

Systematic Review: Comparative Effectiveness and Harms of Disease-Modifying Medications for Rheumatoid Arthritis

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Background: The comparative effectiveness of rheumatoid arthritis therapies is uncertain.

Purpose: To compare the benefits and harms of disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis.

Data Sources: Records limited to the English language and studies of adults were identified by using MEDLINE, EMBASE, The Cochrane Library, and International Pharmaceutical Abstracts from 1980 to September 2007.

Study Selection: Two persons independently selected relevant head-to-head trials and prospective cohort studies with at least 100 participants and 12-week follow-up and relevant good- or fair-quality meta-analyses that compared benefits or harms of 11 drug therapies. For harms, they included retrospective cohort studies.

Data Extraction: Information on study design, interventions, outcomes, and quality were extracted according to a standard protocol.

Data Synthesis: Head-to-head trials ($n = 23$), mostly examining synthetic DMARDs, showed no clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab). Monotherapy with anti-tumor necrosis factor drugs resulted in better radiographic outcomes than did methotrexate but no important differences in

clinical outcomes (for example, 20%, 50%, or 70% improvement according to American College of Rheumatology response criteria). Various combinations of biological DMARDs plus methotrexate improved clinical response rates and functional outcomes more than monotherapy with either methotrexate or biological DMARDs. In patients whose monotherapy failed, combination therapy with synthetic DMARDs improved response rates. Numbers and types of short-term adverse events were similar for biological and synthetic DMARDs. The evidence was insufficient to draw conclusions about differences for rare but serious adverse events for biological DMARDs.

Limitation: Most studies were short-term efficacy trials conducted in selected populations with few comorbid conditions.

Conclusion: Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

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Rheumatoid arthritis is an autoimmune disease that affects more than 2 million adults in the United States. Disease onset generally occurs between 30 and 55 years of age, and women are affected more often than men. Disease hallmarks are inflammation of the synovium, progressive bone erosion, joint malalignment and destruction, and subsequent weakness of surrounding tissues and muscles. Presentations range from mild to severe, although the typical patient has a progressive course leading to functional limitations.

Treatment aims at controlling pain and inflammation and slowing or arresting the progression of joint destruction. Therapies generally used in the United States include corticosteroids; synthetic disease-modifying antirheumatic

drugs (DMARDs), such as hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine; and biological DMARDs, such as abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab. The American College of Rheumatology (ACR) recommends beginning DMARD therapy within 3 months of diagnosis (1). Often, treatment with a single DMARD does not adequately control symptoms, leading clinicians to consider various combination strategies.

Experts do not agree about the comparative benefits of different combination therapies. Many questions remain about the risks of these agents across a spectrum of adverse events from relatively minor side effects to severe and possibly life-threatening problems. Given this uncertainty, the Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review to compare the benefits and safety of rheumatoid arthritis drugs (2).

METHODS

We developed and followed a standardized protocol for all steps of the review. The full technical report (2) describes study methods in detail and gives evidence tables of individual studies.

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Literature Search

We searched MEDLINE, EMBASE, The Cochrane Library, and the International Pharmaceutical Abstracts for studies from 1980 to September 2007. Search terms included Medical Subject Headings or keywords when appropriate. We combined terms for rheumatoid arthritis with 11 drugs of interest (corticosteroid, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, etanercept, infliximab, adalimumab, abatacept, anakinra, and rituximab). We limited electronic searches to studies involving adults and humans and studies in English.

We manually searched reference lists of review articles and letters to the editor. In addition, we searched the Center for Drug Evaluation and Research database (September 2007) to identify unpublished research submitted to the U.S. Food and Drug Administration. In early to mid-2006, the Oregon Scientific Resource Center invited pharmaceutical manufacturers to submit dossiers on all published and unpublished studies on a specific drug. Five companies (Abbott, Amgen, Bristol-Myers Squibb, Centocor, and Genentech) provided dossiers.

Study Selection

Two persons, each blinded to the other's results, independently reviewed titles, abstracts, and sometimes full text to identify studies meeting preestablished criteria. To assess efficacy regarding symptoms, quality of life, functional capacity, and radiographic progression, we included head-to-head controlled trials and prospective cohort studies comparing any of the therapies. For harms (specific adverse events, rates of adverse events, and discontinuation attributable to adverse events) and subgroups, we also examined data from retrospective observational studies and placebo-controlled trials. For efficacy and harm data, we selected studies with 100 or more participants and at least 12 weeks of follow-up. Finally, if we found no evidence about efficacy from direct head-to-head comparison studies, we included evidence from fair- or good-quality meta-analyses that indirectly compared placebo-controlled trial data across drugs.

Data Abstraction and Quality Assessment

Trained reviewers abstracted each study by using a Web-based system (SRS 4.0, TrialStat, Ottawa, Ontario, Canada). A senior reviewer read each abstracted article and evaluated completeness of data extraction. We recorded intention-to-treat results if available. We assessed the internal validity (quality) of trials on the basis of predefined criteria from the U.S. Preventive Services Task Force (rating of good, fair, or poor) (3) and the National Health Service Centre for Reviews and Dissemination (4). Elements of internal validity for trials included randomization, allocation concealment, similarity of compared groups at baseline, intention-to-treat analysis, and overall and differential loss to follow-up. To assess the quality of observational studies, we used criteria outlined by Deeks and colleagues (5). Items assessed included sample selec-

Context

Which disease-modifying antirheumatic drugs (DMARDs) best reduce symptoms, improve function, and prevent radiographic progression in patients with rheumatoid arthritis?

Contribution

This systematic review of trials that compared DMARDs in adults with rheumatoid arthritis found few direct comparisons of different agents but no important differences among synthetic DMARDs or anti-tumor necrosis factor drugs. Combination therapy improved response rates and functional outcomes in patients whose monotherapy failed. Numbers and types of short-term adverse events were similar among DMARDs.

Implication

Of several monotherapies for adults with rheumatoid arthritis, no regimen is clearly superior. Combination therapies improve response rates in some patients previously receiving monotherapy.

—The Editors

tion, adjustment for confounders, methods of outcomes assessment, length of follow-up, and statistical analysis.

Data Synthesis

We primarily synthesized the literature qualitatively; we reported some quantitative syntheses from fair- to good-quality meta-analyses. Drug comparisons that were not quantitatively analyzed in meta-analyses had insufficient data or noncomparable study samples and did not merit additional quantitative analyses. We examined data within 3 main drug classes (corticosteroids, synthetic DMARDs, and biological DMARDs) and between drug classes and combination therapies.

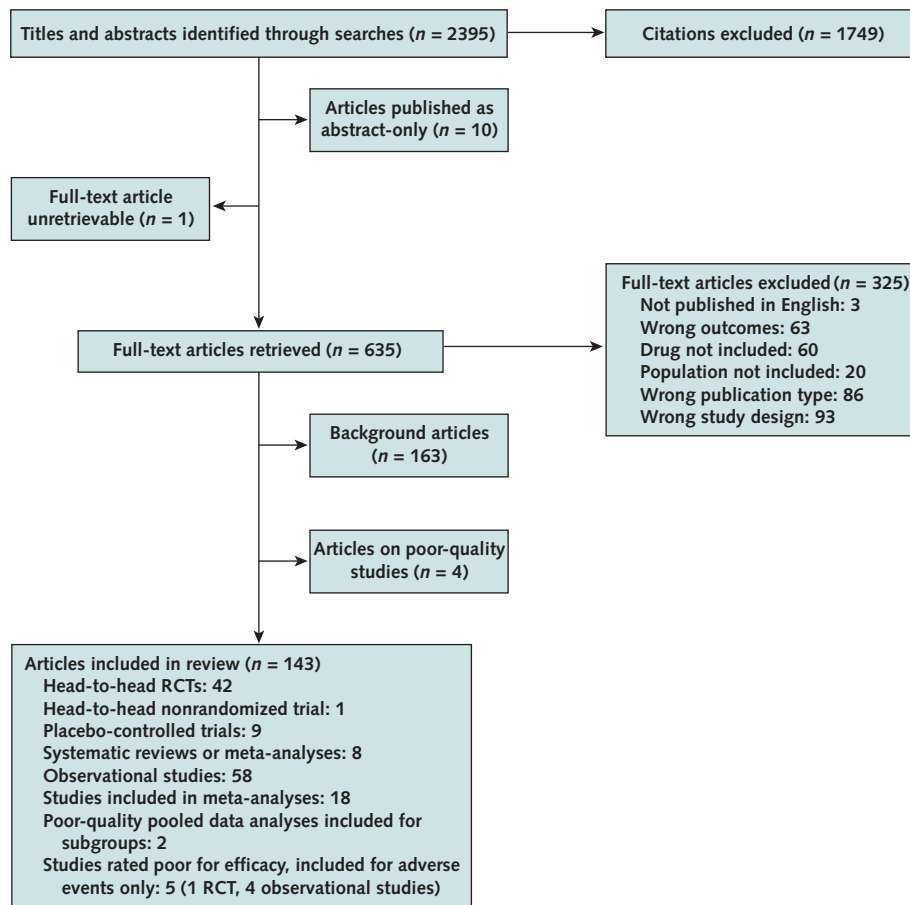
Strength of Evidence Ratings

We rated the strength of the available evidence in a 3-part hierarchy (high, moderate, and low) (2) based on a modified Grading of Recommendations, Assessment, Development, and Evaluation approach (6, 7). Grades reflect the strength of evidence for a given comparison with respect to specific outcomes, such as 20% improvement in ACR response criteria (ACR 20), radiographic changes, or adverse events.

Role of the Funding Source

Agency for Healthcare Research and Quality staff participated in formulating initial study questions and reviewed methods, data analysis, and the draft report. The funding source did not participate in the literature search, determination of study eligibility, or evaluation of individual studies.

Figure. Study flow diagram.



Numbers of included articles and included studies differ because some studies have multiple publications. RCT = randomized, controlled trial.

RESULTS

Characteristics of Reviewed Studies

We identified 2395 citations (Figure). Working from 635 articles retrieved for full review, we included 143 published articles reporting on 101 studies (Table 1). Of the 101 included studies, 49 (48.5%) were supported by pharmaceutical companies, 20 (19.8%) by governmental or independent funds, and 11 (10.9%) by a combination of pharmaceutical and governmental funding. We could not determine the source of support for 21 (20.8%) studies.

Comparative Effectiveness and Harms

We found few fair- or good-quality head-to-head trials for each drug comparison (Table 1). Most trials were efficacy trials in highly selected populations with few comorbid conditions. Most trials used ACR 20, disease activity scores to measure clinical improvement, and Sharp or Sharp–van der Heijde scores to measure radiologic progression of the disease. Trials examining quality of life used the Health Assessment Questionnaire (HAQ) or Medical Out-

comes Study Short Form 36 (SF-36). Table 2 summarizes results.

Monotherapy versus Monotherapy Synthetic DMARDs

One good systematic review that included a meta-analysis of 2 trials suggested that more patients receiving methotrexate achieved ACR 20 at 1 year than did patients receiving leflunomide (odds ratio, 1.43 [95% CI, 1.15 to 1.77]). The ACR 20 benefit was lower and more uncertain at 2 years (odds ratio, 1.28 [CI, 0.98 to 1.67]) (8). However, patients receiving methotrexate showed less improvement in health-related quality of life than did patients receiving leflunomide (odds ratio for SF-36 physical component, -3.00 [CI, -5.41 to -0.59]). Radiographic outcomes over 2 years seemed similar.

For leflunomide versus sulfasalazine, data are limited to 1 trial (9) involving 358 participants with 2-year follow-up (10, 11). Leflunomide yielded more patients achieving ACR 20, ACR 50, and greater improvement in

functional capacity (ACR 20, 82% vs. 60% [$P = 0.008$]; ACR 50, 52% vs. 25% [$P = 0.040$]; HAQ, -0.50 vs. -0.29 [$P \leq 0.030$]). Radiographic changes were similar for the 2 drugs (Larsen score change at 2 years, 0.010 for either drug) (9).

Three trials involving 479 participants and lasting up to 52 weeks compared methotrexate with sulfasalazine and found similar response rates in ACR 20, disease activity scores, or functional capacity (12–14). Two trials included patients with disease for longer than 1 year and used a lower dose of weekly methotrexate (7.5 mg) than that generally used in the United States (13, 14). The overall attrition rate for these studies ranged from 19% to 28.5%.

We found no statistically significant differences in frequency of serious adverse events for leflunomide, methotrexate, and sulfasalazine in 3 efficacy trials lasting 6 to 12 months (9, 15, 16) and 1 meta-analysis of up to 2 years of data (ending December 2001) (8). Serious adverse events ranged from 1% to 8%, but differed by 2 percentage points or fewer between drugs in each study. Serious adverse events included nonfatal sepsis (leflunomide), aminotransferase elevations (leflunomide and methotrexate), pneumonitis or pneumonia (methotrexate), and agranulocytosis (sulfasalazine). In the meta-analysis, 2-year withdrawals attributed to adverse events were 8.2% for leflunomide and 5.9% for methotrexate (relative risk, 1.19 [CI, 0.89 to 1.6]) and 10% for leflunomide and 15% for sulfasalazine (relative risk of leflunomide vs. sulfasalazine, 0.77 [CI, 0.45 to 1.33]) (8). However, in 1 fair-quality meta-analysis of 71 trials and 88 observational studies (end search date, August 1997), more patients continued methotrexate therapy than sulfasalazine therapy at 5 years (36% vs. 22%; combined numbers at risk at baseline, 2875 [methotrexate] and 1418 [sulfasalazine]) (17). Discontinuation rates because of adverse events did not substantially differ, ranging between 10% and 19%.

Biological DMARDs

No randomized trial compared one biological DMARD with another. The head-to-head evidence is limited to 1 nonrandomized, open-label effectiveness trial (18) and 2 prospective cohort studies (19, 20) comparing etanercept with infliximab. The cohort studies reported faster response for etanercept during the first months but no clinically important differences in efficacy thereafter. The faster onset of etanercept might be attributable to necessary dose adjustments for patients treated with infliximab. One study, however, attributed differences to lower rates of adherence among patients receiving infliximab than among those receiving etanercept. These findings are consistent with results from adjusted indirect comparisons based on 1 good-quality and 3 fair-quality meta-analyses (21–24).

Adjusted indirect comparisons also showed no differences in efficacy among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab) with respect to ACR 20 and ACR 50. They indicated that anakinra has lower efficacy than anti-tumor necrosis factor drugs (21, 23). Although not all results reached statistical significance, anakinra had consistently lower response rates of ACR 20 (relative risk, 1.64 [CI, 1.04 to 2.56]) and ACR 50 (relative risk, 1.89 [CI, 0.98 to 3.57]) than did anti-tumor necrosis factor drugs as a class (21).

Diarrhea (7% to 18% of patients), headache (12% to 18%), injection site reactions (19% to 56%), nausea (8% to 20%), rhinitis (8% to 18%), and upper respiratory tract infections (9% to 24%) were commonly reported adverse events among biological DMARDs (21). In long-term extension studies and postmarketing surveillance, adverse event rates did not increase over time (25–32). One 12-month nonrandomized, open-label trial of 2 biological DMARDs (etanercept vs. infliximab) reported similar adverse event rates (for example, 7 vs. 10 serious adverse events per 100 years) (33).

Table 1. Summary of Head-to-Head Reviewed Studies, by Drug Comparison*

Intervention	Study Design	Studies, <i>n</i>	Quality		Participants, <i>n</i>
			Good	Fair	
Corticosteroids vs. corticosteroids	RCT	1	–	1	143
Synthetic DMARDs vs. synthetic DMARDs	RCT	6	–	6	2318
	Meta-analysis	1	1	–	1732
Synthetic DMARD combinations	RCT	9	4	5	1877
	Observational	2	–	2	40 844
Biological DMARDs vs. biological DMARDs	RCT	1	–	1	242
	Non-RCT	1	–	1	369
	Meta-analysis	4	2	2	12 995†
	Observational	2	–	2	2320
Biological DMARDs vs. synthetic DMARDs	RCT	2	–	2	1431
	Non-RCT	1	–	1	369
	Observational	2	–	2	2454
Biological DMARD + synthetic DMARD combinations	RCT	7	1	6	4354
	Observational	3	2	1	7288

* Numbers do not sum to total number of included studies because some studies had multiple groups in different drug comparison categories. DMARD = disease-modifying antirheumatic drug; RCT = randomized, controlled trial.

† Number reported for 3 of 4 studies.

Table 2. Summary of Comparative Findings on Efficacy and Harms of Rheumatoid Arthritis Drugs

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Monotherapy vs. monotherapy		
Synthetic DMARDs		
Leflunomide vs. methotrexate	Similar 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) Similar work productivity outcomes (Moderate)	No obvious major differences in adverse events and discontinuation rates (Moderate)
Leflunomide vs. sulfasalazine	Higher ACR 20 and ACR 50 response rates and greater improvement in functional capacity for leflunomide (Low) Similar radiographic responses (Low)	No obvious major differences in adverse events and discontinuation rates (Moderate)
Sulfasalazine vs. methotrexate	Similar ACR 20 response rates, disease activity scores, functional capacity, and radiographic responses (Moderate)	No obvious major differences in adverse events; more patients receiving methotrexate than sulfasalazine (Moderate)
Biological DMARDs		
Biological DMARDs vs. biological DMARDs		
Anti-TNF drugs (adalimumab, etanercept, infliximab) vs. anti-TNF drugs	Similar ACR 20 and ACR 50 response rates among anti-TNF drugs (Moderate)	Insufficient evidence (Low)
Biological DMARDs vs. biological DMARDs	3 indirect comparisons based on fair- and good-quality meta-analyses 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 higher for anakinra than for adalimumab and etanercept (Moderate)
Biological DMARDs vs. synthetic DMARDs		
Anti-TNF drugs vs. methotrexate	In patients with early RA, similar clinical response, functional capacity, and quality of life between adalimumab or etanercept and methotrexate; in patients receiving biological DMARDs, better radiographic outcomes than synthetic DMARDs (Moderate) In patients whose initial RA treatment failed, greater functional independence and remission for anti-TNF drugs as a class than synthetic DMARDs as a class (Moderate)	No obvious major differences in adverse events in efficacy studies (Low) Insufficient evidence on differences in the risk for rare but severe adverse events (Low)
Combination therapy vs. monotherapy		
Synthetic DMARDs vs. synthetic DMARDs		
Sulfasalazine plus methotrexate vs. monotherapy	In patients with early RA, similar ACR 20 response rates or radiographic changes (Moderate) In all patients, similar functional capacity (Moderate) In patients with early RA, significantly better disease activity scores with combination therapy (Low)	No obvious major 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 receiving 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 obvious major differences in discontinuation rates (Moderate)
Biological DMARD combinations		
Biological DMARDs vs. biological DMARDs	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 2 biological DMARDs than from monotherapy (Moderate)
Biological DMARDs plus methotrexate vs. biological DMARDs	Better clinical response rates, functional capacity, and quality of life from combination therapy with biological DMARDs plus methotrexate than from monotherapy with biological DMARDs (Moderate) In methotrexate-naive patients with early aggressive RA, better ACR 50 response, greater clinical remission, and less radiographic progression in the combination therapy group (Low)	No obvious, major differences in adverse events in efficacy studies (Low) Insufficient evidence on differences in the risk for rare but severe adverse events (Low)
Biological DMARDs plus synthetic DMARD other than methotrexate vs. biological DMARDs	Similar clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy (Low)	No obvious, major differences in adverse events in efficacy studies (Low) Insufficient evidence on differences in the risk for rare but severe adverse events (Low)

Table 2—Continued

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biological DMARD plus methotrexate vs. methotrexate	Better clinical response rates, functional capacity, and quality of life from combination therapy of biological DMARDs and methotrexate than from methotrexate monotherapy (Moderate)	No obvious, major differences in adverse events in efficacy studies (Low) Insufficient evidence to make conclusions 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 receiving monotherapy, higher ACR 20 and ACR 50 response rates for triple therapy than for 2-drug combinations (Moderate) In patients with no previous use of study drugs, higher ACR 20 and ACR 50 response rates in the triple combination therapy group than in the methotrexate plus sulfasalazine group or methotrexate plus hydroxychloroquine group (Low)	No obvious, major 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 with 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 obvious, major differences in serious adverse events between groups (Low)

* Based on a modified approach of the Grading of Recommendations, Assessment, Development, and Evaluation working group (7): “High” indicates that further research is very unlikely to change our confidence in the estimate of effect; “moderate” indicates that further research is likely to have an important effect on our confidence in the estimate of the effect and may change the estimate; and “low” indicates that further research is very likely to have an important effect on our confidence in the estimate of the effect and is likely to change the estimate. 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 = Short Form-36; TNF = tumor necrosis factor.

In a good-quality systematic review, mean crude incidence rates of injection site reactions were substantially higher in patients receiving anakinra (67.2% [CI, 38.7% to 95.7%]) than in patients receiving adalimumab (17.5% [CI, 7.1% to 27.9%]) or etanercept (22.4% [CI, 8.5% to 36.3%]) (21). In a prospective cohort study, rates of serious infections were similar for adalimumab, etanercept, and infliximab (51.9 events per 1000 person-years, 51.3 events per 1000 person-years, and 55.2 events per 1000 person-years, respectively) (34). However, 3 fair-quality observational studies, based on the U.S. Food and Drug Administration Adverse Event Reporting System, indicated that infliximab might have a higher risk for granulomatous infections than etanercept (239 vs. 74 infections per 100 000 patients) (35–37). Evidence on comparative discontinuation rates is limited to 3 observational studies. In 1 large, retrospective cohort study, more patients discontinued anakinra treatment (41%) than etanercept (31%; $P = 0.004$) or infliximab (35%; $P = 0.03$) (38).

Biological DMARDs Versus Synthetic DMARDs

Three trials compared the efficacy of 2 anti-tumor necrosis factor drugs (adalimumab or etanercept) with methotrexate (39–45). Two trials enrolled exclusively methotrexate-naïve patients with early rheumatoid arthritis (39, 43–45). The third included a mixed sample of methotrexate-naïve patients and patients whose synthetic DMARD therapy other than methotrexate failed (40–42). We found no substantial or clinically important differences

in clinical response, functional capacity, or quality of life between adalimumab or etanercept and methotrexate in any of the 3 studies. In the adalimumab study, 25% of patients achieved remission in each treatment group (39). Radiographic outcomes, however, were better in patients receiving biological DMARDs than in those receiving methotrexate. For example, in the ERA (Early Rheumatoid Arthritis) study (43–45), 72% of patients receiving etanercept and 60% receiving methotrexate had no radiographic disease progression during 12 months of follow-up ($P = 0.007$).

In a prospective cohort study of patients whose initial rheumatoid arthritis treatment failed, those receiving biological DMARDs had, after 12 months, almost 4 times higher odds of achieving functional independence (odds ratio, 3.88 [CI, 1.71 to 8.79]) and almost 2 times higher odds of achieving remission (odds ratio, 1.95 [CI, 1.20 to 3.19]) than those receiving synthetic DMARDs (46). Only half of patients in both groups who had remission at 6 months achieved a sustained remission until 12 months.

Frequency of adverse events, such as headache, upper respiratory tract infections, rhinitis, or diarrhea, were generally similar between biological and synthetic DMARDs. The ERA study, however, reported significantly higher rates of mouth ulcers (14% vs. 5%; $P < 0.050$) and nausea (29% vs. 17%; $P < 0.050$) for patients receiving methotrexate than for those receiving etanercept (43). We could not assess differences in rare but severe adverse events be-

cause the studies were too small. In the largest prospective study, an open-label, 12-week trial with 6610 participants, serious adverse events occurred at similar rates for patients receiving adalimumab or adalimumab plus 1 DMARD (7.3% vs. 5.5%; P value not reported) (47).

Combination Therapy versus Monotherapy Synthetic DMARDs

Sulfasalazine–Methotrexate versus Monotherapy. In 2 trials, each lasting 4 years, ACR response rates, radiographic changes, and functional capacity were similar in patients with early rheumatoid arthritis (ACR 20, 65% vs. 59% with monotherapy; modified Sharp score, 3.5 vs. 4.5; change from baseline HAQ at 52 weeks, -0.51 with combination therapy vs. -0.46 with methotrexate and -0.32 with sulfasalazine [14]; change from baseline HAQ at 1 year, -0.70 with combination therapy vs. -0.73 with methotrexate vs. -0.74 with sulfasalazine; $P > 0.050$) (13, 14). Another study in patients with rheumatoid arthritis for up to 10 years found no difference in functional capacity at 6 months (change in HAQ was -0.50 with combination therapy, -0.25 with sulfasalazine, and -0.19 with methotrexate; $P = 0.51$ and 0.57 for combination therapy vs. sulfasalazine and combination therapy vs. methotrexate, respectively) but reported improved disease activity scores at 18 months with combination therapy (change in disease activity score, -0.67 vs. -0.30 with sulfasalazine and -0.26 with methotrexate; $P = 0.023$ for combination therapy vs. methotrexate) (12).

Synthetic DMARDs with Corticosteroids versus Monotherapy. Three trials examined combination strategies of 1 or more synthetic DMARDs with corticosteroids against synthetic DMARD monotherapy (48–51). Combination strategies had better outcomes, although each study used different outcome measures. One RCT comparing a combination of a synthetic DMARD (either methotrexate or sulfasalazine) and a corticosteroid with synthetic DMARD monotherapy had a higher remission rate in the combination group than in the monotherapy group (remission [defined as a disease activity score < 2.6], 55.5% vs. 43.8%; $P < 0.001$) (51). Patients with early rheumatoid arthritis had less radiographic progression and fewer eroded joints with combination treatment.

One open-label trial (48) compared synthetic DMARD use with and without prednisolone. The prednisolone group had greater improvement in function than the other group; the magnitude of improved function was small and not clinically important.

Combination studies involving 2 synthetic DMARDs, including sulfasalazine and methotrexate, compared with 1 DMARD showed similar withdrawal rates because of adverse events (combination therapy, 10% to 25%; monotherapy, 5.7% to 26.5%) (12–14). These studies involved 479 participants for up to 52 weeks. Two combination studies, a 56-week controlled trial ($n = 155$) and a 2-year

open-label RCT ($n = 250$), in patients with early rheumatoid arthritis comparing prednisone with 1 or more DMARDs versus DMARD monotherapy also showed similar discontinuation rates between groups (48, 49) (2.7% and 8.1%, respectively, for the shorter trial and 21.8% and 18%, respectively, for the open-label trial).

Biological DMARDs

Biological DMARD Combination versus Monotherapy. One trial detected no additional effect of combination treatment with etanercept and anakinra compared with etanercept monotherapy (52). In 2 trials, a combination of 2 biological DMARDs led to substantially higher rates of severe adverse events than those of biological DMARD monotherapy (52, 53). In a study comparing etanercept monotherapy with a combination of etanercept and anakinra, the incidence of serious adverse events was substantially higher with the combination treatment (14.8% vs. 2.5%; P value not reported) (52). Similarly, a study assessing the safety of abatacept with different background treatments (anakinra, adalimumab, etanercept, or infliximab) also reported an increase in serious adverse events with biological DMARD combinations (22.3% vs. 11.7% to 12.5%; P value not reported) (53).

Biological DMARD Combination with Methotrexate versus Biological DMARD Monotherapy. Four trials and 2 prospective cohort studies suggested that a combination of adalimumab, etanercept, infliximab, or rituximab with methotrexate achieved better clinical response rates than monotherapy with biological DMARDs (20, 39, 40, 54–56). In 1 trial (39), more patients receiving adalimumab plus methotrexate than did patients receiving adalimumab monotherapy achieved ACR 50 after 2 years of treatment (59% vs. 37%; $P < 0.001$). Likewise, more patients receiving etanercept plus methotrexate achieved remission than did those receiving etanercept monotherapy (disease activity score < 1.6 , 35% vs. 16%; $P < 0.001$) during TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) (40–42). Both trials found that a combination of either adalimumab or etanercept with methotrexate improved functional capacity or health-related quality of life more than monotherapy with a biological DMARD. In methotrexate-naïve patients with early, aggressive rheumatoid arthritis, the combination therapy group demonstrated better ACR 50 response rates, greater clinical remission, and less radiographic progression.

Biological DMARD Combination with Other Synthetic DMARDs versus Biological DMARD Monotherapy. One study combined sulfasalazine (a synthetic DMARD) with a biological DMARD (57). After 24 weeks, the combination regimen did not achieve better outcomes than etanercept monotherapy (ACR 20, 74.0% vs. 73.8%). Patients receiving combination therapy had higher frequencies of infectious (31% vs. 13%) and noninfectious (72% vs. 29%) adverse events than did patients receiving sulfasalazine.

Biological DMARD Combination with Methotrexate versus Methotrexate Monotherapy. Two trials found that a combination of adalimumab plus methotrexate (39) or infliximab plus methotrexate (58) in methotrexate-naïve patients with early, aggressive rheumatoid arthritis led to better clinical and radiographic outcomes than did methotrexate monotherapy. After 2 years, 59% of patients receiving adalimumab plus methotrexate and 43% of patients receiving methotrexate monotherapy achieved ACR 50 ($P < 0.001$) (39). Likewise, in ASPIRE (Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset), more patients in the infliximab plus methotrexate combination groups (6 mg and 3 mg of infliximab) than in the methotrexate group had remission (31% vs. 21% vs. 15%, respectively) (58). Both trials and 1 prospective cohort study (20) found greater improvements in functional capacity and quality of life with combination therapies (adalimumab, infliximab, or etanercept plus methotrexate) than with methotrexate alone.

We found similar frequencies of adverse events. A large retrospective cohort study ($n > 19\,000$; 89 710 person-years of observation) of the National Databank for Rheumatic Diseases reported similar risk for lymphoma in patients receiving an anti-tumor necrosis factor drug plus methotrexate and those who received methotrexate monotherapy (odds ratio, 1.1 [CI, 0.6 to 2.0]) (59). A safety trial, however, found a higher rate of serious infections with high-dose infliximab plus methotrexate therapy than with methotrexate monotherapy (relative risk, 3.1 [CI, 1.2 to 7.9]) (60).

Combination Therapy Comparisons or Other Treatment Strategies

Two trials reported better response rates at 2 years for the combination of sulfasalazine, methotrexate, and hydroxychloroquine than for 1 or 2 drugs in patients previously receiving monotherapy (61, 62). The ACR 20 response rates were 78% for triple therapy, 60% for methotrexate and hydroxychloroquine ($P = 0.05$), and 49% for methotrexate and sulfasalazine ($P = 0.002$). Withdrawal rates did not differ by group (61).

One effectiveness trial in patients with early rheumatoid arthritis reported less radiographic progression over 12 months with methotrexate, sulfasalazine, and high-dose tapered prednisone (group A) or methotrexate and infliximab (group B) versus sequential DMARD therapy (group C) or step-up combination therapy (group D) (median modified Sharp-van der Heijde score change, 2.0, 2.5, 1.0, and 0.5, respectively; $P = 0.003$ for group A vs. group C, $P < 0.001$ for group A vs. group D, $P = 0.007$ for group B vs. group C, and $P < 0.001$ for group B vs. group D). Patients given 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 at 12 months

(assessed by using the Dutch Health Assessment Questionnaire) than those treated with sequential DMARD therapy starting with methotrexate (63), but the magnitude of difference was small. The 2-year follow-up study reinforced the conclusion that patients in the initial combination therapy groups had less radiographic progression. However, at 2 years, all groups had similar disease activity according to disease activity score values, regardless of which initial therapy they received (64). Predefined serious adverse events did not differ in year 1 or year 2; gastrointestinal adverse events were most frequently reported (8.2% to 12.6% in year 2).

Effects, by Age Subgroups

Two subgroup analyses by age (1 analysis within 4 trials; 1 pooled data analysis) suggested no differences in adverse events, infections, or malignant conditions in patients treated with methotrexate or etanercept (65, 66). For methotrexate, the odds of major clinical improvement decreased slightly as age increased, but age did not affect methotrexate efficacy or the rate of side effects (65).

DISCUSSION

Scant head-to-head evidence showed no major or clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab). When we compared anti-tumor necrosis factor drugs and methotrexate, we saw better radiographic outcomes but no important differences in clinical outcomes (such as ACR 20, 50, or 70 response rates). Various combinations of biological DMARDs plus methotrexate had better clinical response rates and functional outcomes than monotherapy with either methotrexate or biological DMARDs. In patients previously receiving monotherapy, combination therapy with synthetic DMARDs improved response rates. Numbers of short-term adverse events were similar with biological and synthetic DMARDs.

Evidence is insufficient to draw conclusions about differences in risk for rare but serious events. It is also insufficient to draw conclusions on whether one combination or treatment strategy outweighs another or is the best treatment regimen for early rheumatoid arthritis and whether subgroups experience different outcomes.

Several areas warrant further research on the comparative efficacy, effectiveness, quality of life, and harms of medications for rheumatoid arthritis. Clinical decision making would benefit from examining the timing of initiation of therapies, applicability of combination strategies and biological DMARD therapy in community practice, and specific head-to-head comparisons focusing on different combination strategies and different biological DMARDs. Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that rheumatoid arthritis onset generally

occurs in middle age, when the risk for comorbid conditions increases. The risk for rare but serious adverse events, including malignant conditions, serious infections, demyelination, severe infusion reactions, or congestive heart failure, must be established in well-conducted observational studies with active harms surveillance. The balance of risks and benefits of biological DMARDs can be determined reliably only if good long-term data on such harms are available.

Several limitations of our review should be considered. First, most studies were efficacy trials conducted in highly selected populations; their applicability to average patients with rheumatoid arthritis might be limited. Findings from available effectiveness trials or observational studies, however, were consistent with those from efficacy studies. Second, the number of studies per drug comparison was low. The extent to which findings from available studies can be extrapolated to other drugs within the same class remains unclear. Third, publication bias is a concern in all systematic reviews; selective availability of studies with positive results can seriously bias conclusions. In addition, we might have missed information on benefits and harms by limiting our evidence to studies with at least 100 participants, studies with minimum follow-up of 3 months, and English-language publications. Finally, most of our findings stem from short-term efficacy trials. Although most efficacy trials used objective scales for adverse events assessment, drawing firm conclusions on the net benefit of these medications is difficult because of the absence of long-term safety studies for some drugs (primarily for biological DMARDs). Long-term safety issues may considerably shift the balance between benefits and harms for some of these drugs.

Several therapies are available for persons with rheumatoid arthritis; no regimen is clearly better than another. Combination therapies improve response rates in patients previously receiving monotherapy, but available evidence does not allow firm conclusions about which combination strategy is best. Future studies, including those with good applicability to patients seen in community practices, will be useful; researchers should plan to perform subgroup analyses a priori in older patients and patients with comorbid conditions. Long-term adverse event studies, particularly with the newer agents, will help clinicians and patients better weigh the benefits of these drugs.

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