeks	Active PsA; failed at least one DMARD	ADA (40 mg every other week) vs. placebo 51% received concomitant MTX	Mean change in HAQ-DI at 24 weeks: ADA -0.4 vs. Placebo -0.1, *P* < 0.001 Mean change in SF-36 PCS at 24 weeks: ADA 9.3 vs. placebo 1.4, *P* < 0.001 Mean change in SF-36 MCS at 24 weeks: ADA 1.8 vs. 0.6, *P* = 0.288 Mean change in Dermatology Life Quality Index (DLQI) at 24 weeks: -6.1 vs. -0.7 (*P* < 0.001)	Fair
Etanercept vs. Placebo					
Mease et al., 2000[34]	RCT 60 12 weeks	Active PsA; failed at least one DMARD	ETN (25 mg twice a week) vs. placebo 51% received concomitant MTX	Improvement in HAQ from baseline ETN 83% vs. placebo 3% (*P* < 0.0001)	Fair
Mease et al., 2004[35,42]	RCT 205 72 weeks (24 blinded, 48 open-label)	Active PsA; failed at least one DMARD	ETN (25 mg twice a week) vs. placebo 41% received concomitant MTX	Improvement in HAQ from baseline ETN 54% vs. placebo 6% (*P* < 0.0001)	Fair
Golimumab vs. Placebo					
*Kavanaugh et al., 2009[36] GO-REVEAL	RCT 405 14 weeks	Treatment resistant active PsA despite therapy with DMARDs or NSAIDs; multinational	GOL (50 mg every 4 wks) vs. GOL (100 mg every 4 wks) vs. placebo At week 16, pts with < 10% improvement from baseline in both SJC and TJC entered early escape = dose escalation from	Mean change in HAQ at 14 weeks was not reported. Mean change at 24 weeks, including the early escape phase: GOL (50 mg) 0.33 vs. GOL (100 mg) 0.39 vs. -0.01 placebo, *P* < 0.001for either GOL group vs. placebo Mean change in SF-36 PCS at 14 weeks: GOL (50 mg) 6.53 vs. GOL (100 mg) 7.85 vs. 0.63 placebo, *P* < 0.001 for	Good

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

Table 15. Biologic DMARD vs. placebo studies: functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
			placebo to 50 mg GOL every 4 wks or from 50 mg GOL to 100 mg GOL every 4 wks	either GOL group vs. placebo Mean change in SF-36 MCS: NR	
Infliximab vs. Placebo					
Antoni et al., 2005[37,38] 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	Mean % improvement in HAQ at week 16: 49.8 vs. -1.6 ; P < 0.001	Fair
Antoni et al., 2005[39,40,45] 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	Mean % improvement in HAQ, at week 14: 48.6% vs. -18.4%; *P* < 0.001 SF-36 PCS; change from baseline: • to week 14: 9.1 vs. 1.1; *P* < 0.001 • to week 24: 7.7 vs. 1.3; *P* < 0.001 SF36 MCS; change from baseline to week 14: 3.8 vs. -1.2; *P* = 0.001 to week 24: 3.9 vs. 0.4; *P* = 0.047 Improvement in employment status from unemployed at baseline to employed at Week 14: 11.5% vs. 0%; *P* = 0.084 from part-time to fulltime employment: 30.0% vs. 10.0%; *P* = 0.582 No significant difference in percentage of missed workdays in past 4 weeks at 14 weeks: 13% vs. 3.7%; *P* = 0.138	Fair

Adalimumab. Two RCTs compared adalimumab (40 mg every other week) with placebo.[31,32,44] In both studies, patients were allowed to continue current MTX therapy as long as the dose had been stable. Both enrolled subjects who had an inadequate response or intolerance to previous treatments. Both studies found greater improvement in functional capacity for subjects treated with adalimumab than those treated with placebo. For health-related quality of life, several outcome measures were reported in both studies; results for each measure either statistically significantly favored adalimumab or were not statistically significantly different but point estimates favored adalimumab.

The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) 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.[32,44] 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. Subjects treated with adalimumab had greater improvements in functional capacity (mean change in HAQ: -0.4 vs. -0.1; $P < 0.001$) and two quality of life measures (mean change in SF-36 PCS: 9.3 vs. 1.4, $P < 0.001$; mean change in DLQI: -6.1 vs. -0.7, $P < 0.001$) than those who received placebo.

The other RCTs enrolled 102 subjects with PsA and at least 3 swollen joints and three tender joints who were receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response.[31] Subjects treated with adalimumab had greater improvements in functional capacity (mean change in HAQ: -0.3 vs. -0.1; $P = 0.01$) than those who received placebo. Differences between groups for quality of life outcome measures were not statistically significantly different between groups, but there was a trend toward greater improvement in subjects treated with adalimumab.

Etanercept. Two studies that examined the efficacy of etanercept included a total of 265 patients with active PsA who were not adequately responding to conventional DMARD therapies.[34,35,42] 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);[34] the other was double-blinded for 24 weeks (N = 205).[35] Both studies had the same dosing regimen of 25 mg of etanercept twice weekly by subcutaneous injections. Functional capacity improved significantly in both studies. Mean improvements from baseline in HAQ 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 and 6 percent, respectively ($P < 0.0001$).

Golimumab. The 'Golimumab-A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody' (GO-REVEAL) study[36] randomized 405 subjects with active PsA to golimumab 50mg every 4weeks, golimumab 100mg every 4 weeks or placebo.[36] The subjects maintained the treatment to which they were randomized for the first 14 weeks; at week 16, subjects with less than 10 percent improvement from baseline in both swollen joint count and tender joint count entered early escape, with dose escalation from placebo to 50 mg golimumab (every 4 weeks) or from 50 mg to 100 mg golimumab (every 4 weeks). Subjects in both golimumab groups had greater improvements in functional capacity than those in the placebo group (mean change in HAQ at 24 weeks, for 50 mg vs. 100mg vs. placebo: 0.33 vs. 0.39 vs. -0.01, $P < 0.001$). Subjects in both golimumab groups had greater improvements in quality of life as measured by the SF-36 physical component score (PCS) than those in the placebo group (mean change from baseline in SF-36 PCS at 14 weeks: 6.53 vs. 7.85 vs. 0.63, $P < 0.001$).

Infliximab. Two studies, 'Infliximab Multinational Psoriatic Arthritis Controlled Trial' (IMPACT) and IMPACT 2, randomized a total of 304 patients with active PsA who were not adequately responding to conventional DMARD therapies to infliximab or placebo.[37,39] 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);[37] 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.[39] 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. Subjects treated with infliximab had significantly greater improvement in functional capacity than those treated with placebo in both studies. In the IMPACT study, the mean percent improvement on the HAQ was 49.8 percent for subjects treated with infliximab

and -1.6 percent for subjects treated with placebo ($P < 0.001$). In IMPACT 2, subjects treated with infliximab had greater improvement in functional capacity and quality of life than those treated with placebo. At 14 weeks the mean percent improvement on the HAQ was 48.6 percent for subjects treated with infliximab and -18.4 percent for subjects treated with placebo ($P < 0.001$). Increases in the physical and mental component summary (PCS and MCS) scores and all eight scales of the SF-36 in the infliximab group were greater than those in the placebo group at week 14 ($P \leq 0.001$). These benefits were sustained through week 24. Compared with the placebo group, higher proportions of patients in the infliximab group improved employment status from unemployed at baseline to employed at Week 14 (11.5% vs. 0%; $P = 0.084$) and from part-time to fulltime employment (30.0% vs. 10.0%; $P = 0.582$).

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

Overview

Oral DMARDs. The use of leflunomide vs. placebo can increase the likelihood of diarrhea. It can also lead to clinically significant increases in alanine aminotransferase. The rates of adherence are similar for leflunomide and placebo. The strength of evidence is insufficient.

Biologic DMARDs. Seven placebo-controlled studies of biologics, including two each on adalimumab, etanercept, and infliximab, and one on golimumab, provide indirect evidence on harms. When the individual drugs were compared with placebo, the authors reported few differences in the rate of adverse events. Exceptions to this were increased rates of injection site reactions with the use of adalimumab and etanercept and increased rates of infections and malignancies with golimumab. Adalimumab-treated patients had fewer reports of aggravated psoriasis compared with placebo-treated paitents. Based on data from a prospective cohort study, etanercept had a statistically significantly lower risk of discontinuation due to adverse events than infliximab. No evidence addressed adherence. The strength of evidence is insufficient.

Key Points

Very limited information is available for harms, tolerability, adverse events, and adherence for patients with psoriatic arthritis. The available studies include mostly placebo-controlled studies; there are no head-to-head studies. One relatively small prospective cohort (register) provides comparative data. The strength of evidence is insufficient (Table 16).

Table 16. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARD vs. Biologic DMARD						
ADA vs. ETN vs. INF 1 observational N = 261	Medium cohort/ fair	Unknown, single study	Direct	Imprecise	ETN had lower risk of withdrawals due to AEs than INF. Concomitant MTX lowered withdrawals.	Insufficient
Oral DMARD vs. placebo						
LEF vs. placebo 1 RCT N = 143	Medium RCT/ fair	Unknown, single study	Indirect	Imprecise	Higher rates of diarrhea and increased ALT levels for LEF vs. placebo	Insufficient
Biologic DMARD vs. placebo						
ADA vs. placebo 2 RCT N = 415	Medium RCT/2 fair	Consistent	Indirect	Imprecise	Infusion reactions with ADA; worsened psoriasis with placebo	Insufficient
ETN vs. placebo 2 RCT N = 265	Medium RCT/2 fair	Consistent	Indirect	Imprecise	No difference in adverse events except for more ISRs with ETN	Insufficient
GOL vs. placebo 1 RCT N = 405	Medium RCT/1fair	Unknown, single study	Indirect	Imprecise	More infections and malignancies GOL than placebo	Insufficient
INF vs. placebo 2 RCT N = 304	Medium RCT/2 fair	Consistent	Indirect	Imprecise	No differences in adverse events for INF and placebo	Insufficient

ADA, adalimumab; AE, adverse event; ALT, alanine aminotransferase; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; GOL, golilumab; INF, infliximiab; ISR, injection site reaction; LEF, leflunomide; MTX, methotrexate; N, number; RCT, randomized controlled trial; vs., versus.

Psoriatic Arthritis: Detailed Analysis

A total of eight RCTS and one observational study compared tolerability, harms, and adherence. Details are found in Evidence Tables 5 and 6 in Appendix G.

Table 17 provides information on studies primarily examining comparative efficacy and safety. The drugs examined in RCTs included one oral DMARD (leflunomide) and four biologic DMARDs (adalimumab, etanercept, golimumab, or infliximab), all in comparison with placebo. A prospective cohort study included patients on adalimumab, etanercept, and infliximab (with or without MTX), and all of these groups were compared with each other.

Table 17. Studies assessing adverse events, discontinuation rates, and adherence in psoriatic arthritis

Study	Study Design Duration	Study Population	Drug	Results	Quality Rating
		Oral DMARDs			
Kaltwasser et al., 2004[29]	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). Compliance of ≥ 80% to < 110%: LEF, 85%; placebo, 78%.	Fair
		Biologic DMARDs			
Antoni et al., 2005[37] 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[39] 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
*Genovese et al., 2007[31]	RCT 102 12 weeks	Patients with active PsA despite synthetic DMARD treatment	ADA	More adverse events for placebo (79.6%) than ADA (52.9%); *P* ≤ 0.01. Aggravation of psoriasis more common for placebo (16.3%) than ADA (3.9%); *P* ≤ 0.05	Fair
*Kavanaugh et al., 2009[36] GO-REVEAL	RCT 405 24 weeks	Patients with active PsA despite synthetic DMARD or NSAID treatment	GOL	Infections and malignancies more common with GOL than placebo (for all, *P* = NR)	Fair
*Kristensen et al., 2008[43]	Prospective cohort 261 12 months	Patients with active PsA, Biologic DMARD naïve	ADA, ETN, INF, MTX	Concomitant MTX associated with significantly fewer withdrawals due to adverse events (HR, 0.25; 95%CI, 0.11-0.52; P< 0.01). Compared with INF, ETN had lower risk of withdrawals due to adverse events (HR, 0.30; 95%CI, 0.11-0.80, P = 0.02)	Fair
Mease et al., 2000[34]	RCT 60 12 weeks	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETN	No statistically significant differences in adverse events except for ISRs. ETN 20% vs. placebo 3% (P = NS)	Fair
Mease et al., 2005[46]	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

* Studies added during update; ADA, adalimumab; ALT, alanine aminotransferase; ANK, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GOL, golimumab; INF, infliximab; ISR, injection site reaction; LEF, lefluonomide; MTX, methotrexate; NR, not reported; NS, not significant; NSAID, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; RCT, randomized controlled trial.

Table 17. Studies assessing adverse events, discontinuation rates, and adherence in psoriatic arthritis (continued)

Study	Study Design Duration	Study Population	Drug	Results	Quality Rating
Mease et al., 2006[42]	RCT 205 72 weeks (24 blinded, 48 open-label)	Patients with active PsA despite background biologic or synthetic DMARD treatment	ETN	No statistically significant differences in adverse events except for ISRs. ETN 20% vs. placebo 9% ($P \leq 0.001$)	Fair

Oral 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.[29]

Specific adverse events. This same trial showed some differences in specific adverse events, in particular diarrhea (leflunomide, 24%; placebo, 13%; P = NR) and increases in alanine aminotransferase (leflunomide, 13%; placebo, 5%; P = NR).[29]

Adherence. This same trial also reported adherence in the treatment of PsA.[29] Over 24-weeks 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.

Biologic DMARDs. *Overall tolerability.* Based on a Swedish prospective cohort study that included patients treated with adalimumab, etanercept, and infliximab, severe adverse events occurred in 5-6% of patients per year.[43] Two anaphylactic infusion reactions occurred, both with infliximab. Other adverse event rates were similar. Concomitant MTX was associated with significantly fewer withdrawals due to adverse events (HR, 0.25; 95% CI, 0.11-0.52; $P < 0.01$). Compared with infliximab, etanercept had a lower risk of withdrawal due to advese events (HR, 0.30; 95% CI, 0.11-0.80; $P = 0.02$).[43] In efficacy trials for patients with PsA, overall tolerability profiles appeared to be similar for biologic DMARDs (adalimumab, etanercept, infliximab) and placebo.[29,31,32,34,36,37,39,42] Injection site reactions, dizziness, headaches, and upper respiratory tract infections were the most commonly reported individual adverse events. Of these, injection site reactions appeared 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%) than the placebo group (3.1%; P = NR).[32] Two other studies comparing etanercept to placebo also showed higher rates of injection site reactions in the active arms.[34,42] 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).[34] In an RCT with 205 patients, however, the difference between these two groups was statistically different.[42] 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 ($P < 0.001$).

Most studies reported no statistically significant differences in adverse events between active treatment and placebo. In the only RCT of golimumab, more infections and malignancies were reported in golimumab-treated patients than placebo-treated patients (P = NR).[36]

Adherence. No study specifically addressed adherence with biologic DMARDs in the treatment of PsA.

Key Question 4: Benefits and Harms for Selected Populations

No studies met our inclusion criteria for this key question.

Chapter 4. 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 psoriatic arthritis (PsA). These include corticosteroids, oral 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 18 summarizes our findings and the strength of evidence for the key questions (KQs) addressed by this report. In brief, the KQs involved benefits of these drugs, alone or in combination, in terms of slowing or limiting the progression of radiographic joint damage, and maintaining remission (KQ 1); reducing patient-reported symptoms, 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).

Table 18. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Oral DMARDs		
Methotrexate	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, methotrexate resulted in greater improvement in physician assessment of disease activity than placebo INSUFFICIENT	
Sulfasalazine	No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo in one fair study, sulfasalazine improved disease activity INSUFFICIENT	
Leflunomide	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. INSUFFICIENT 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. INSUFFICIENT	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. INSUFFICIENT

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

Table 18. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Biologic DMARDs		
	The current evidence is limited to one cohort. Compared to anti-TNF monotherapy (ADA, ETN or INF), MTX plus anti-TNF monotherapy produce similar response rates. LOW No head-to-head evidence met inclusion criteria. Current evidence is limited to placebo-controlled trials. Compared with placebo, adalimumab, etanercept, golimumab and infliximab led to greater improvement in disease activity, functional capacity and health-related quality of life. INSUFFICIENT	Etanercept had a lower rate of withdrawals due to adverse events than infliximab in a prospective cohort study. LOW Additional evidence is limited to placebo-controlled efficacy trials. In these, 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; golimumab had more malignancies; and adalimumab had fewer events of aggravated psoriasis than placebo INSUFFICIENT

Data are quite limited for PsA patients, and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either oral or biologic DMARDs in this condition.

Key Findings

No head-to-head controlled trials meeting inclusion criteria exist for any drugs in this review for treating patients with PsA. One cohort study with low evidence indicated that the combination of an anti-TNF (adalimumab, etanercept, or infliximab) with MTX only was not different in treatment response[43] than anti-TNF only.

Parenteral high-dose MTX and sulfasalazine improved physician assessment of disease activity compared with placebo.[27] Additionally, patients taking leflunomide had higher response rates and quality of life outcomes than those taking placebo.[29,30] Similarly, patients taking sulfasalazine had greater improvement in disease activity than placebo.[27]

Evidence supports the general efficacy of adalimumab, etanercept, golimumab, and infliximab for the treatment of PsA.[31-40,42] 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, certolizumab, golimumab, etanercept, infliximab, rituximab, and tocilizumab 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 a relatively small prospective cohort study and 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 PsA.

- For this condition, the available evidence is limited to a cohort study (one study) and placebo-controlled trials (nine studies and two systematic reviews). The quality of studies on oral DMARDs is sparse and fraught with methodological issues.
- Head-to-head RCTs have to establish the comparative efficacy and safety of different treatment strategies with and without corticosteroids, oral 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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