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Summary of AHRQ's Comparative Effectiveness Review of Drug Therapy for Rheumatoid Arthritis (RA) in Adults – An Update

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Target Audiences

This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers.

Learning Objectives

Based on the findings from AHRQ's comparative effectiveness review of research of drug therapy for rheumatoid arthritis (RA) in adults, participants should be able to:

1. Evaluate the comparative effectiveness of RA drug therapies on disease activity, functional capacity, patient adherence, and adverse events.
2. Assess the benefits and harms of RA medications among important patient subgroups.
3. Evaluate evidence on the comparative efficacy of RA therapies to make informed clinical decisions.

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Davecia Cameron is an employee of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers.

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Summary of AHRQ's Comparative Effectiveness Review of Drug Therapy for Rheumatoid Arthritis (RA) in Adults

Jasvinder Singh, MD, and Davecia R Cameron, MS

ABSTRACT

BACKGROUND: In 2011, the Agency for Health Care Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of disease-modifying anti-rheumatic drugs (DMARDs) used to treat adults with rheumatoid arthritis (RA). The publication was an update to a 2007 report. A total of 258 published articles were used in the AHRQ review to compare the effectiveness of corticosteroids, and oral and biologic DMARDs in the treatment of RA. Head-to-head studies and prospective cohort trials were used to compare one drug to another in determining efficacy and effectiveness. AHRQ compiled this report in an attempt to summarize and integrate the available data for clinicians to make evidence-based practice decisions for their patients since there is limited consensus among the medical community regarding the comparative effectiveness of drugs used to treat RA. The report reveals there is still much research to be done concerning the side effects of these agents and their influence in different patient subgroups.

OBJECTIVES: To: (a) utilize review findings to make diagnostic and treatment management decisions in clinical practice, (b) inform clinicians on the findings from the updated AHRQ's 2011 comparative effectiveness review on drug therapy for RA in adults, and (c) identify shortcomings in the current research and future directions revealed by the report.

SUMMARY: Rheumatoid arthritis is a major public health burden. The 2011 updated AHRQ report includes several new medications approved by the FDA since 2007. The review includes 31 head-to-head randomized clinical trials (RCTs), 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. Most of the studies used for the comparative analysis are of fair quality with an insufficient to moderate strength of evidence assigned to the findings (Table 1). A mixed treatment comparisons (MTC) meta-analysis from the AHRQ report found that the biologic etanercept has a higher probability of improvement in disease activity compared with other biologic DMARDs, but the MTC findings have a low strength of evidence and caution is recommended in the interpretation of this weak evidence. For patients with early RA, limited evidence precludes conclusions about the superiority of one combination therapy versus another.

The data are also inconclusive for comparisons of therapeutic similarity among oral DMARDs including the limitation created by differences in methotrexate (MTX) dosing across trials. Extensive clinical experience over the years support the preferred use of MTX in most patients versus other oral DMARDs as well as its use in multidrug regimens, whereas there is little data on the use of oral DMARDs in combination with biologic agents. The review does not support a specific biologic DMARD over another due to the lack of head-to-head trials comparing these agents using validated RA outcome measures. The data show that the majority of biologics have approximately the same efficacy except for anakinra, which was found to be less effective.

The biologic and oral DMARDs are similar in overall tolerability, but several studies suggest that adverse events are more common with biologic DMARDs versus oral DMARDs. Based on limited evidence, the oral DMARDs do not appear to have an increased risk of severe adverse events including cardiovascular events and cancer. Although most studies also found no increased risk of cardiovascular events or cancer with the biologic DMARDs, cohort studies show an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

The updated AHRQ review synthesizes the current literature on therapies used for the treatment of RA in adults. The investigators are also able to identify pertinent research gaps in the literature that can be addressed with future research.

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The Centers for Disease Control and Prevention (CDC) estimates that nearly 1.5 million adults are currently diagnosed with rheumatoid arthritis (RA), a chronic, systemic autoimmune inflammatory disorder.¹ The disease is characterized by synovial inflammation which causes joint swelling, stiffness, and tenderness, which can eventually lead to cartilage damage, bone erosions, and joint destruction, associated with significant activity limitations and disability. RA patients are at increased risk of cardiovascular disease and thus increased mortality.² Because RA is associated with a decreased quality of life, it can contribute to reduced employment rates and increased direct and indirect costs. It was estimated that the total cost of arthritis and other rheumatic conditions in the United States in 2003 was approximately \$128 billion, equivalent to 1.2% of the 2003 U.S. gross domestic product.¹

Diagnosing RA is based primarily on a clinical evaluation of the patient. It involves an assessment of the patient history of joint pain and stiffness, clinical examination of synovitis and laboratory tests. Laboratory tests include radiographs, and inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), autoantibodies (rheumatoid factor) and anti-cyclic citrullinated peptide (anti-CCP) antibodies.^{3,4} A set of classification criteria aimed at diagnosing patients with RA was developed by The American College of Rheumatology (ACR) in 1987. Since this set of criteria was not sensitive to patients with early RA, a revised table was published by a joint working group of ACR and the European League Against Rheumatism (EULAR) in 2010. The modified criteria (Table 2) can be used to identify RA patients at an earlier point in the disease process by placing greater emphasis on serology and acute phase reactants rather than focusing primarily on joint inflammation.⁵ Using the 2010 criteria, patients with a score of 6 are considered to have RA.

Genetic susceptibility plays an important role in the pathophysiology of RA. While the exact etiology of the disease is not known, research has identified several important factors including T cells, B cells, and cytokines. Several cytokines that play especially critical roles are tumor necrosis factor (TNF), interleukin (IL-2) and IL-6. Studies have shown that TNF is a key regulator of mesenchymal cells responsible for releasing matrix metalloproteinases that ultimately lead to tissue

Summary of AHRQ's Comparative Effectiveness Review of Drug Therapy for Rheumatoid Arthritis (RA) in Adults

TABLE 1 Summary of Findings with Strength of Evidence

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. (Low) No clinically significant difference for functional capacity. (Low) Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. (Low)	No consistent differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient)
Leflunomide vs. sulfasalazine	Mixed ACR response rates. (Insufficient) No differences in radiographic changes. (Low) Greater improvement in functional capacity for leflunomide. (Low)	No differences in tolerability and discontinuation rates. (Low) Mixed results for specific adverse events. (Insufficient)
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes. ^a (Moderate) No differences for functional capacity. ^a (Moderate)	No differences in tolerability; more patients stayed on MTX long term. (Low) Mixed results for specific adverse events. (Insufficient)
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. (Moderate) No differences in functional capacity. (Moderate)	Withdrawal rates attributable to adverse events higher with combination. (Low) Insufficient evidence for specific adverse events. (Insufficient)
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. (Insufficient) Less radiographic progression in patients on DMARD plus prednisone. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints. (Low) Greater improvement in functional capacity for one oral DMARD plus prednisone than for oral DMARD monotherapy. (Moderate) No difference in quality of life. (Low)	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. (Moderate) No differences in specific adverse events, except addition of corticosteroid may increase woundhealing complications. (Low)
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. (Low)	Discontinuation rates and severe adverse events higher with infliximab. (Low)
Biologic vs. biologic (Mixed treatment comparisons)	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. (Low) Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. (Low) Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. (Low)	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. (Low) Risk for injection site reactions apparently highest with anakinra. (Low) Mixed results for specific adverse events. (Insufficient)
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. (Moderate) No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. (Low; Insufficient) Faster improvement in quality of life with etanercept than MTX. (Low)	No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient)
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. (Low)	Substantially higher rates of serious adverse events from combination of 2 biologic DMARDs than from monotherapy. (Moderate)

TABLE 1 Summary of Findings with Strength of Evidence (continued)

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. (Moderate) In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. (Low) In MTX-naive subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life. (Low) In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. (Low)	No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient)
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. (Low)	No differences in adverse events in efficacy studies. (Low) Insufficient evidence on differences in the risk for rare but severe adverse events. (Insufficient)
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. (High) for clinical response and functional capacity, (Moderate) for quality of life.	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from metaanalysis. (Low) Mixed evidence on differences in the risk for rare but severe adverse events. (Insufficient)
Strategies in Early RA		
2 oral DMARDs plus prednisone vs. oral DMARD	In patients on 2 oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. (Low) More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. (Low)	No differences in discontinuation rates. (Moderate)
3 oral DMARDs plus prednisone vs. one oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. (Low) In patients with early RA, significantly lower radiographic progression and fewer eroded joints. (Low)	No differences in discontinuation rates. (Moderate)
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. (Low)	No differences in serious adverse events between groups. (Low)

Source: Table A in Donahue KE, Jonas DE, Hansen RA, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis in adults – an update. AHRQ Comparative effectiveness review No. 55. April 2012.⁷

^aAt MTX doses ranging from 7.5-25 mg per week.

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

breakdown.⁶ Understanding the pathophysiology of RA is a key step in the development of more effective treatments. Novel biologic therapy that builds on these premises include agents that work by selectively inhibiting mechanisms required in the inflammatory and immune response such as TNF inhibitors or monoclonal antibodies that bind specifically to TNF.⁶

The purpose of pharmacologic therapies for RA is to manage inflammation and pain with the ultimate goal of achieving remission or at least low disease activity for all patients. RA

treatments include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs (Table 3). With the numerous treatment options available in conventional and biologic DMARD classes, consensus about the comparative effects of available therapies on disease activity and quality of life has yet to be achieved. Additionally, there are concerns about the effectiveness and safety of various DMARD combinations, and the short- and long-term safety risks of RA medications, especially for use in different patient

TABLE 2 2010 Rheumatoid Arthritis Classification Criteria

Criteria	Score
Joints	
1 large joint	0
2–10 large joints	1
1–3 small joints (large joints excluded)	2
4–10 small joints (large joints excluded)	3
>10 joints (at least 1 small joint)	5
Serology	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive ACPA (≤ 3 times the upper limit of normal)	2
High-positive RF or high-positive ACPA (> 3 times the upper limit of normal)	3
Symptom Duration	
<6 weeks	0
≥ 6 weeks	1
Acute Phase Reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

Source: Aletaha D, Neogi T, Silman AJ, et al. *Arthritis Rheum.* 2010;62(9):2569-81.⁵ ACPA = anti-citrullinated protein antibody; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

subpopulations such as the elderly, pregnant women, patients with comorbidities and in different ethnic groups. Therefore, a comprehensive review of published research in RA for different subpopulations and for RA in general would be important to clinicians who manage these patients.

■ AHRQ's Comparative Effectiveness Review of Drug Therapy for RA in Adults

In June 2011, the Agency for Healthcare Research and Quality (AHRQ) published an update to a 2007 comparative effectiveness review of drug therapy for RA in adults. The current review was carried out by investigators at the RTI International University of North Carolina Evidence Practice Center (RTI-UNC EPC).⁷ The original report from 2007 and the preliminary questions were developed through a collaborative process involving the public, the Scientific Resource Center for the Effective Healthcare program of AHRQ and various stakeholder groups. The group at RTI-UNC EPC updated the original key questions and the report by investigating new medications that were approved after the release of the initial report.

The investigators focused the comparative effectiveness review on 4 key clinical questions that are listed below:

Key Question 1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?

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

Key Question 3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

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

For each key question, head-to-head studies, observational studies, and systematic reviews were included and RA drugs were compared using the following categories:

- Oral DMARDs versus oral DMARDs
- Oral DMARD combinations
- Biologic DMARDs versus biologic DMARDs
- Biologic DMARDs versus oral DMARDs
- Biologic DMARDs + oral DMARD combinations
- Corticosteroids
- Early RA strategies

Comparative Effectiveness Review Methods

This section summarizes the methods by which the EPC investigators conducted their comparative effectiveness review of studies on RA therapies. The topic for this review was nominated publicly and refined by the EPC researchers based on public commentary and input from a panel of technical experts. The process was guided by AHRQ's commitment to assuring relevance for all key stakeholders. Complete details about the systematic review methods are available in the full technical report.⁷

Literature Search Strategy

The investigators of the AHRQ review identified relevant articles by searching databases such as MEDLINE, Embase, the Cochrane Library, Scopus, and the International Pharmaceutical Abstracts. In addition, the database from the Center for Drug Evaluation and Research (CDER) was hand-searched to locate unpublished research submitted to the U.S. Food and Drug Administration (FDA). The original review covered publications from 1990 to September 2006. This update included literature from June 2006 to January 2011 and searches were done earlier than June 2006 to account for any delays in indexing. The queries included literature from randomized controlled trials (RCTs), reviews and meta-analyses. Study selection criteria were based on application to the 4 key clinical questions. Studies were selected for the review based on the following criteria:

- Research in humans and published in the English language
- Studies with sample sizes of at least 100 and duration of at least 3 months

TABLE 3 Pharmaceutical Treatments for Rheumatoid Arthritis

Class	Mechanism	Generic Name (Trade Name)
Corticosteroids	A synthetic form of cortisol, a hormone produced by the adrenal glands. Achieves anti-inflammatory and immunosuppressive activity by interacting with steroid-specific receptors and inhibiting the movement of inflammatory cells into the inflammation site thereby preventing neutrophil activity and prostaglandin production.	methylprednisolone (e.g., Medrol, Depo-Medrol, Solu-Medrol) prednisone (e.g., Deltasone, Sterapred, LiquiPred) prednisolone (e.g., Orapred, Pediapred, Prelone, Delta-Cortef, Econopred)
Oral DMARDs	Affect inflammatory conditions by acting on the immune system. The various drugs are not members of one class but work by a variety of mechanisms. All are slow acting, given orally, and work on reducing or preventing joint damage, improving symptoms and preserving structure and function.	hydroxychloroquine (e.g., Plaquenil) leflunomide (e.g., Arava) methotrexate (e.g., Trexall, Folex, Rheumatrex) sulfasalazine (e.g., Azulfidine, EN-tabs, Sulfazine)
Biologic DMARDs	Novel injectable DMARDs that target certain parts of the immune system. Examples include: <ul style="list-style-type: none"> • TNF inhibitors that inhibit particular cytokines • IL-1/IL-6 receptor antagonists that block the IL-1/IL-6 receptor stopping various inflammatory and immunological responses • Anti-CD20 monoclonal antibodies that bind to CD20 antigen and remove B cells that may play a part in the autoimmune and inflammatory process 	abatacept (Orencia) adalimumab (Humira) anakinra (Kineret) certolizumab pegol (Kineret) etanercept (Enbrel) golimumab (Simponi) infliximab (Remicade) rituximab (Rituxan) tocilizumab (Actemra, RoActemra)

Source: Tables 2-4 in Donahue KE, Jonas DE, Hansen RA, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis in adults—Update. AHRQ Comparative effectiveness review No. 55. April 2012.⁷

Anti-CD20=Anti-Cluster of Differentiation 20; DMARD=disease-modifying antirheumatic drug; IL=interleukin; TNF=tumor necrosis factor.

- Studies that used doses within the recommended dosing range or doses that would be considered equivalent to the recommended range
- Head-to-head trials and prospective cohort trials comparing one drug to another for efficacy and effectiveness
- Placebo-controlled, double-blind RCTs for biologic DMARDs
- Head-to-head trials, high-quality systematic reviews and observational studies to compare harms and tolerability, and efficacy and effectiveness in different subgroups

Of the total of 3,868 citations identified in the searches, 258 published articles reporting on 211 studies were included in the review report. These 258 articles included 31 head-to-head RCTs, 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies.

Assessments of Study Quality and Strength of Evidence

To evaluate the methodological quality of studies included in their assessment, the investigators of this review employed a grading system established on criteria detailed in AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁸ The quality of individual studies was graded as *good*, *fair*, or *poor* based on the following definitions:

- Good studies are considered valid and relatively unbiased, as evidenced by clear descriptions of their patient populations, settings, interventions, and treatment

groups. Moreover, good studies are characterized by valid approaches to allocating patients to groups, low dropout rates, and appropriate methods for preventing bias, measuring outcomes, and analyzing results.

- Fair studies are susceptible to bias, although not to a degree that invalidates the results. Fair studies may also be characterized by missing information or methodological weaknesses.
- Poor studies have significant bias that may invalidate their results. Moreover, poor studies tend to have large amounts of missing information and serious errors in design, analysis, or reporting.

In addition to assessing the methodological quality of studies included in the review, the EPC investigators evaluated the strength of study evidence, using a modified version of an instrument developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group.⁸ This evaluation considers factors regarding evidence such as directness, precision, consistency across studies, magnitude of effect, applicability, and the potential for publication bias. The evidence was graded as *high*, *moderate*, *low*, or *insufficient*. The first 3 of these grades indicate the investigators' confidence in the extent to which the evidence reflects true or systematic treatment effects. A grade of *insufficient* indicates that evidence does not either exist or permit the estimation of effects.

TABLE 4 Disease Activity, Radiographic Progression, Functional Capacity, and Quality-of-Life Measures Included in the AHRQ Review

Name of Measure or Instrument (Abbreviated name)	Range of Scores	How Improvement is Reflected:	Clinically Significant Improvement
American College of Rheumatology % improvement from baseline to endpoint (ACR-N)	0 to 100%	Increase	
ACR response scores based on 20%, 50%, or 70% criteria for improvement (ACR 20/50/70)	0 to 100%	Increase	ACR 20 is 20% minimal improvement; ACR 50/70 considered more clinically significant
Arthritis-Specific Health Index - Medical Outcomes Study Short Form SF-36 Arthritis-Specific Health Index (ASHI)	0 to 100	Increase	
Disease Activity Score (DAS)	0 to 10	Decrease	DAS <1.6 correlates with remission
Disease Activity Score Short Form (DAS28)	0 to 10	Decrease	DAS28 <2.6 correlates with remission
Dermatology Life Quality Index (DLQI)	0 to 30	Decrease	
EuroQol Quality of Life Questionnaire (EQ-5D)	0 to 1	Increase	
European League Against Rheumatism response (EULAR response)	N/A	N/A	
Health Assessment Questionnaire (HAQ) - Dutch Version (D-HAQ)	0 to 3	Decrease	HAQ ≥0.22 change
Disability Index of the Health Assessment Questionnaire (HAQ-DI)	0 to 3	Decrease	
Medical Outcomes Study Short Form 36 Health Survey (SF-36)	0 to 100	Increase	SF-36 physical or mental component—2 standard errors of the mean
Sharp/van der Heijde Method (SHS) for Scoring Radiographs ^a	0 to 148	Decrease	Changes in joint damage around the level of 5 units of the Sharp/van der Heijde method as minimally clinically important

Source: Table 8 in Donahue KE, Jonas DE, Hansen RA, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis in adults—Update. AHRQ Comparative effectiveness review No. 55. April 2012.⁷

^aSHS is frequently modified by individual authors to meet study requirements and needs; there is no standard modified SHS.

ACR=American College of Rheumatology; ACR-N=American College of Rheumatology N index of improvement in rheumatoid arthritis; N/A=not applicable; SF-36=short form 36.

Description of Outcome Measures

Several tools have been developed for diagnosing RA and/or evaluating treatment outcomes in clinical trials and practice settings. Commonly used tools assess laboratory measures of inflammation, symptoms reflecting disease activity, functional status, and quality of life. Table 4 lists the diagnostic scales and health status or quality of life instruments that were used in studies included in the AHRQ comparative effectiveness review.

Efficacy and Effectiveness of Oral and Biologic DMARDs

The following section focuses on the AHRQ review findings in response to key question 1 and 2. Investigators assessed the ability of oral and biologic DMARDs and DMARD combinations to reduce disease activity, to slow or limit progression of radiographic joint damage or to maintain remission. Additionally the ability of the drug therapies to improve functional capacity for patients was reviewed to address key question 2.

Comparisons of Oral DMARDs

Oral DMARD monotherapy is the common initial pharmacologic treatment of RA in clinical practice, and dosages are adjusted as necessary to achieve low disease activity or remission. MTX is the oral DMARD preferred by clinicians unless there are contraindications such as liver impairment, alcohol abuse, pregnancy, or lung disease. The CER review compared

the efficacy and effectiveness of MTX with the other oral DMARDs (leflunomide, hydroxychloroquine and sulfasalazine).

Four studies were used to assess leflunomide's activity; 2 RCTs compared leflunomide at 20 mg per day to MTX (doses ranged from 7.5 mg per week to 15 mg per week), and there were 2 reviews with meta-analysis of leflunomide.^{9,10} The 2 RCTs collectively found no clinically significant difference in functional capacity for leflunomide versus MTX; 1 of the RCTs showed no significant difference in the proportion of patients who met ACR 20 response criteria at 12 months for leflunomide versus MTX (52% vs. 46%, *P* value not reported [NR]), and there was also no difference in the proportion of patients who met ACR 50 and ACR 70 criteria.⁹ The other RCT of leflunomide versus MTX found a lower proportion of patients meeting ACR 20 response criteria in the leflunomide arm compared with MTX monotherapy (50.5% vs. 64.8%, *P*<0.001) at 1 year, but there was no difference at 2 years (64.3% vs. 71.7%, *P*=not significant [NS]).¹⁰ Both systematic reviews showed no significant differences comparing leflunomide to MTX in patients achieving ACR 20 at 12 months.^{11,12}

The effectiveness of leflunomide was found to be similar to sulfasalazine in a 2-year follow up clinical trial and 1 systematic review of a meta-analysis. Both studies found no significant difference in ACR 20 response at 12 months; leflunomide was more efficacious at 24 months (82% vs. 60%, *P*=0.0085), but

the long-term results were limited because of attrition rates of 65% to 70%.^{11,13}

Sulfasalazine was compared with MTX in 3 RCTs¹⁴⁻¹⁶ and 1 systematic review, and the findings showed similar improvement rates in ACR, DAS (disease activity score) and radiological outcomes.¹² The efficacy of combination sulfasalazine plus MTX was compared with MTX alone in 3 RCTs, 1 systematic review, and 1 observational cohort.¹⁴⁻¹⁸ Two of the RCTs found no significant differences in ACR, DAS, or radiological outcomes between the combinations. However, a third study which included patients with RA duration of up to 10 years showed DAS results favoring the sulfasalazine-MTX combination versus MTX monotherapy.¹⁴⁻¹⁶

One study with a low strength of evidence found greater improvement in quality of life (SF-36 physical component score [PCS]) for leflunomide compared with MTX (mean PCS improvement at 12 months of 7.6 vs. 4.6, $P < 0.01$).¹⁹ Another RCT with a low strength of evidence found that leflunomide exhibited greater improvement in functional capacity up to 24 months compared with sulfasalazine (improvement in HAQ at 2 years, -0.65 vs. -0.36 , $P < 0.01$).^{13,20}

Comparisons of Biologic DMARDs

For comparison of the biologic DMARDs, 1 head-to-head RCT, 1 nonrandomized, open-label effectiveness trial, and 6 prospective cohort studies were used. Therapies that were compared included etanercept with infliximab, adalimumab with infliximab, adalimumab with etanercept, abatacept with infliximab and rituximab compared with other anti-tumor necrosis factor (TNF) agents. All of the studies enrolled patients who were initiating treatment with biologic agents and who had advanced RA (mean disease duration of 7.3 to 14.5 years).

The only head-to-head RCT provided a low strength of evidence that abatacept decreased disease activity at 1 year compared with infliximab but there was no difference in DAS remission at 1 year;²¹ the primary endpoint was DAS28 in this RCT rather than the customary ACR 20. All other comparisons evaluated have used nonrandomized, open-label and prospective cohort study designs, and therefore findings from these studies should be interpreted with caution because of the methodological limitations of observational research. Cohort studies that compared etanercept to infliximab found no differences in efficacy according to ACR 20 and ACR 50 criteria.²²⁻²⁷ One prospective cohort reported a greater decrease in DAS28 for etanercept (1.8) versus infliximab (-1.2) at 1 year ($P < 0.05$), although the strength of evidence is low for this comparison.²³ Two cohort studies provided low strength of evidence that adalimumab decreased RA disease activity (DAS28 and ACR 70) at 1-year duration when compared with infliximab. The same studies showed no differences in ACR 70 achievement when adalimumab was compared with etanercept.^{26,27}

A cohort study of 116 patients compared the effectiveness

of rituximab with other anti-TNF agents in patients who were inadequate responders to prior anti-TNF therapy.²⁸ The low strength of evidence showed that patients who used rituximab had a greater reduction in disease activity at 6 months compared with patients treated with other anti-TNF therapies. The EPC investigators also used mixed treatment comparisons (MTC) which showed higher efficacy for etanercept in improving disease activity compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab, but these MTC results should be interpreted with caution because they are indirect and were graded as low strength of evidence.

Population-based, observational evidence from prospective cohort studies and RCTs of individual drugs (direct comparative trials) were used for comparing biologic DMARDs to oral DMARDs. These comparisons with a moderate strength of evidence show that the biologic DMARDs as a class (adalimumab, anakinra, etanercept, and infliximab) were more efficacious than oral DMARDs, as reflected by ACR 20/50 and remission of DAS28 compared with the oral DMARDs as a class (MTX, leflunomide). Additionally, adalimumab, and etanercept were reported to have better radiographic outcomes compared with patients treated with MTX, but the strength of the evidence for this comparison is low.^{22,23,29-31}

There are no synergistic effects of combination therapies of etanercept and anakinra or etanercept with abatacept compared with etanercept alone, and combinations of biologic DMARDs have higher rates of serious adverse events compared with biologic DMARD monotherapy (low strength of evidence).^{32,33} The strength of evidence is moderate, however, for results showing some benefit in ACR response and radiographic progression for combinations of MTX with adalimumab, infliximab, or rituximab compared with biologic DMARD monotherapy;^{23,29,34-37} infliximab is not FDA-approved for use as monotherapy and no RCT compared the efficacy or effectiveness of infliximab plus MTX versus infliximab used alone in patients with RA. In general, there is a high level of evidence for combinations of biologic DMARDs with oral DMARDs versus oral DMARDs alone. Compared with MTX alone, combinations using MTX with abatacept, adalimumab, etanercept, golimumab, or infliximab resulted in significantly greater improvements in disease activity reflected by ACR 20/50 response criteria.^{29,35,38-42}

There is no quality evidence to show differences in quality of life outcomes between biologic treatments. The strength of evidence is low or insufficient for data from 3 prospective cohort studies comparing biologic DMARDs with no suggestion of differences in functional capacity or quality of life between etanercept, infliximab, or adalimumab.^{23,25,26} One RCT that compared abatacept or infliximab with placebo in patients with RA who had received prior treatment with MTX found no difference in functional capacity between the cohorts, but the strength of evidence for this trial is low.²¹ AHRQ investigators found insufficient evidence in comparing the functional

capacity and quality of life outcomes of biologics versus oral DMARDs.^{29,30,38,43}

Regarding the combination of biologic and oral DMARDs, the reviewers conclude based on 2 RCTs that biologic DMARDs plus MTX compared with biologic DMARDs alone result in greater improvements in functional capacity (moderate strength of evidence) and quality of life (low strength of evidence), for patients who have not recently received MTX or are MTX-naïve.^{29,38} However, there is no difference in improvements in functional capacity or quality of life for biologic DMARD plus an oral DMARD compared with biologic DMARD alone when the patients have active RA despite treatment with same oral DMARD used in the combination oral DMARD plus biologic DMARD therapy (moderate strength of evidence).^{23,44,45} The combination of a biologic DMARD plus oral DMARD compared with an oral DMARD alone results in greater improvement in functional capacity (high strength of evidence, based on 7 RCTs and 1 prospective cohort trial) and greater improvement in quality of life (moderate strength of evidence based on 4 RCTs). These trials compared MTX monotherapy with combination therapy regimens of abatacept plus MTX, adalimumab plus MTX, golimumab plus MTX, infliximab plus MTX, or etanercept plus MTX, and etanercept plus sulfasalazine versus sulfasalazine alone.^{23,29,35,38-40,42,46,47}

■ Benefits and Risks of Oral and Biologic DMARDs

The following section addresses key question 3 and how different RA drug therapies vary in harms, tolerability, or adverse effects. One nonrandomized controlled trial, 66 RCTs, 99 observational studies and 28 systematic reviews were used for these comparisons. It must be noted however that methods of assessing adverse events differed greatly between studies; few used objective scales such as the Utvalg for Kliniske Undersogelser Side Effect Scale (UKU-SES) or adverse reaction terminology as defined by the World Health Organization (WHO). Because of this the AHRQ reviewers explain any serious adverse events as individual studies described and reported them.

Oral DMARDs and Combinations – Discontinuation and Adverse Events

Overall the strength of evidence is low when looking at the tolerability and discontinuation rates across studies comparing oral DMARD monotherapy. Similar rates of tolerability and discontinuation were found in 3 efficacy trials and 1 meta-analysis for leflunomide, MTX and sulfasalazine up to 2 years of follow-up.^{10,11,13,19,49,50} One retrospective cohort study showed improved tolerability with leflunomide,⁵¹ while a meta-analysis of 71 RCTs and 88 observational studies showed a higher proportion of patients staying on MTX than on sulfasalazine at 5 years (36% vs. 22%, *P* value not reported).⁵² Strength of evidence is also low when comparing combinations of

DMARDs with DMARD monotherapy. Several trials including 2 meta-analyses looking at combinations of 2 or 3 DMARDs (sulfasalazine, MTX, hydroxychloroquine, etanercept) versus 1 or 2 DMARDs found similar withdrawal rates due to adverse events. The discontinuation rates were comparable among all the drugs, but the studies evaluating sulfasalazine plus MTX showed higher rates versus monotherapy with either drug.^{14-17,53-58}

Specific Adverse Events

Four observational studies found a decrease or no difference in risk for cardiovascular or cerebrovascular events with monotherapy or combinations of oral DMARD treatment, but the strength of evidence associated with these studies was low.⁵⁹⁻⁶² A low level of evidence was associated with studies that showed that hepatic events were similar in patients treated with MTX, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept.^{51,63} Evidence from 12 studies suggested that oral DMARDs do not affect the risk of infection, and there was insufficient evidence for the comparison of risk of infections among the oral DMARDs; 1 nested case-control study rated good quality showed a lower rate of infection associated with MTX and hydroxychloroquine compared to other oral DMARD combinations.^{51,64-68}

Biologic DMARDs – Discontinuation and Adverse Events

Comparisons of patients randomized to receive biologic DMARDs found that fewer patients discontinued treatment compared with patients receiving placebo or MTX alone (odds ratio [OR] of discontinuation, 0.51; 95% CI=0.40-0.65). A meta-analysis that reviewed withdrawals due to lack of efficacy found that patients treated with biologic DMARDs were less likely to stop treatment compared with patients treated with MTX or placebo (OR=0.21, 95% CI=0.17-0.27). Reviewers concluded that efficacy had a stronger influence on continuation of therapy regimen than adverse events and this was based on evidence that showed overall withdrawal rates were more favorable with the biologics compared with placebo.⁷ Two meta-analyses with good ratings described elevated incidence of withdrawals due to adverse events for infliximab and a higher incidence of withdrawals because of adverse events for adalimumab, anakinra, and infliximab compared with etanercept.^{72,73} Observational studies provide more evidence for discontinuation rates. Several of these studies showed higher discontinuation rates associated with infliximab, adalimumab, and anakinra while other studies found no clinically or statistically significant differences.^{27,74-81}

Based on 1 RCT and 1 retrospective cohort study of adverse events with the biologic DMARDs, serious adverse events were more common in patients treated with infliximab versus abatacept, adalimumab, and etanercept, but the strength of evidence was rated low.^{21,82} Overall tolerability profiles based

on indirect evidence from efficacy trials, cohort studies and meta-analyses were found to be similar for biologic and oral DMARDs, and combinations of both.^{22,25,29,37-40,47,77,83-96} Yet other studies indicate that adverse events were more frequent with biologic DMARD combinations than with oral DMARDs or biologics alone.⁹⁷⁻¹⁰³ Four RCTs, created to evaluate adverse events rates as primary outcomes, showed similar rates for abatacept, adalimumab, anakinra, infliximab, and placebo. Overall adverse event rates were higher with biologic DMARDs than with placebo in other efficacy trials.^{85,104-106}

Specific Adverse Events

Serious adverse events such as acute infections, congestive heart failure, or autoimmunity, while rare, are still a concern for patients using biologic DMARDs. The comparative risk, however, could not be accurately evaluated due to insufficient data. The EPC investigators did not find any studies that compared biologic DMARDs to each other for the risk of cardiovascular or cerebrovascular events. Studies that did consider the effects of individual biologics gave conflicting results.¹⁰⁷⁻¹⁰⁹

The strength of evidence for infections caused by biologic DMARDs was rated moderate. Results from several systematic reviews and meta-analyses that analyzed serious adverse events showed an increase in risk of infection with the use of biologic DMARDs.^{93,95,110-113} The more commonly and consistently reported adverse events from efficacy studies for biologic DMARDs are infusion and injection site reactions. Studies reported up to 0.5% of patients treated with infliximab experience severe acute reactions similar to acute anaphylactic shock or convulsions.¹¹⁵ In an RCT comparing abatacept to infliximab, infusion reactions were more commonly associated with infliximab.²¹ Rituximab has also been linked to severe and even fatal infusion reactions.¹¹⁶ A review of the literature has shown infusion reactions are commonly associated with the biologics administered via intravenous infusion (abatacept, infliximab, rituximab, and tocilizumab).⁷ Injection site reactions are common with adalimumab, anakinra, certolizumab, etanercept, and golimumab, with mean, crude incidence rates reported in this review for the 3 older agents: 17.5% for adalimumab, 22.4% for etanercept, and 67.2% for anakinra.⁷

Adherence

Because there are very few efficacy studies that address rates of adherence and the quality of reporting and because analyzing data from these trials is inadequate, the overall strength of this evidence is low or insufficient. Five observational studies, which compared one biologic DMARD to another, reported inconclusive data.⁷ One review indicated that infliximab had greater adherence than etanercept or MTX,¹¹⁷ and another study found greater adherence with infliximab compared with etanercept and anakinra.^{24,27} However, conflicting data were found in 1 prospective cohort study in which etaner-

cept was associated with increased adherence compared with infliximab,²⁴ while another trial found no differences in adherence between etanercept and infliximab.³⁴

Comparative Effectiveness of Corticosteroids

The AHRQ investigators found 1 head-to-head RCT that compared 2 corticosteroids (budesonide 3 mg per day or 9 mg per day vs. prednisolone 7.5 mg per day) for reductions in disease activity, limitations to disease progression and remission maintenance, and the strength of this evidence was deemed low.¹¹⁸ Over 12 weeks, a higher percentage of patients who received high-dose (9 mg per day) budesonide had better response (ACR 20 criteria) compared with patients randomized to the low-dose (3 mg per day) budesonide arm (42% vs. 22%, $P < 0.001$). There was however no difference between high-dose budesonide and prednisolone in DAS score between the budesonide and prednisolone arms.¹¹⁸

The same study was used to address corticosteroid effect on functional capacity and quality of life. Greater improvements in both functional capacity and quality of life were seen with prednisolone compared with budesonide, but again the strength of evidence is low given the inadequate data. Data from 2 RCTs, with moderate strength of evidence showed an increase in functional capacity with a combination of oral DMARD and corticosteroid compared with the use of an oral DMARD alone (difference in mean change in HAQ -0.28 , $P = 0.02$), but a low strength of evidence was associated with the quality of life data that showed no difference among the agents.^{119,120}

Reviewers found a low strength of evidence when addressing the tolerability and adverse events of corticosteroids. The comparative data found in one 3-month trial was similar for all corticosteroids involved while mixed results were reported from 1 RCT and 4 observational trials showing an increase of cardiovascular events with corticosteroids.^{60,118,119,121-123} The risk of infections associated with a moderate strength of evidence was increased in patients using corticosteroids. Likewise, septic (infectious) arthritis and interstitial lung disease were linked to increases with corticosteroid use but with a low strength of evidence.^{64-67,124-130}

Strategies for Early RA

The strength of evidence was low for the comparison of treatments related to disease progression and efficacy for early RA due to the limited and indirect data that were available. Two studies that evaluated MTX and sulfasalazine in combination with a stepped-down version of prednisolone therapy resulted in a decreased radiographic progression compared to sulfasalazine monotherapy in patients with early RA.^{56,131} Decreased radiographic changes were noted in a study for a combination of MTX-sulfasalazine-hydroxychloroquine plus prednisolone.^{132,133} Additionally, a combination of either MTX-sulfasalazine with tapered high-dose prednisone or MTX plus

infliximab reported less changes in radiographic progression in a 12-month period compared to sequential DMARD therapy or a stepped-down version of combination therapy.¹³⁴ In another study, the 3-drug combination of MTX, sulfasalazine, and hydroxychloroquine resulted in lower response by EULAR criteria when compared to infliximab plus MTX.¹³⁵

The strength of evidence for the comparisons of 3 RCTs used to evaluate the effect of corticosteroids on functional capacity and quality of life was low. The data showed that a combination approach with corticosteroids plus multiple oral DMARDs caused immediate improvement in functional capacity with less work disability compared with oral DMARD monotherapy. One of the RCTs reported that for patients with early RA using initial combination therapy with prednisone or initial combination therapy with infliximab had greater functional ability versus patients treated with sequential DMARD monotherapy or with a step-up combination regimen. Over a 2-year period the increase in ability was maintained in all groups but was not significantly different between groups.^{56,131,133,136}

Tolerability and adverse events of corticosteroids were evaluated in studies with prednisone and 1 or more DMARDs for treatment of early RA, and results showed similar discontinuation rates between trial arms.^{120,133,134,137-139} One RCT compared several approaches of combining corticosteroids with biologic and oral DMARDs and discovered similar rates for serious adverse events.^{134,137,138} There was a moderate level of evidence associated with reports that the addition of a glucocorticoid to hydroxychloroquine or MTX added nearly 6 months ($P < 0.05$) to the mean time until withdrawal of DMARD therapy due to adverse events.¹⁴⁰

Effectiveness and Safety of DMARDs for RA Subpopulations

This section addresses the results applicable to key question 4, which focuses on the comparative benefits and harms of drug therapies for RA in specific subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities. Subgroups were defined by stage of disease, concomitant therapies, comorbidities and demographics such as age, sex, race, or ethnicity. Five good or fair quality studies were used to assess the effectiveness and safety of DMARDs in RA subpopulations, including 2 RCTs, 1 subgroup analysis of multiple RCTs, 1 database analysis, and 1 systematic review.

A limited amount of good quality studies were found that addressed the issues of benefits or harms for certain subpopulation; therefore, the evidence was of low strength, making it difficult to arrive at a consensus. One fair quality post-hoc analysis of 2 RCTs was used to evaluate the effect of RA therapies on stage of disease, including analysis of the outcomes for patients with moderate or severe RA treated with either MTX, etanercept, or a combination of both. Patients with moderate RA had overall significantly improved DAS28 and HAQ

scores compared with patients with severe RA, but patients with severe disease activity fared better on MTX or etanercept monotherapy resulting in greater change of DAS28 scores compared with baseline.¹⁴¹

Investigators found no studies that evaluated comparative research by sex, race, or ethnicity and only 1 systematic review of 3 trials of fair value that addressed age.¹⁴² One of the studies evaluated in the review compared the effect of etanercept in patients older than 65 years of age with younger patients between 18 to 64 years old and found no significant functional status differences between the 2 groups.¹⁴³ One observational study, rated fair quality, of a database of Medicare claims found that the immunosuppressive agents azathioprene, cyclosporine, and leflunomide, oral glucocorticoids, and combinations, were associated with an increased risk of cardiovascular events compared with MTX as the reference group; the oral biologics adalimumab, etanercept, and infliximab were not associated with increased risk of cardiovascular events.¹²²

One large placebo-controlled RCT and a systematic review of 11 MTX trials were used to evaluate patients with comorbidities and RA. Results from the studies showed no difference in serious adverse events or infections in patients treated with placebo or anakinra.¹⁴⁴ Patients with renal impairment were found to be at increased risk for toxicity due to MTX therapy compared with those without renal impairment (OR=4.5, 95% CI=0.9-22.6) and baseline renal function was considered a significant predictor of toxicity.¹⁴²

Directions for Future Research

Many issues regarding treatment for RA remain unresolved. In summarizing the comparative effectiveness review, investigators from the University of North Carolina EPC address the future research needed based on limitations and gaps found in the existing data. Further research focusing on comparative efficacy, effectiveness, quality of life and harms of RA therapies may direct clinicians, researchers, and all stakeholders to make better choices regarding these treatments. Three essential areas that will guide future health policies include:

- Head-to-head assessments for a variety of combination approaches and different biologic DMARDs
- Staging and timing of therapy start times
- Applicability of combination therapy and biologic agents in community practice

Many of the systematic reviews, placebo-controlled trials, and observational studies that were used for this analysis did not allow for robust comparisons of biologic DMARDs. While some MTC meta-analyses were able to show variations among therapies, head-to-head trials are a requirement to corroborate the result findings within the AHRQ review.

Current research on RA is insufficient in assessing the comparative efficacy and safety of oral DMARDs in a subgroup of patients who do not meet the criteria for treatment with a

biologic DMARD. There is uncertainty regarding more novel oral DMARDs like leflunomide and whether they have a better, long-term adverse event profile than older oral DMARDs such as MTX. In addition, research that addresses the effect of RA therapies on different subgroups such as by age or coexisting conditions is a necessity since RA often occurs in middle age where comorbidities can be more prevalent. Future trials would help gauge the long-term advantages, effectiveness and safety profiles of various combination regimens on different subgroups of patients.

Another issue that requires more research is whether aggressive early treatment has a positive effect on the course and prognosis of RA. RCTs carried out for multiple years, that examine the efficacy and effectiveness of various drug regimens with different combinations of corticosteroids, oral or biologic DMARDs, and the adverse effects of such combinations will provide much needed data to prevent or minimize disease effects for patients with early RA.

Future trials also need to take examples from real life clinical situations such as switching therapy in patients who do not respond after a certain amount of time, differences in route and frequency of administration for biologic agents, and inconsistencies in adherence to certain drugs and adverse events. Overall, future research needs to consider applicability to community practices, disease severity and duration, route of drug administration, safety profiles, and patient demographics such as age, sex, ethnicity, race and comorbidities.

■ Conclusions

Although most of the evidence used in the comparative analysis of RA therapies was of low or moderate strength, some conclusions can be reached for comparisons of oral and biologic DMARDs. There are data that support comparable efficacy and effectiveness rates for MTX and sulfasalazine. There is a low strength of evidence associated with findings regarding disease activity with sulfasalazine and leflunomide, although patients did show increased functional capacity on leflunomide therapy. From analysis of short-term efficacy trials, MTX, sulfasalazine, and leflunomide showed similar discontinuation rates due to adverse events. Despite an improved response in many patients using DMARD monotherapy, there is a subset of patients with persistent early RA that do not reach satisfactory response, regardless of aggressive management. Another trial which evaluated various treatment regimens in patients with early RA, concluded that tight disease control and a personalized treatment plan are integral aspects of RA treatment response and disease remission. Several efficacy trials show that combinations of biologic and oral DMARDs versus monotherapy are more successful in patients failing DMARD therapy. The available research shows that combination therapy of up to 3 oral DMARDs including corticosteroids is more favorable than regimens of only 1 or 2 drugs. Combinations of biologic

DMARDs with MTX also show better clinical outcomes, functional capacity gains, and improved quality of life in patients on biologic DMARD monotherapy who are MTX-naïve or have not used MTX recently. Combinations of 2 biologic DMARDs showed no further benefit and had higher rates of serious adverse events compared with patients using only 1 biologic DMARD. For early RA, there are insufficient data in the literature to either support the use of biologic DMARDs or identify the superior combination strategy.

There is a moderate strength of evidence that combinations of 2 or 3 DMARDs with MTX, sulfasalazine, hydroxychloroquine, and etanercept have comparable withdrawal rates due to adverse events to regimens of only 1 or 2 DMARDs. Combinations that included prednisone plus 1 or more DMARDs had similar rates of discontinuation. Additionally, patients on regimens of biologic and oral DMARDs were not as likely to withdraw from therapy due to lack of efficacy compared with the group receiving an oral DMARD alone. Although the rates of side effects were similar for both biologic and oral DMARD combinations compared with monotherapies, long-term safety data are missing for many newer biologic therapies. Because many biologic DMARDs require administration intravenously, the rare but serious threat of severe infusion reactions is of concern. Anakinra appears to have an increased rate of injection site reactions compared to other anti-TNF agents (low strength of evidence). Abatacept, infliximab, and rituximab can also cause severe infusion reactions, and fatal cases were reported for infliximab and rituximab.

RA is a progressive chronic disease, and it is not known whether early initiation with any RA therapy, particularly biologic DMARDs, will improve the long-term prognosis of RA. In addition to the need for studies of longer duration, further research is needed for subpopulations defined by age and coexisting conditions, in part because RA onset occurs in middle age when the risk of comorbidities is higher

■ Commentary: Managed Care Perspective on Comparative Effectiveness of Medications used to Treat Rheumatoid Arthritis

With the introduction in recent years of new treatments for rheumatoid arthritis, there is a lack of clarity on the relative effects of disease-modifying antirheumatic drugs (DMARDs) and combinations of drugs on the progression of the disease and symptom control. Since the 2007 AHRQ review, several new biologic medications have been approved by the FDA for the treatment of rheumatoid arthritis. As the current review indicates, there are limited data available comparing individual or combination therapy, and the majority of the evidence available is of low to moderate strength. Although there are some data on efficacy, there is a general lack of effectiveness information for the DMARDs. When these data are evaluated in the context of the significant direct cost of some of these

medications, making coverage decisions for the oral and biologic DMARDs is challenging. However, it is possible to draw some conclusions at this time to assist managed care organizations in this process.

A lack of data continues to preclude recommending one biologic DMARD over another. The exception is anakinra, which has been shown to be less effective than other biologic agents. A subgroup of biologics (adalimumab, anakinra, etanercept, infliximab) were found to have greater efficacy in symptom reduction (ACR 20 and ACR 50, and remission assessed by DAS28) compared with 2 oral DMARDs (MTX, leflunomide). There is a low strength of evidence indicating no additive clinical benefit and an increased risk of adverse events when 2 biologic agents are combined. In contrast, there is evidence that combining MTX with a biologic is superior to biologic or oral DMARD monotherapy in patients who have not recently taken MTX.

One concern about the use of the biologic agents is the lack of long-term safety data. Comparative reviews showed similar tolerability for oral and biologic DMARDs, but short-term adverse events were more common with the biologic agents. Infusion-related reactions and injection site reactions are common with the biologic agents. Severe infusion reactions have been most commonly reported with abatacept, infliximab, and rituximab, and fatal reactions have been reported with infliximab and rituximab. An increase in the risk of infection has also been observed with biologic agents.

Both oral and biologic agents are important in the treatment of rheumatoid arthritis. The large number of possible combination therapies underscores the need for additional comparative effectiveness research, especially in subgroups such as early rheumatoid arthritis and the elderly.

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