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Effective Health Care

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

Executive Summary

Background

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

Treatment of patients with RA and PsA aims to control pain and inflammation and, ultimately, to slow the progression of joint

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destruction and disability. Available therapies for RA include corticosteroids; synthetic disease-modifying antirheumatic drugs, or DMARDs (hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine); and biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab). Three biologics (adalimumab, etanercept, and infliximab) are also classified as anti-tumor necrosis factor (anti-TNF) drugs.

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

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

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

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

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

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

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

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

Conclusions

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

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

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

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

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

Monotherapy vs. Monotherapy

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

For leflunomide vs. sulfasalazine, data are limited to one RCT with 2-year followup that reported that leflunomide resulted in a higher proportion of patients reaching ACR 20-percent improvement and ACR 50-percent improvement criteria and greater improvement in functional capacity (ACR 20: 82 percent vs. 60 percent, P < 0.01; ACR 50: 52 percent vs. 25 percent, P < 0.01; HAQ: -0.50 vs. -0.29, P < 0.03). Radiographic changes were not different for those treated with leflunomide and those treated with sulfasalazine.

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

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

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

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

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

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

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

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

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

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

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

Combination Therapy vs. Monotherapy

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

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

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

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

Combination studies involving two synthetic DMARDs, including sulfasalazine and methotrexate, vs. one DMARD showed no differences in withdrawal rates because of adverse events. Combination studies including prednisone with one or more DMARDs also had no differences in discontinuation rates between groups.

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

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

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

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

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

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

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

Combination Therapy Comparisons or Other Treatment Strategies

Evidence is insufficient to draw firm conclusions about whether one combination strategy is better than any other. Two RCTs reported more improved response rates at 2 years for the combination of sulfasalazine, methotrexate, and hydroxychloroquine than for one or two drugs in patients who had previously been on monotherapy. ACR 20 response rates were 78 percent

for triple therapy, as contrasted with 60 percent for methotrexate and hydroxychloroquine (P = 0.05) and 49 percent for methotrexate and sulfasalazine (P = 0.002). Groups did not differ in withdrawal rates.

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

Remaining Issues

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

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

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

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

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

Addendum

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

Rheumatoid Arthritis

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

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

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

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

Psoriatic Arthritis

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

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

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