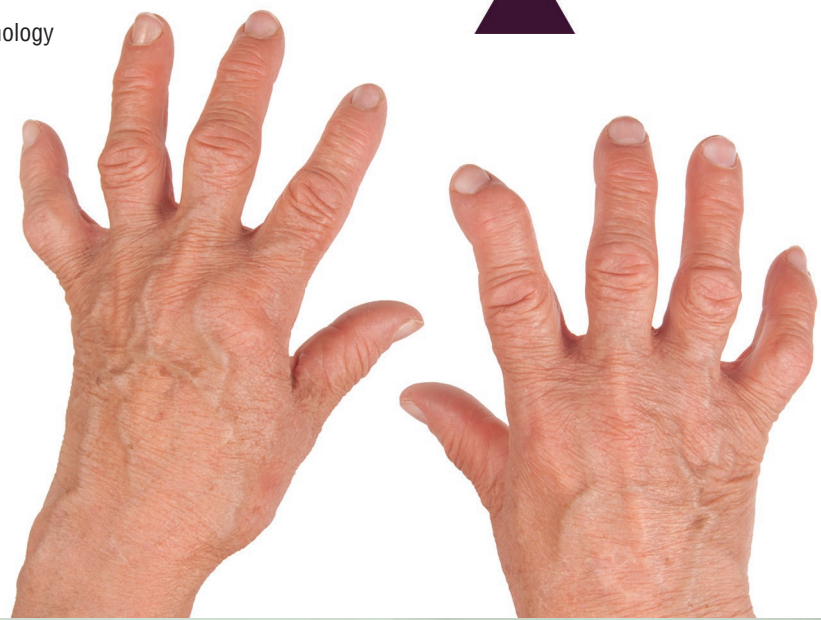
A CME/CE-CERTIFIED SUPPLEMENT TO
Rheumatology News®

Issues in Rheumatoid Arthritis Treatment
Clinical Implications of Current Evidence

FACULTY

Jeffrey Curtis, MD
William J. Koopman Endowed Professor in Rheumatology and Immunology
Director, UAB Arthritis Clinical Intervention Program
Division of Clinical Immunology and Rheumatology
University of Alabama at Birmingham School of Medicine
Birmingham, Alabama

Jonathan Kay, MD
Timothy S. and Elaine L. Peterson Chair in Rheumatology
Professor of Medicine, University of Massachusetts Medical School
Director of Clinical Research, Division of Rheumatology
UMass Memorial Medical Center
Worcester, Massachusetts



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This continuing education supplement was developed from interviews with the faculty. It is the final activity in the three-part curriculum, *Advancing the Management of Rheumatoid Arthritis: Applying Evidence-Based Strategies to Improve Patient Outcomes*. The supplement content brings together the key teaching points from the previous two online activities, which may be found at: http://tinyurl.com/AdvanceRA.

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Global Academy for Medical Education

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Jeffrey Curtis, MD
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Target Audience

This supplement is intended for rheumatologists, primary care physicians, nurse practitioners, nurses, physician assistants, pharmacists, and other health care providers who treat patients with rheumatic diseases.

Educational Needs

In the absence of a cure for rheumatoid arthritis (RA), the goals of therapy for all patients remain reduction of signs and symptoms, prevention of radiologic progression and subsequent disability, and improved quality of life. Available therapies include tumor necrosis factor (TNF) alpha inhibitors, the interleukin-1 receptor antagonist anakinra, the selective T-cell costimulation modulator abatacept, the CD20-directed cytolytic antibody rituximab, the interleukin-6 receptor antibody tocilizumab, and the Janus kinase inhibitor tofacitinib.

Clinicians face clinical challenges with respect to choosing appropriate treatment regimens for individual patients. Some patients fail to respond to initial treatment with a selected agent (primarily due to treatment failure). Other patients improve initially with a treatment regimen but experience a loss of response over time. Options for patients with inadequate response to TNF inhibitors include the use of alternative TNF inhibitors, non-TNF biologics, or tofacitinib. Some of these agents may be used as monotherapy, reducing risk for the side effects of methotrexate. However, clinicians should be aware of and carefully evaluate the monotherapy studies involving these agents. This educational program provides evidence-based information in an accessible format for clinicians, with the overall goals of increasing the clinician's confidence and skill in adopting newer treatment approaches, including options following TNF failure and monotherapy with biologics that have mechanisms of action other than TNF inhibition.

Learning Objectives

After reading and studying this journal supplement, participants should be better able to:

- Identify the appropriate use of newer therapies for rheumatoid arthritis (RA) management based on recent trial data
- Identify all approved first-line therapy options for patients with RA
- Apply strategies for using monotherapy as an appropriate option for managing patients with RA
- Describe pharmacologic strategies for the treatment of RA as they relate to the mechanism of action of therapeutic interventions
- Discuss the potential reasons for anti–tumor necrosis factor (TNF) failure
- Describe the benefits and limitations of anti-TNF cycling in disease control and patient outcomes
- Discuss whether biologic therapies with mechanisms of action other than TNF inhibition are appropriate when managing patients in whom anti-TNF therapy has failed
- Assess approaches to managing anti-TNF cycling and switching to an agent with a different mechanism of action
- Recognize the impact of Healthcare Effectiveness Data and Information Set (HEDIS) measures and Centers for Medicare & Medicaid Services (CMS) Five-Star Quality Rating System on reimbursement for management of patients 18 years and older who were diagnosed with RA

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Field Testers: This activity was pilot-tested for time required by: *Physicians:* **Daniel Grabell, MD**, **Shreya Patel, MD**, and **Cliff Stermer, MD**. *Nurses:* **Geraldine Bocchieri, BSN, RN**; **Rosalind Julius Mickel, MSN, RN**; and **Carol Ruland, RN**. The field testers have no relevant financial relationships to disclose.

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Introduction

New therapeutic agents introduced in the last 2 decades have transformed the treatment of rheumatoid arthritis (RA). These disease-modifying antirheumatic drugs (DMARDs) now allow clinicians to manage patients with the realistic expectation that they can achieve low disease activity or even remission in a majority of individuals.[1,2] This "treat-to-target" approach mirrors advances in the management of other chronic diseases, such as hypertension and diabetes, and involves the intensification of therapy until the goal of better disease control (in this case, remission) is achieved.[3] The key agents enabling this approach to RA include certain conventional DMARDs (eg, methotrexate) and biologic agents (eg, tumor necrosis factor [TNF] inhibitors).

However, selecting appropriate treatment regimens for individual patients with RA remains a clinical challenge. Patients may not respond to initial treatment with a selected agent (primary nonresponse) or lose response to treatments over time (secondary nonresponse). In some patients, the side effects of DMARDs may require dose adjustments or discontinuation, necessitating alternative strategies.

This journal supplement reviews current evidence and guidelines describing strategies to manage patients who have an inadequate response to a DMARD therapy or who do not tolerate the cornerstone DMARD, methotrexate. Also included are data from practicing rheumatologists who completed online educational activities on the topics of TNF cycling (switching from one anti-TNF drug to another) and biologic monotherapy. These data complement the information in this supplement and provide insight into real-world practice patterns and concerns of rheumatologists who treat patients with RA.

New Guidelines, New Agents

The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) each published new guidelines for RA in the last 2 years.[1,2] These guidelines emphasize the treat-to-target approach and delineate strategies for pharmacologic treatment based on disease activity, treatment history, and other patient variables.

In the last few years, several new agents have been approved for the treatment of RA, including biologic agents with mechanisms of action other than TNF inhibition (eg, tocilizumab) and the first small-molecule inhibitor of Janus kinases (JAKs) (tofacitinib). Available therapies for RA now include TNF inhibitors, the interleukin (IL)-1 receptor antagonist anakinra, the selective T-cell costimulation modulator abatacept, the CD20-directed cytolytic antibody rituximab, the IL-6 receptor antibody tocilizumab, and the JAK inhibitor tofacitinib (**Table 1**).[1,2,4-13] The introduction of agents with alternative mechanisms of action provides clinicians with effective new options for patients with RA, including those who fail TNF-inhibitor therapy.

The new ACR and EULAR guidelines incorporate these newer agents, as well as emerging evidence regarding specific aspects of RA treatment, such as the management of RA in patients with comorbid conditions.[1,2]

TABLE 1. DMARD Options for the Management of Rheumatoid Arthritis[1,2,4-13]

Drug Class	Agent	Application
Conventional DMARDs	Methotrexate	First line, monotherapy or in combination with other agents
	Leflunomide	
	Hydroxychloroquine	Most often used as part of combination therapy with methotrexate
	Sulfasalazine	
TNF inhibitors	Adalimumab	First or second line, monotherapy or with methotrexate
	Certolizumab pegol	
	Etanercept	
	Golimumab	First or second line with methotrexate
	Infliximab	
Biologic agents with other mechanisms of action	Abatacept	First or second line, monotherapy or with methotrexate
	Anakinra	Second line, monotherapy or with methotrexate
	Rituximab (with methotrexate)	
	Tocilizumab	
Small molecule targeted therapy	Tofacitinib	

DMARD=disease-modifying antirheumatic drug; TNF=tumor necrosis factor.

Treat-to-Target

Evidence strongly supports a treat-to-target approach to optimize outcomes in patients with RA. This approach relies on routine assessments of disease activity using a quantitative disease activity measure and intensification of treatment to achieve the goal of remission (or low disease activity).

In studies using a treat-to-target approach, early intensification of therapy with combinations of conventional DMARDs and/or TNF inhibitors led to significant reductions in disease activity and improved long-term outcomes.[14,15] As suggested by several authors, these trials demonstrated the effectiveness of the overall strategy (ie, treatment intensification to achieve remission), rather than recommending any specific agent or sequence or combination of agents.[16]

Based on this evidence, the ACR has endorsed quality measures to support the implementation of treat-to-target in clinical practices.[17,18] Among the ACR-endorsed quality measures are several that pertain directly to the treat-to-target approach, including the use of DMARD therapy and regular monitoring of disease activity with quantitative measures that can classify a patient's level of RA disease activity (**Table 2**).[18]

To maximize reimbursement by Centers for Medicare & Medicaid Services (CMS), rheumatologists must now report the implementation of ACR quality measures in their patient population through the CMS Physician Quality Reporting System (PQRS). The PQRS for RA includes the following measures: initiation of DMARD therapy; assessment of disease activity, functional status, and prognosis; tuberculosis screening; and documentation of a glucocorticoid management plan.[18]

Assessing Disease Activity

Once DMARD therapy is initiated, periodic quantitative assessment of disease activity is essential to determine the need for treatment intensification to achieve remission. Several disease activity measures have been validated in patients with RA, including the following scales noted by the ACR[19]:

- Disease Activity Score (28-joint count) – DAS28
- Clinical Disease Activity Index – CDAI
- Simplified Disease Activity Index – SDAI
- Patient Activity Scale – PAS and PAS II
- Routine Assessment of Patient Index Data – RAPID-3

When asked to rate their awareness of requirements for reporting clinical performance with the PQRS RA measures, nearly one-third of rheumatologists said they were "not at all aware." Only 11% were "very aware."

Each tool has the advantage of measuring disease activity on a continuous linear measure and patients can be categorized as being in remission or having low, moderate, or high disease activity. In contrast, other measures that are not by themselves recommended (eg, physical global assessment on a 0-10 scale) do not permit such classification because they lack defined disease activity cut points.

The ACR does not recommend any one disease activity measure over the others, and studies have documented a modest degree of correlation between these measures.[19] However, there are several features to consider, especially for use in routine clinical settings. First, does the measure include a tender and swollen joint count, which requires data based on examination by a physician? The CDAI, SDAI, and DAS28 include formal physician joint counts. A count of swollen and tender joints provides an objective assessment of the extent of joint involvement at a point in time and is recommended by guidelines as standard practice.[20] For an experienced physician, accurate joint counts can be completed in approximately 90 seconds, but even this amount of time may be one reason why some rheumatologists do not document routine assessments of disease activity.

Second, does the measure require objective laboratory tests? The SDAI and DAS28 both require levels of acute phase reactants (C-reactive protein [CRP] for SDAI; CRP or erythrocyte sedimentation rate [ESR] for DAS28). However, laboratory findings are typically not available at the time of the visit, preventing clinicians from completing these disease activity measures while the patient is present and possibly delaying changes in therapy that might be indicated by disease activity level.

Conversely, the patient-driven measures (PAS, PAS II, and RAPID-3) use information provided by patients during the visit and require little or no physician time. These measures may be considered to encompass a broader evaluation of patient health and function. The RAPID-3, for example, includes the Multidimensional Health Assessment Questionnaire (MDHAQ), an assessment of function. As noted, assessment of patient functional status is an ACR quality measure and should be performed at least annually in patients with RA.[18]

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TABLE 2. ACR-Endorsed Quality Measures for Rheumatoid Arthritis[18]

Disease activity measurement	Percentage of patients ≥18 years with a diagnosis of RA and ≥50% of total number of outpatient encounters in the measurement year with assessment of disease activity using a standardized measure
Functional status assessment	Percentage of patients ≥18 years with a diagnosis of RA for whom a functional status assessment was performed at least once during the measurement period
Tuberculosis screening	Percentage of patients ≥18 years with a diagnosis of RA who have documentation of a TB screening performed within 12 months prior to receiving a first course of therapy using a biologic DMARD
DMARD therapy	Percentage of patients ≥18 years with a diagnosis of RA who are prescribed DMARD therapy

ACR=American College of Rheumatology; DMARD=disease-modifying antirheumatic drug; RA=rheumatoid arthritis; TB=tuberculosis.

Achieving Remission: How to Manage TNF-Inhibitor Failure

As recommended by the ACR and EULAR guidelines, the first-line DMARD for most patients is methotrexate.[1,2] For patients who do not achieve remission with methotrexate alone, the ACR recommends either combination synthetic DMARD therapy (hydroxychloroquine, sulfasalazine) or adding or switching to a TNF inhibitor or to a biologic agent with another mechanism of action.[2]

The efficacy of TNF inhibitors in RA is well established, and many patients may achieve and maintain remission with a TNF inhibitor, with or without methotrexate. But what about patients who do not respond or lose response to TNF inhibitors?

Patients who do not achieve remission with initial TNF therapy may have a primary or secondary nonresponse. Although strong data from head-to-head trials are scant, evidence suggests that patients with a primary nonresponse to TNF inhibitors may benefit from an agent with a different mechanism of action. Following a secondary nonresponse to a first TNF inhibitor, either a different TNF inhibitor or an agent with a different mechanism of action may be considered. For patients who fail two or more TNF inhibitors, observational data suggest diminishing benefit from additional anti-TNF therapy. Biologic agents with other mechanisms of action that have demonstrated efficacy in this setting include abatacept, rituximab, tocilizumab, and tofacitinib. The 2015 ACR guidelines incorporate these findings and recommend TNF inhibitors or other biologic agents for patients with insufficient response to one TNF inhibitor, and biologic agents with other mechanisms of action for patients who fail two or more TNF inhibitors.[2] When other biologic agents are not an option, following multiple anti-TNF failures, tofacitinib is preferred over another TNF inhibitor.

Nonresponse to TNF Inhibitors

Even in clinical trials, approximately one-third of patients do not respond to initial treatment with a TNF inhibitor.[20] How to manage RA in these patients remains an open question.

A decade ago, when there were few other options, a survey found that 94% of rheumatologists selected an alternative TNF inhibitor after failure of a first agent.[26] More recent studies have found that this approach is somewhat less common now; in one study, 69% of rheumatologists selected a second TNF inhibitor following failure of a first anti-TNF agent.[27] However, evidence describing the optimal strategy following anti-TNF failure remains mixed, and head-to-head, randomized trials comparing TNF inhibitors with other biologic therapies following failure of a TNF inhibitor have not yet been published.

Retrospective and observational studies suggest that many patients who fail initial anti-TNF therapy may respond to a second anti-TNF agent, but the likelihood of response may be greater when a biologic agent with a different mechanism of action is selected.[27-30] Response to a subsequent TNF-inhibitor appears to be influenced by the reason for initial TNF-inhibitor failure. The results of several retrospective studies suggest that patients who discontinued anti-TNF therapy because of adverse events or intolerability are more likely to respond to a second anti-TNF agent than patients who experienced primary nonresponse to a TNF inhibitor.[27-29] Particularly when patients failed a TNF inhibitor because of lack of efficacy, studies have reported significantly higher drug survival and/or response rates when patients are switched to a biologic agent with an alternative mechanism of action, rather than to a different TNF inhibitor.[30,31]

These findings could relate to a class effect of TNF inhibitors in certain patients, perhaps, in part, due to genetic differences.[32,33] However, no biomarker that identifies responders to TNF inhibitors has yet been validated. In contrast, the presence of circulating rheumatoid factor correlates with greater efficacy of rituximab in patients with RA.[34]

One of the few prospective, head-to-head studies comparing strategies following an initial anti-TNF failure was the SWITCH-RA study, an observational study in routine clinical settings that compared the anti-CD20 agent rituximab to TNF inhibitors in 1,112 subjects with inadequate response to initial anti-TNF therapy.[34] At 6 months, the mean change in DAS28 was small but significantly greater for the rituximab group than the TNF inhibitor group (-1.5 vs -1.1, respectively; P=0.007). This difference remained significant when comparing subjects who had discontinued initial anti-TNF therapy due to lack of efficacy, but not among those who discontinued due to intolerance. The difference in response rates was greatest among seropositive patients. These data support the use of an agent with an alternative mechanism of action for patients who have a nonresponse to anti-TNF therapy due to lack of efficacy.

Secondary nonresponse to TNF inhibitors is also common. In one study, approximately half of all patients who responded initially to infliximab therapy lost response within 1 year.[35] The reasons for loss of response are not well understood. Poor adherence could contribute to lack of efficacy, as can the development of anti-drug antibodies (ADAs).

The development and impact of ADAs is the subject of much research. These antibodies likely play a role in some cases of secondary nonresponse, but are not detected in all patients who lose response to TNF inhibitors.[36,37] Factors that affect immunogenicity with biologic agents include the concomitant use of methotrexate, which can reduce ADA formation and promotes TNF inhibitor persistence.[38] Although immunogenicity may play a role in loss of response to biologic therapy in RA, testing for the presence of ADAs or trough serum drug levels is not a common practice among US rheumatologists and will likely not impact treatment decisions in the near term.

Strong data are currently lacking regarding the management of RA in patients for whom TNF inhibitor therapy is not efficacious. Observational studies suggest that a high proportion of patients who lose response to one TNF inhibitor will respond to a second TNF inhibitor.[39-42] Although the efficacy of a second TNF inhibitor varies between studies, data suggest similar or slightly lower response rates and treatment survival compared to the initial TNF inhibitor.[41-45] Some studies suggest that the second TNF inhibitor may be discontinued for the same reason as the first (ie, loss of efficacy vs side effects).[42,43]

What is your typical treatment approach for a patient with RA who develops secondary nonresponse to anti-TNF therapy?

Choice	Proportion of Learners
Manage with conventional DMARDs	0%
Increase dose or frequency of anti-TNF drug	3%
Test for ADAs and trough serum drug levels	27%
Switch to biologic agent with another mechanism of action	30%
Switch to alternative anti-TNF drug	40%

ADA=anti-drug antibody; DMARD=disease-modifying antirheumatic drug; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

For example, a prospective, observational analysis of RA registry data from Sweden identified patients who switched between TNF inhibitors once (n=337) or twice (n=36).[44] ACR50 response rates for patients switching once and twice were 27% and 18%, respectively; DAS28 remission rates were 16% and 6%, respectively. Further analysis identified lower age and Health Assessment Questionnaire (HAQ) scores and higher DAS28 values as predictors of response to second-line treatment. Patients who switched agents because of adverse events rather than inefficacy were also more likely to respond to second-line anti-TNF therapy.

An observational study from Spain yielded similar findings. Using the BIOBADASER registry of patients with rheumatology (68% with RA), investigators identified people treated with TNF inhibitors.[43] Drug survival rates for patients taking a first TNF inhibitor were 0.83 and 0.75 at 1 and 2 years, respectively. Of the 488 patients who were treated with more than one TNF inhibitor, drug survival for the second TNF inhibitor fell to 0.68 and 0.60 at 1 and 2 years, respectively. As demonstrated in the Swedish registry study, drug persistence was better in patients switching TNF inhibitors because of adverse events (hazard ratio [HR], 0.55 for discontinuation) than because of inefficacy. Persistence on the TNF inhibitor was relatively decreased for patients over 60 years of age (HR, 1.10).

A prospective cohort study, also from Spain, observed 417 patients with RA treated with TNF inhibitors at three hospitals.[43] EULAR responses were good in 42% and moderate in 33% of patients treated with a first TNF inhibitor. With a second TNF inhibitor, good response occurred in 20% of patients, whereas 53% had no response. With a third TNF inhibitor, 28% of patients demonstrated a good response and 72% had no response.

Although these data are observational, they suggest a trend toward diminishing returns with continued cycling through TNF inhibitors following failure of the first agent. In the second Spanish study, nearly three-quarters of patients taking a third TNF inhibitor failed to respond to treatment. Predictors of response included switching TNF inhibitors due to adverse events and younger age.

Switching to Non-TNF Inhibitors

Biologic agents with other mechanisms of action that have demonstrated efficacy in RA following failure of anti-TNF therapy include abatacept, rituximab, tocilizumab, and tofacitinib.[46]

The utility of abatacept as second-line therapy was evaluated in the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN).[47] In this study, subjects with an inadequate response to etanercept or infliximab were randomized to receive either abatacept or placebo. ACR50 response rates after 6 months of treatment were 20.3% with abatacept and 3.8% with placebo (P<0.001). These results suggest that a large proportion of patients who fail TNF therapy will have a robust response to abatacept.

With regard to multiple anti-TNF failures, a Dutch registry study of patients who failed two TNF inhibitors compared the initiation of a third TNF inhibitor to that of the B-cell–targeted agent rituximab.[48] Overall, the results favored rituximab. Change in DAS28 scores over the first 12 months of treatment was significantly greater (P=0.0044), and ESR (P=0.0008) and CRP (P=0.0287) levels were significantly lower with rituximab therapy.

In clinical trials, tocilizumab demonstrated efficacy in patients with RA who failed treatment with methotrexate[49,50] and/or TNF inhibitors.[51] For example, the efficacy of tocilizumab was evaluated in an open-label study of 1,681 subjects with RA who failed prior therapy (976 TNF-naïve and 705 TNF-experienced).[51] In this study, DAS28 remission was achieved by 61.6% of TNF-naïve subjects and by half of subjects with prior anti-TNF exposure (48.5% with remote anti-TNF use and 50.4% with recent anti-TNF use).

As of this writing, tofacitinib is the novel therapeutic agent most recently approved by the US Food and Drug Administration (FDA) to treat RA. In randomized trials, the efficacy of tofacitinib was comparable to that of adalimumab when used in combination with methotrexate,[52] and was superior to that of methotrexate when used as monotherapy.[53] In a randomized trial, tofacitinib (5 mg twice a day or 10 mg twice a day) was compared to placebo, both with methotrexate, in 399 subjects with active RA who had failed prior TNF-inhibitor therapy.[54] After 3 months of treatment, ACR20 response rates (41.7% for 5 mg, 28.1% for 10 mg, 24.4% for placebo) and DAS28 remission rates (6.7% for 5 mg, 8.8% for 10 mg, 1.7% for placebo) were significantly greater among patients treated with tofacitinib compared with those treated with placebo.

Overall, evidence suggests that patients with RA who have failed at least two TNF inhibitors will respond less well to subsequent TNF inhibitors. In these individuals, switching to a biologic agent with another mechanism of action should be considered. Data suggest the efficacy of abatacept, rituximab, tocilizumab, and tofacitinib in this patient population. When selecting a biologic agent with another mechanism of action, clinicians should consider side effect profiles, routes of administration, and their own comfort and familiarity with individual agents. ■

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Treat-to-Target

The RAPID-3 is completed by patients and requires only about 5 seconds to score manually. Electronic tools (eg, tablet-based) that allow for direct patient data capture and automatic electronic scoring are also available. In clinical trials and routine practice, the RAPID-3 has demonstrated good correlation with several other disease activity measures and (in clinical trials) the ability to discriminate between active treatment and placebo.[21-24] The main advantages of this type of measure are that it is simple, brief, and completed only by patients.

Which disease activity measure do you most often use to evaluate your patients with RA?

Choice	Proportion of Learners
DAS28	14%
CDAI	14%
SDAI	3%
RAPID-3	14%
Other	9%
Do not routinely use a disease activity measure	46%

CDAI=Clinical Disease Activity Index; DAS28=Disease Activity Score (28-joint count); RA=rheumatoid arthritis; RAPID-3=Routine Assessment of Patient Index Data; SDAI=Simplified Disease Activity Index.

In clinical trial settings, composite measures, such as the DAS28, are commonly used to integrate formal joint counts with laboratory measures. In clinical practice, any of the measures may be appropriate. Clinicians should select a disease activity measure that they can incorporate into their workflow for every visit by a patient with RA. Notably, the routine, quantitative assessment of disease activity has been shown to yield an increased likelihood of changing DMARDs in patients with RA.[25] ■

Monotherapy: Which Agent, Which Patient?

The antimetabolite methotrexate, approved for RA in the late 1980s, was the first disease-modifying drug used in RA, and remains the gold standard for first-line therapy and the anchor drug for combination therapy with other DMARDs.[20,55] Overall, methotrexate is effective and well tolerated in most patients when used in the relatively low doses that are effective for RA. However, methotrexate may not be an optimal choice for all patients with RA. For example, some patients have contraindications to methotrexate, such as pregnancy, breastfeeding, alcoholism, chronic liver disease, immunodeficiency, or blood dyscrasias.[56] Furthermore, methotrexate has the potential to cause significant adverse effects, some of which can be severe or difficult to tolerate. Patient adherence to methotrexate may be reduced in the context of poor tolerability (eg, nausea or other gastrointestinal [GI] upset, oral ulcers), limited efficacy, or polypharmacy.[55]

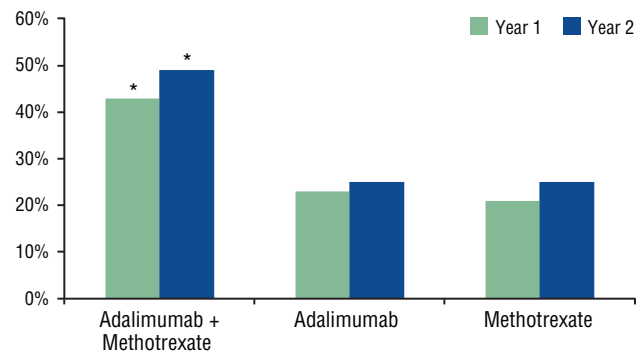
Approximately what proportion of your patients with RA are managed with biologic monotherapy?

Proportion of Patients on Monotherapy	Proportion of Learners
<10%	34%
11%-20%	18%
21%-30%	24%
31%-40%	16%
>40%	8%

RA=rheumatoid arthritis.

Although some patients do not tolerate or respond to methotrexate, studies have reproducibly demonstrated that TNF inhibitors are more effective when used in combination with methotrexate. For example, the PREMIER study compared the combination of adalimumab and methotrexate to monotherapy with either agent.[57] At 1 and 2 years, the combination produced significantly greater response and remission rates compared to either drug as monotherapy (**Figure 1**). Rates of adverse events were similar in all three groups. Studies with other TNF inhibitors have reported similar results.[58,59] A likely mechanism underlying the potentiation of efficacy with combination therapy is the suppression of ADA formation by methotrexate with a resulting increase in trough serum drug levels.[38]

FIGURE 1. Results of the PREMIER study, comparing adalimumab and methotrexate as combination or monotherapy in rheumatoid arthritis.[57]



*P<0.001 vs monotherapy.

Why Monotherapy?

Given the results of studies such as PREMIER, why even consider biologic monotherapy?

First, some patients experience serious side effects (eg, significant abnormalities in laboratory tests) and do not tolerate methotrexate. Others may instead have nonserious but persistently bothersome symptoms (eg, malaise, nausea). Second, a significant proportion of patients does not respond adequately to methotrexate and may require additional therapy. Third, evidence suggests that certain biologic agents, such as tocilizumab, have advantages when used as monotherapy compared to when they are used in combination with methotrexate.

Tolerability of Methotrexate

To evaluate the long-term safety of methotrexate as monotherapy in RA, Salliot and colleagues conducted a systematic literature review to support the EULAR recommendations for RA treatment.[60] The review was restricted to studies of patients treated for at least 2 years with methotrexate monotherapy. A total of 88 studies were included; a pooled analysis was performed of adverse events from 21 prospective cohorts, totaling 3,463 patients. In this analysis, the mean dose of methotrexate was low at 8.8 mg/week and the mean duration of therapy was 36.5 months. Overall, an average of 72.9% of patients experienced an adverse event and 10.5% permanently discontinued methotrexate because of an adverse event. The most commonly reported adverse events were GI and hepatic. The prevalence of elevated transaminases was 13%, and 3.7% of patients discontinued methotrexate because of liver toxicity. The incidence of hepatic fibrosis was 2.7% after 4 years of treatment.

A recent update to a Cochrane review of the use of methotrexate in RA was published in 2014.[61] This analysis identified seven controlled trials, including 732 subjects with RA. Follow-up ranged from 12 to 52 weeks. With regard to adverse events and tolerability, patients treated with methotrexate monotherapy were twice as likely to discontinue treatment because of adverse events as were those treated with placebo (16% vs 8%; relative risk [RR], 2.1; 95% CI, 1.3-3.3). The total rate of adverse events at 12 weeks was 45% with methotrexate monotherapy and 15% with placebo (RR, 3.0; 95% CI, 1.4-6.4).

What proportion of your patients with RA report adverse events with methotrexate?

Proportion of Patients With AEs	Proportion of Learners
<10%	19%
11%-20%	24%
21%-30%	32%
31%-40%	22%
>40%	3%

AE=adverse event; RA=rheumatoid arthritis.

These reviews also evaluated the tolerability of methotrexate in clinical trials and observational data sources. Evidence from routine clinical settings suggests higher rates of intolerance and discontinuation than in clinical trial populations. For example, retrospective reviews of clinical experience from single centers have reported that up to one-third of patients in clinical practice discontinue methotrexate because of adverse effects.[62-64] In one study, 48% of these patients eventually restarted methotrexate.[62] The most

common adverse events leading to discontinuation were hematologic side effects and elevated liver enzyme values. A Kaplan-Meier analysis identified a 74% 5-year probability of remaining on methotrexate. Similarly, a US single-center evaluation of methotrexate in routine clinical care (N=248) reported a 79% probability of continuing methotrexate over 5 years.[64] In this study, 19% of patients discontinued methotrexate, of whom 57% discontinued because of adverse events and 33% because of poor efficacy. The most common adverse events leading to discontinuation were GI. As shown in this study, intolerance is not the only reason for which patients may discontinue methotrexate; about one-third discontinue because of insufficient efficacy.

Together, these data suggest that the rate of methotrexate discontinuation in clinical practice is approximately twice as high as that reported in clinical trials. Nevertheless, most patients remain on methotrexate over an extended period of time.

What proportion of your patients with RA discontinue methotrexate because of side effects?

Proportion of Patients With AEs	Proportion of Learners
<5%	9%
5%-15%	35%
16%-25%	26%
26%-35%	18%
>35%	12%

AE=adverse event; RA=rheumatoid arthritis.

TABLE 3. DMARDs (and Their Targets) Indicated for Use as Monotherapy or Combination Therapy[4-13]

Indicated for Monotherapy	Combination Therapy Only
Abatacept (T cell)	Golimumab (TNF)
Adalimumab (TNF)	Infliximab (TNF)
Anakinra (IL-1)	Rituximab (TNF)
Certolizumab pegol (TNF)	
Etanercept (TNF)	
Tocilizumab (IL-6)	
Tofacitinib (JAK)	

DMARD=disease-modifying antirheumatic drug; IL=interleukin; JAK=Janus kinase; TNF=tumor necrosis factor.

Biologic Monotherapy: What's the Evidence?

Of the 10 biologic agents currently approved by the US FDA for the treatment of RA, seven are indicated for use as monotherapy (**Table 3**).[4-13] The remaining agents—golimumab, infliximab, and rituximab—are indicated only for use in combination with methotrexate or other non-biologic DMARDs. As discussed, the efficacy of TNF inhibitors appears to be enhanced when used in combination with methotrexate. Suppression of ADAs may be one reason for improved efficacy. However, data regarding the immunogenicity of several TNF inhibitors suggest that immunogenicity is a greater problem for the monoclonal anti-TNF antibodies than for certolizumab pegol (a pegylated Fab′ fragment) or etanercept.[65]

Ideally, the biologic agent used as monotherapy should be superior to methotrexate monotherapy and also to the combination of that agent with methotrexate.

Most of the biologic agents approved for use as monotherapy have demonstrated efficacy that is at least comparable to that of methotrexate (**Table 4**).[49,50,53,57,58,66-79] Several randomized clinical studies have reported significantly greater efficacy of biologic monotherapy compared to methotrexate monotherapy.[50,53,58,73]

One such study is the Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy (AMBITION), a randomized trial that compared tocilizumab to methotrexate, each as monotherapy, in subjects with active RA who had not failed previous therapy.[75] A total of 673 subjects were randomized, and 570 were included in the intent-to-treat (ITT) analysis. At 24 weeks, there was a significantly greater ACR20 response rate with tocilizumab than with methotrexate in the ITT analysis (69.9% vs 52.5%; $P<0.001$). ACR50 and ACR70 response rates were also significantly greater in the tocilizumab group, as were remission rates, defined as a DAS28 score <2.6 (**Figure 2** on page 10). Overall, subjects in the tocilizumab group were five times more likely to achieve DAS28 remission. Studies such as AMBITION suggest potential advantages to newer biologic agents over methotrexate when used as monotherapy.

Other trials include the ERA trial, which compared etanercept to methotrexate over 1 year and reported significantly greater ACR20 rates (72% vs 59%; $P=0.005$) and lower rates of radiographic progression ($P=0.017$) with etanercept.[58] However, other studies of etanercept monotherapy have reported conflicting results regarding the relative efficacy of etanercept and methotrexate.[74]

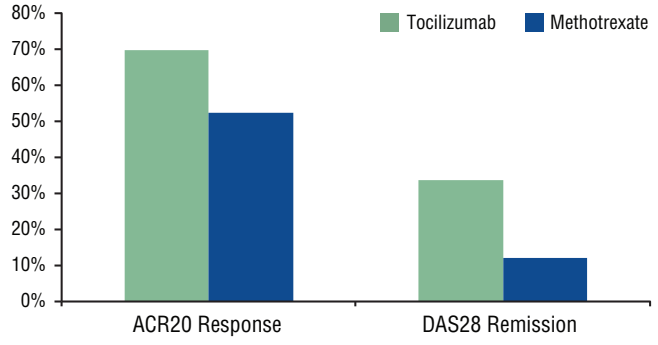
One trial comparing tofacitinib monotherapy to methotrexate monotherapy has been published. This 2-year, randomized study reported significantly greater ACR70 response rates and reduced radiographic progression ($P<0.001$) at 6 months with tofacitinib compared to methotrexate (tofacitinib, 25.5% at 5 mg and 37.7% at 10 mg; methotrexate, 12%; $P<0.001$ both comparisons).[53]

TABLE 4. Evidence Describing the Use of Biologic Agents as Monotherapy for Rheumatoid Arthritis[49,50,53,57,58,66-79]

Agent	Monotherapy > Placebo	Monotherapy at Least = Methotrexate	Monotherapy > Methotrexate	Monotherapy > Combination (Agent + Methotrexate)
Abatacept	+	NR	NR	–
Adalimumab	+	+	–	–
Anakinra	+	NR	NR	NR
Certolizumab pegol	+	NR	NR	NR
Etanercept	NR	+	+/–	–
Tocilizumab	+	+	+	+/–
Tofacitinib	NR	+	+	NR

NR=not reported.

FIGURE 2. Outcomes of the AMBITION trial, which compared tocilizumab and methotrexate as monotherapy.[75]



P<0.001
AMBITION=Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy; DAS28=Disease Activity Score (28-joint count).

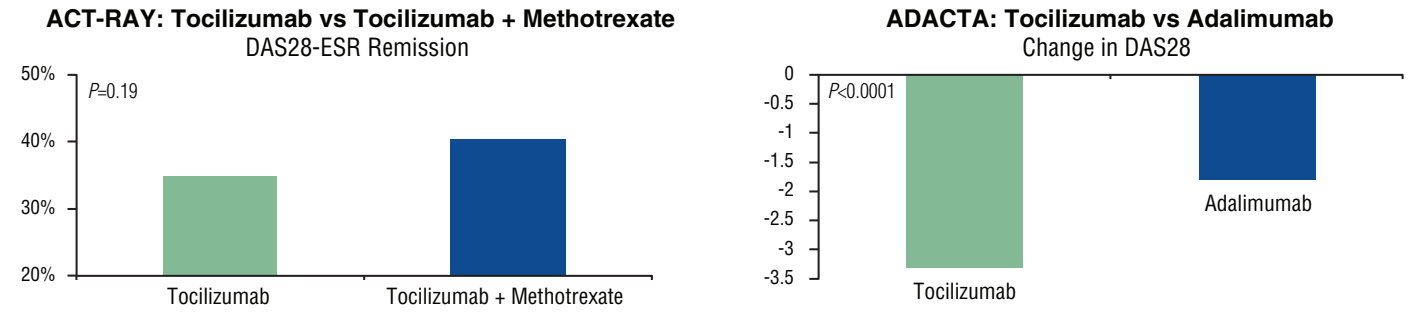
As described, the AMBITION trial reported significantly superior outcomes, both in response and remission rates, with tocilizumab monotherapy compared to methotrexate monotherapy.[75] Recent trials presented at the 2015 EULAR Annual Scientific Meeting reported different results regarding the comparative efficacy of tocilizumab and methotrexate as monotherapy. In these studies, tocilizumab was superior to methotrexate in some outcome measures but not in others; in one study, significant early differences between groups disappeared with long-term treatment.[76-78] In the FUNCTION trial, for example, 1,162 methotrexate-naïve subjects with early RA were randomized to receive tocilizumab 4 mg/kg with methotrexate, tocilizumab 8 mg/kg either with methotrexate or as monotherapy, or methotrexate monotherapy.[80] At 24 weeks, significantly more subjects in the 8 mg/kg tocilizumab groups (with or without methotrexate) achieved DAS28 remission compared to the methotrexate monotherapy group (45%, 39%, and 15%, respectively; *P*<0.0001).

Overall, the preponderance of evidence currently supports efficacy of tocilizumab as monotherapy. In fact, some evidence suggests that tocilizumab monotherapy has similar efficacy to tocilizumab plus methotrexate.[49,68] In the 2-year ACT-RAY study, 566 patients with active RA despite treatment with methotrexate were randomized either to add or switch to tocilizumab.[49,68,69] A planned interim analysis was performed of the 512 subjects who completed 24 weeks of treatment. At this time point, DAS28-ESR remission rates were not significantly different between groups although response rates were higher with combination therapy than with tocilizumab monotherapy (40.4% and 34.8%, respectively; *P*=0.19) (**Figure 3**). Other outcomes, including adverse events, were similar between groups. One- and two-year follow-up studies confirmed these results, with some measures exhibiting a trend to slightly favor combination therapy.

In the ADACTA trial, one of the few head-to-head studies of biologic monotherapies, tocilizumab was compared to adalimumab in subjects who were intolerant of or inappropriate for methotrexate.[50] This parallel-group study compared tocilizumab 8 mg/kg every 4 weeks to adalimumab 40 mg every 2 weeks. At 24 weeks, the change from baseline in DAS28 scores was significantly greater with tocilizumab than with adalimumab (**Figure 3**). Rates of adverse events were similar between groups.

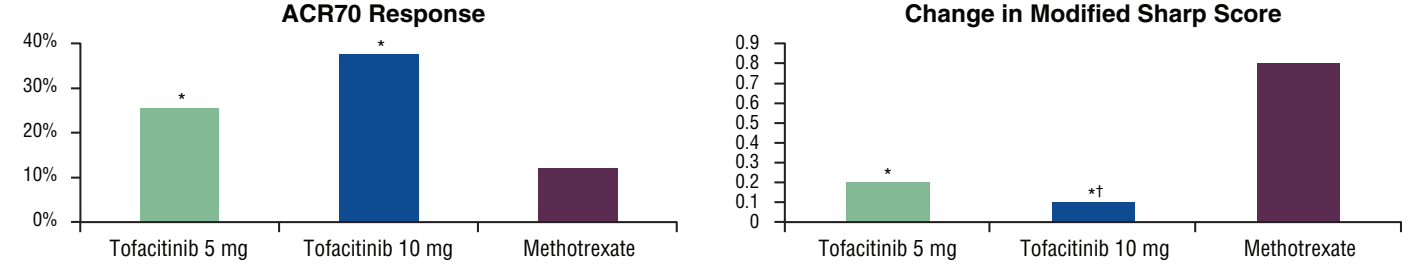
Tofacitinib has also been compared to methotrexate as monotherapy. The ORAL Start study randomized 958 subjects with RA who were methotrexate-naïve (or had not received therapeutic doses of methotrexate) to one of three groups: tofacitinib 5 mg twice a day, tofacitinib 10 mg twice a day, or methotrexate (titrated up to 20 mg per week).[53] A total of 956 subjects received at least one dose of a study drug. The primary endpoints were change in modified Sharp score (higher scores indicate greater structural damage) and ACR70 response rate. At 6 months, significant differences were found between the tofacitinib groups and the methotrexate group in both primary endpoints (**Figure 4**). The mean changes from baseline in Sharp score were modest overall, but were significantly lower with tofacitinib (*P*<0.001), reflecting less structural damage to the joint, a key outcome in RA that correlates with patients' ability to function.

FIGURE 3. Outcomes of ACT-RAY and ADACTA trials, which evaluated tocilizumab as monotherapy in rheumatoid arthritis.[49,50]



DAS28=Disease Activity Score (28-joint count); ESR=erythrocyte sedimentation rate.

FIGURE 4. Response rates and radiographic outcomes from the ORAL Start study, which evaluated tofacitinib as monotherapy in rheumatoid arthritis.[53]



**P*<0.001 vs methotrexate. †Sharp score change <0.1. ACR=American College of Rheumatology.

Methotrexate: More Problematic in Clinical Practice Than Clinical Trials?

In most RA clinical trials, methotrexate is used as first-line monotherapy or in combination with biologic agents. Overall, studies have reported greater efficacy of TNF inhibitors when combined with methotrexate than when used as monotherapy. However, clinical trials use highly controlled conditions and carefully selected patient populations. Furthermore, adherence rates are relatively high and discontinuation rates are relatively low in these studies, compared with rates typically observed in clinical settings. In highly controlled clinical studies, discontinuation rates among patients taking methotrexate range from 5% to 15%.[72]

Conversely, evidence suggests that many patients treated with methotrexate in the clinical setting do not use the drug as prescribed, and many discontinue methotrexate without telling their rheumatologist (**Table 5**).[72,81-88] Observational studies of routine clinical practice have reported methotrexate discontinuation rates of 10% to as high as 77% after 3 to 12 years of treatment.[72]

Analyses of registry data have found that more than half of patients who are prescribed their first biologic agent do not fill their prescriptions for methotrexate.[81,82] Poor adherence to methotrexate may contribute to the frequent use of biologic monotherapy in clinical practice. A study reported at the 2015 EULAR Annual Scientific Meeting used registry data to demonstrate that as many as 40% of patients with RA are treated with biologic monotherapy.[83] Data from the United States also suggest that a high proportion of RA patients in routine care settings receive monotherapy. In one study, 30% of patients with RA initiated biologic agents as monotherapy, compared with 36% who initiated biologic agents with methotrexate.[84]

Despite challenges with adherence to methotrexate, registry data clearly demonstrate improved persistence of treatment with biologic agents when they are combined with methotrexate.[85-87] One study of a registry database reported significantly greater 4-year TNF-inhibitor survival rates when etanercept or adalimumab was combined with methotrexate, as compared to monotherapy with either agent.[87]

However, even with prescriptions for combination therapy that includes a biologic agent and methotrexate, many patients do not fill their DMARD prescriptions, especially those for methotrexate.[81,82,88] Studies of drug plan databases have found high rates of nonadherence to methotrexate following the prescription of a biologic agent.[81,82] One study of public and private drug plans in Quebec and Ontario, Canada, examined records of 6,744 patients with RA.[81] All patients who purchased a biologic agent over a 1-month period (in 2009) were monitored for 90 days before and after purchase of the biologic agent. Among patients taking their first biologic agent for more than 6 months, 45% did not purchase a DMARD; 41% taking biologic therapy for more than 24 months did not purchase a DMARD (**Figure 5**). With regard to methotrexate, 58% of subjects taking a biologic agent for more than 6 months did not purchase methotrexate, and 54% taking a biologic agent for more than 24 months did not purchase methotrexate. Findings were similar for patients taking their second biologic agent: 36% to 38% did not purchase the DMARD that had been prescribed in combination with the biologic agent.

Managing Methotrexate Therapy

There are several options to help manage side effects from methotrexate. First, all patients taking methotrexate should also take supplemental folate; lack of folate supplementation may contribute to higher rates of side effects. For patients with GI intolerance or who need greater efficacy than that provided by oral methotrexate, parenteral (subcutaneous) formulations are available to treat RA. Recent data suggest some advantages to subcutaneous formulations, including reduced GI side effects, higher bioavailability, and possibly greater efficacy.[89-91] Antiemetics and other adjunctive therapies can also be considered for patients with GI side effects. Finally, if methotrexate is simply not an option, other DMARDs can be used instead.

After intolerance, the second most common reason for discontinuation of methotrexate is lack of efficacy, although patients much more commonly have a partial, incomplete response to methotrexate than no response at all.[72,81,82,88]

FIGURE 5. Registry data describing poor adherence to methotrexate in clinical settings.[81]

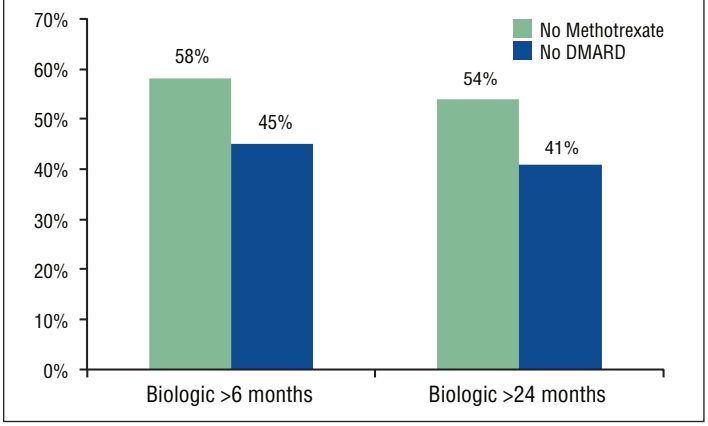


TABLE 5. Differences in Methotrexate Use and Response Between Clinical Trials and Clinical Practice Settings[72,81-88]

Clinical Trial	Clinical Practice
• MTX recommended first-line therapy, alone or with biologic agents	• Biologic monotherapy common (30%-40% of patients with RA)
• High adherence rates • Low discontinuation rates (5%-15% with MTX)	• Up to 50% or more patients treated with a biologic agent do not fill prescriptions for MTX • Higher rate of discontinuation (10%-77% with long-term use) • High rate of AEs with MTX, especially GI effects • Inefficacy second most common reason for discontinuation
• TNF inhibitors show better efficacy with MTX	• Persistence with biologic agents improved with MTX
• Highly selected patient population	• Heterogeneous patient population
• Cost of medications covered	• Economic considerations

AE=adverse event; GI=gastrointestinal; MTX=methotrexate; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

Obviously, suboptimal efficacy must be addressed in order to achieve the target of remission or low disease activity.[20] Several options are available to increase the efficacy of methotrexate in patients with RA. The first is to ensure that the methotrexate dose is optimized. Clinical inertia may be one reason for suboptimal methotrexate dosing. Also, parenteral formulations of methotrexate have demonstrated greater bioavailability than oral formulations, and thus may also provide greater efficacy.[89-92] As recommended by guidelines, the addition of other conventional synthetic DMARDs and/or biologic agents should be considered.[20] Switching to a biologic agent that has been shown to be effective as monotherapy can be considered.

Switching from methotrexate to leflunomide is another option. In randomized trials, leflunomide has demonstrated roughly comparable efficacy compared to methotrexate over long-term treatment, both as monotherapy and in combination with TNF inhibitors.[93-97] Preliminary studies also suggest equivalent efficacy of leflunomide and methotrexate, when either is combined with tocilizumab or rituximab.[98,99] The reported incidence of side effects is generally similar with either methotrexate or leflunomide.[100]

Methotrexate and Anti-drug Antibodies

ADAs to biologic agents have been identified in clinical trials in patients with RA. Reported prevalence rates vary widely (**Table 6**).[36,101-106] Factors that can affect detection and prevalence of ADAs include timing of sampling relative to dosing of the biologic agent, duration of treatment, molecular structure of the biologic agent, and the assay used to detect antibodies.[38] Although overall prevalence rates vary, within-study comparisons demonstrate an effect of methotrexate on suppression of ADA levels. Concomitant methotrexate use has also been associated with greater clinical response (as in the PREMIER study, for example) and longer survival on a given biologic agent.

It is believed that all biologic agents are immunogenic, and ADAs have been reported in association with commonly used biologic agents in RA.[107] Strong evidence links the development of antibodies to some biologic agents such as the monoclonal antibodies (infliximab and adalimumab) to reduced serum drug levels, and loss of efficacy, and hypersensitivity (infusion) reactions.[108] Less evidence exists for other biologic agents (golimumab, certolizumab, and etanercept) regarding the development and impact of ADAs.

Evidence reported at the 2015 EULAR Annual Scientific Meeting suggests that tocilizumab poses a low risk for immunogenicity, possibly as a result of its mechanism of action, although serious cases of hypersensitivity (including anaphylaxis) have been reported.[109,110] Lack of standardization among assays for ADAs limits our understanding of the true incidence of these antibodies in clinical practice, and assays for ADAs and trough serum drug levels are not available in the United States for most biologic agents.[107] Concomitant use of immunosuppressants, such as methotrexate, has been shown to reduce the incidence of ADAs and improve drug persistence and efficacy of biologic agents, especially TNF inhibitors.[107,108,111]

In clinical practice, patients who do not respond to biologic therapy, especially those who lose response over time, should be evaluated for the presence of ADAs (if an ADA assay is available for that biologic agent). Trough serum drug testing, if available, will help determine the impact of ADAs. For patients who are responding poorly to treatment with a biologic agent and who have ADAs with low trough serum drug levels, the addition of methotrexate (if not already used) or switching to another biologic agent could be considered. For patients without ADAs, change to an alternative mechanism of action is probably warranted. ■

TABLE 6. Incidence of Antibodies Against Biologic Agents in RA When Used With or Without Methotrexate[36,101-106]

Study	Agent	N	Follow-up (months)	ADA %, DMARD	ADA %, No DMARD	*P* Value
Maini et al, 1998	Infliximab	101	6	0-15	7-53	NA
Bendtzen et al, 2006	Infliximab	106	18	40 (methotrexate only)	50 (methotrexate only)	NA
Pascual-Salcedo et al, 2011	Infliximab	85	6	32	37	0.073
Bartelds et al, 2007	Adalimumab	121	6	12	38	0.003
Bartelds et al, 2011 Krieckaert et al, 2012	Adalimumab	232	36	12-35	<50	<0.001
Emery et al, 2009	Golimumab	315	6	1.9-3.7	13.5	NA

ADA=anti-drug antibodies; DMARD=disease-modifying antirheumatic drug; NA=not available; RA=rheumatoid arthritis.

Summary

Rheumatologists now have more options than ever to manage patients with RA, although a cure remains elusive. When tailored appropriately to the needs of individual patients, DMARD treatment can help many patients with RA achieve and maintain remission. Remission is the desired goal of treatment and may be attainable by up to one-third of patients with RA treated appropriately, particularly if they were diagnosed in the contemporary era and therapy was initiated promptly. Managing a poor response to DMARDs requires clinicians to understand the data describing the optimal sequencing of agents and the use of biologic DMARDs as monotherapy or combined with conventional DMARDs. Current evidence suggests that the reason for initial TNF-inhibitor failure may influence response to subsequent TNF inhibitors. In general, many patients who do not respond or who lose response to treatment with their first TNF inhibitor will respond to a second TNF inhibitor. However, continued cycling through TNF inhibitors produces diminishing results, and changing to another biologic agent with an alternative mechanism of action probably is preferable. Newer agents, such as tocilizumab and tofacitinib, have demonstrated efficacy both as monotherapy and in combination with methotrexate, providing clinicians with effective new strategies to manage this chronic and potentially debilitating disease.

References

1. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73:492-509.
2. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68:1-26.
3. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631-637.
4. Kineret [prescribing information]. Stockholm, Sweden: Orphan Biovitrium AB; 2015.
5. Orencia [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
6. Actemra [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2014.
7. Xeljanz [prescribing information]. New York, NY: Pfizer Laboratories; 2016.
8. Cimzia [prescribing information]. Smyrna, GA: UCB, Inc.; 2013.
9. Simponi [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2013.
10. Remicade [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2013.
11. Rituxan [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2014.
12. Enbrel [prescribing information]. Thousand Oaks, CA: Immunex Corporation; 2013.
13. Humira [prescribing information]. North Chicago, IL: AbbVie, Inc.; 2014.
14. Vermeer M, Kuper HH, Hoekstra M, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: Results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum*. 2011;63:2865-2872.
15. Stoffer MA, Schoels MM, Smolen JS, et al. Evidence for treating rheumatoid arthritis to target: Results of a systematic literature search update. *Ann Rheum Dis.* 2016;75:16-22.
16. Pincus T, Castrejón I. Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. *Bull Hosp Jt Dis (2013).* 2013;71(suppl 1):S33-40.
17. Saag KG, Yazdany J, Alexander C, et al. Defining quality of care in rheumatology: The American College of Rheumatology white paper on quality measurement. *Arthritis Care Res (Hoboken).* 2011;63:2-9.
18. American College of Rheumatology. ACR Endorsed Measures: Rheumatoid Arthritis. 2016; Available at: http://www.rheumatology.org/Practice-Quality/Clinical-Support/Quality-Measurement/ACR-Endorsed-Measures. 2016. Accessed April 1, 2016.
19. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken).* 2012;64:640-647.
20. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64:625-639.
21. Pincus T, Bergman MJ, Yazici Y, Hines P, Raghupathi K, Maclean R. An index of only patient-reported outcome measures, routine assessment of patient index data 3 (RAPID3), in two abatacept clinical trials: similar results to disease activity score (DAS28) and other RAPID indices that includes physician-reported measures. *Rheumatology (Oxford).* 2008;47:345-349.
22. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: Proposed severity categories compared to disease activity score and clinical disease activity index categories. *J Rheumatol.* 2008;35:2136-2147.
23. Pincus T, Swearingen CJ, Bergman MJ, et al. RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): Agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds. *Arthritis Care Res (Hoboken).* 2010;62:181-189.
24. Pincus T, Furer V, Keystone E, Yazici Y, Bergman MJ, Luijtens K. RAPID3 (Routine Assessment of Patient Index Data 3) severity categories and response criteria: Similar results to DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) in the RAPID 1 (Rheumatoid Arthritis Prevention of Structural Damage) clinical trial of certolizumab pegol. *Arthritis Care Res (Hoboken).* 2011;63:1142-1149.
25. Dougados M, Soubrier M, Perrodeau E, et al. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: Results of a prospective, multicentre, randomised, controlled trial (COMEDRA). *Ann Rheum Dis.* 2015;74:1725-1733.
26. Kamal KM, Madhavan SS, Hornsby JA, Miller LA, Kavookjian J, Scott V. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine.* 2006;73:718-724.
27. Bergman MJ, Elkin EP, Ogale S, Kamath T, Hanburger MI. Response to biologic disease-modifying anti-rheumatic drugs after discontinuation of anti-tumor necrosis factor-α agents for rheumatoid arthritis. *Rheumatol Ther.* 2014;1:21-30.
28. Du Pan SM, Scherer A, Gabay C, Finckh A. Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. *Ann Rheum Dis.* 2012;71:997-999.
29. Rémy A, Avouac J, Gossec L, Combe B. Clinical relevance of switching to a second tumour necrosis factor-α inhibitor after discontinuation of a first tumour necrosis factor-α inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis. *Clin Exp Rheumatol.* 2011;29:96-103.
30. Favalli EG, Biggioggero M, Marchesoni A, Meroni PL. Survival on treatment with second-line biologic therapy: A cohort study comparing cycling and swap strategies. *Rheumatology (Oxford).* 2014;53:1664-1668.
31. Plenge RM, Criswell LA. Genetic variants that predict response to anti-tumor necrosis factor therapy in rheumatoid arthritis: Current challenges and future directions. *Curr Opin Rheumatol.* 2008;20:145-152.
32. Kim HL, Lee MY, Park SY, et al. Comparative effectiveness of cycling of tumor necrosis factor-α (TNF-α) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-α inhibitor using a Bayesian approach. *Arch Pharm Res.* 2014;37:662-670.
33. Liu C, Batliwalla F, Li W, et al. Genome-wide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis. *Mol Med.* 2008;14:575-581.
34. Emery P, Gottenberg JE, Rubbert-Roth A, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis.* 2015;74:979-984.
35. Buch MH, Bingham SJ, Bryer D, Emery P. Long-term infliximab treatment in rheumatoid arthritis: Subsequent outcome of initial responders. *Rheumatology (Oxford).* 2007;46:1153-1156.
36. Bartelds GM, Krieckaert CL, Nurmohamed MT, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA.* 2011;305:1460-1468.
37. Krintel SB, Grunert VP, Hetland ML, et al. The frequency of anti-infliximab antibodies in patients with rheumatoid arthritis treated in routine care and the associations with adverse drug reactions and treatment failure. *Rheumatology (Oxford).* 2013;52:1245-1253.
38. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology (Oxford).* 2014;53:213-222.
39. Chatzidionysiou K, Askling J, Eriksson J, Kristensen LE, van Vollenhoven R, ARTIS Group. Effectiveness of TNF inhibitor switch in RA: Results from the national Swedish register. *Ann Rheum Dis.* 2015;74:890-896.
40. Virkki LM, Valleala H, Takakubo Y, et al. Outcomes of switching anti-TNF drugs in rheumatoid arthritis--a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). *Clin Rheumatol.* 2011;30:1447-1454.
41. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ, British Society for Rheumatology Biologics Registry. Outcomes after switching from one anti-tumor necrosis factor-α agent to a second anti-tumor necrosis factor-α agent in patients with rheumatoid arthritis: Results from a large UK national cohort study. *Arthritis Rheum.* 2007;56:13-20.
42. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP, BSR Biologics Register. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. *Rheumatology (Oxford).* 2008;47:1000-1005.
43. Gomez-Reino JJ, Carmona L, BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: An observational study of 488 patients over a four-year period. *Arthritis Res Ther.* 2006;8:R29.
44. Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: Results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford).* 2008;47:507-513.
45. Navarro-Sarabia F, Ruiz-Montesinos D, Hernandez B, et al. DAS-28-based EULAR response and HAQ improvement in rheumatoid arthritis patients switching between TNF antagonists. *BMC Musculoskelet Disord.* 2009;10:91.
46. Emery P. Optimizing outcomes in patients with rheumatoid arthritis and an inadequate response to anti-TNF treatment. *Rheumatology (Oxford).* 2012;51(suppl 5):v22-v30.
47. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor-α inhibition. *N Engl J Med.* 2005;353:1114-1123.
48. Blom M, Kievit W, Donders AR, et al. Effectiveness of a third tumor necrosis factor-α-blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. *J Rheumatol.* 2011;38:2355-2361.
49. Dougados M, Kissel K, Sheeran T, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis.* 2013;72:43-50.
50. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): A randomised, double-blind, controlled phase 4 trial. *Lancet.* 2013;381:1541-1550.
51. Bykerk VP, Östör AJ, Alvaro-Gracia J, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: A large, open-label study close to clinical practice. *Ann Rheum Dis.* 2012;71:1950-1954.
52. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med.* 2012;367:508-519.
53. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med.* 2014;370:2377-2386.
54. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: A randomised phase 3 trial. *Lancet.* 2013;381:451-460.
55. Scher JU. Monotherapy in rheumatoid arthritis. *Bull Hosp Jt Dis (2013).* 2013;71:204-207.
56. Methotrexate [prescribing information]. Columbus, OH: Roxane Laboratories, Inc.; 2015.
57. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54:26-37.
58. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: Double-blind randomised controlled trial. *Lancet.* 2004; 363:675-681.

59. Emery P, Fleischmann R, van der Heijde D, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: Results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum.* 2011;63:1200-1210.
60. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: A systematic literature research. *Ann Rheum Dis.* 2009;68:1100-1104.
61. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. *Cochrane Database Syst Rev.* 2014;6:CD000957.
62. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: Treatment duration and incidence of adverse drug reactions. *Rheumatology (Oxford).* 2005;44:61-66.
63. Nikiphorou E, Negoescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: A retrospective review of discontinuation rates from a large UK cohort. *Clin Rheumatol.* 2014;33:609-614.
64. Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T. Long term safety of methotrexate in routine clinical care: Discontinuation is unusual and rarely the result of laboratory abnormalities. *Ann Rheum Dis.* 2005;64:207-211.
65. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol.* 2013;9:164-172.
66. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
67. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. *Ann Rheum Dis.* 2006;65:1478-1483.
68. Dougados M, Kissel K, Conaghan PG, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: The ACT-RAY study. *Ann Rheum Dis.* 2014;73:803-809.
69. Bykerk VP, Östör AJ, Alvaro-Gracia J, et al. Comparison of tocilizumab as monotherapy or with add-on disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and inadequate responses to previous treatments: An open-label study close to clinical practice. *Clin Rheumatol.* 2015;34:563-571.
70. Nash P, Nayiager S, Genovese MC, et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: Results from a phase III, international, multicenter, parallel-arm, open-label study. *Arthritis Care Res (Hoboken).* 2013;65:718-728.
71. Takeuchi T, Matsubara T, Urata Y, et al. Phase III, multicenter, open-label, long-term study of the safety of abatacept in Japanese patients with rheumatoid arthritis and an inadequate response to conventional or biologic disease-modifying antirheumatic drugs. *Mod Rheumatol.* 2014;24:744-753.
72. Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. *Ann Rheum Dis.* 2013;72:1897-1904.
73. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: Two-year radiographic and clinical outcomes. *Arthritis Rheum.* 2002;46:1443-1450.
74. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* 2006;54:1063-1074.
75. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. *Ann Rheum Dis.* 2010;69:88-96.
76. Takeuchi T, Kaneko Y, Atsumi T, et al. Adding tocilizumab or switching to tocilizumab monotherapy in RA patients with inadequate response to methotrexate: 24-week results from a randomized controlled study (SURPRISE Study). *Ann Rheum Dis.* 2013;72(suppl 3):62.
77. Durez P, Depresseux G, Toukap AN, et al. Rate of remission by tocilizumab or methotrexate induction therapy in early active rheumatoid arthritis: Results of the TOMERA trial. *Ann Rheum Dis.* 2013;72(suppl 3):623.
78. Burmester G, Rigby W, van Vollenhoven R, et al. Tocilizumab in combination and monotherapy versus methotrexate in MTX-naïve patients with early rheumatoid arthritis: Clinical and radiographic outcomes from a randomised, placebo-controlled trial. *Ann Rheum Dis.* 2013;72(suppl 3):63.
79. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012;367:495-507.
80. Burmester GR, Rigby WF, van Vollenhoven RF, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis.* 2015. doi: 10.1136/annrheumdis-2015-207628.
81. Choquette D, Thomas O, Arundine M. Large discrepancy between expected and observed ratios of biologic treated rheumatoid arthritis patients also compliant on DMARDS. *Ann Rheum Dis.* 2011;70:197.
82. Choquette D, Thomas O, Arundine M. Lower than expected levels of DMARD acquisition immediately pre and post biologic initiation in rheumatoid arthritis patients. *Arthritis Rheum.* 2012;64(suppl 10):1841.
83. Herold M, Eichbauer-Sturm G, Puchner R, et al. Commonplace though not approved: Monotherapy with biologics. Data from the Austrian Bioreg registry. *Ann Rheum Dis.* 2015;74(suppl 2):486.
84. Yazici Y, Shi N, John A. Utilization of biologic agents in rheumatoid arthritis in the United States: Analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bull NYU Hosp Jt Dis.* 2008;66:77-85.
85. Soliman MM, Ashcroft DM, Watson KD, et al. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis.* 2011;70:583-589.
86. Zhang J, Xie F, Delzell E, et al. Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2015;67:624-632.
87. Choquette D, Raynauld JP, Haraoui B, Sauvageau D. Better retention rate at 5 years of anti-TNF agents used in conjunction with methotrexate over time in patients with rheumatoid arthritis: Real-life data from RHUMADATA computerized database [abstract AB0458]. *Ann Rheum Dis.* 2012;71(suppl 3):663.
88. Rahal N, Afif N, Ardizzone M, et al. Biologics in monotherapy in rheumatoid arthritis: A multicentric retrospective study of 109 patients. *Ann Rheum Dis.* 2015;74(suppl 2):1055-1056.
89. Braun J, Kastner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum.* 2008;58:73-81.
90. Pichlmeier U, Heuer KU. Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. *Clin Exp Rheumatol.* 2014;32:563-571.
91. Müller RB, Kempis JV, Haile SR, Schiff MH. Effectiveness, tolerability, and safety of subcutaneous methotrexate in early rheumatoid arthritis: A retrospective analysis of real-world data from the St. Gallen cohort. *Semin Arthritis Rheum.* 2015;45:28-34.
92. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: Optimizing therapy among different formulations. Current and emerging paradigms. *Clin Ther.* 2014;36:427-435.
93. Kalden JR, Schattenkirchner M, Sorensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: A five-year followup study. *Arthritis Rheum.* 2003;48:1513-1520.
94. Cohen S, Cannon GW, Schiff M, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. *Arthritis Rheum.* 2001;44:1984-1992.
95. Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: Results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum.* 2000;43:495-505.
96. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford).* 2000;39:655-665.
97. De Stefano R, Frati E, Nargi F, et al. Comparison of combination therapies in the treatment of rheumatoid arthritis: Leflunomide-anti-TNF-α versus methotrexate-anti-TNF-α. *Clin Rheumatol.* 2010;29:517-524.
98. Narvaéz J, Diaz-Torné C, Magallares B, et al. Comparative effectiveness of tocilizumab with either methotrexate or leflunomide in the treatment of rheumatoid arthritis. *PLoS One.* 2015;10:e0123392.
99. Narvaéz J, Diaz-Torné C, Ruiz JM, et al. Comparative effectiveness of rituximab in combination with either methotrexate or leflunomide in the treatment of rheumatoid arthritis. *Semin Arthritis Rheum.* 2011;41:401-405.
100. Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: What is new in 2011? *Curr Opin Rheumatol.* 2011;23:288-292.
101. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor-α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41:1552-1563.
102. Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor-α inhibitor infliximab. *Arthritis Rheum.* 2006;54:3782-3789.
103. Pascual-Salcedo D, Plasencia C, Ramiro S, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology (Oxford).* 2011;50:1445-1452.
104. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: Relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis.* 2007;66:921-926.
105. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis.* 2012;71:1914-1915.
106. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor-α monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;60:2272-2283.
107. Solomon G. Immunogenicity: Implications for rheumatoid arthritis treatment. *Bull Hosp Jt Dis (2013).* 2013;71:200-203.
108. Ruderman EM. The role of concomitant methotrexate in biologic therapy for rheumatoid arthritis. *Bull Hosp Jt Dis (2013).* 2013;71(suppl 1):S29-32.
109. Burmester GR, Bao M, Reiss W, Wallace T, Lacey S, Kivitz A. Immunogenicity, safety and efficacy of subcutaneous tocilizumab in patients who missed doses. *Ann Rheum Dis.* 2015;74(suppl 2):478.
110. Sigaux J, Hamze M, Daien C, et al. The lack of antidrug antibodies among patients treated with tocilizumab: A clue to good efficacy profiles when used as monotherapy. *Ann Rheum Dis.* 2015;74(suppl 2):1050.
111. Iannone F, Gremese E, Atzeni F, et al. Longterm retention of tumor necrosis factor-α inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: An appraisal of predictors. *J Rheumatol.* 2012;39:1179-1184.

Issues in Rheumatoid Arthritis Treatment
Clinical Implications of Current Evidence

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POST-TEST CME/CE QUESTIONS

1. **Which of the following agents is indicated for use ONLY in combination with methotrexate in patients with rheumatoid arthritis?**
   - **A.** Abatacept
   - **B.** Certolizumab pegol
   - **C.** Infliximab
   - **D.** Tocilizumab

2. **According to current guidelines, which of the following agents is reserved for second-line use?**
   - **A.** Abatacept
   - **B.** Adalimumab
   - **C.** Golimumab
   - **D.** Tofacitinib

3. **All of the following describe quality measures endorsed by the American College of Rheumatology EXCEPT:**
   - **A.** At least yearly assessment of functional status assessment
   - **B.** Documented TB screen prior to initiation of biologic therapy
   - **C.** At least 50% of patients maintain remission or low disease activity
   - **D.** Regular assessment of disease activity using a standardized measure

4. **According to registry studies of rheumatology patients, persistence with a second TNF inhibitor was reduced in patients who discontinued a first TNF inhibitor because of what?**
   - **A.** Inefficacy
   - **B.** Adverse effects
   - **C.** Route of administration
   - **D.** Inconvenient dose schedule

5. **According to a prospective cohort study, EULAR good response occurred in 42% of patients treated with a first TNF inhibitor. Approximately what proportion had EULAR good response to a second TNF inhibitor?**
   - **A.** 10%
   - **B.** 20%
   - **C.** 40%
   - **D.** 50%

6. **The PREMIER study, which compared adalimumab alone, methotrexate alone, or both agents together, reported which of the following results?**
   - **A.** Similar remission rates between all three groups
   - **B.** Significantly greater remission rates with adalimumab alone versus methotrexate alone
   - **C.** Significantly greater remission rates with methotrexate alone versus adalimumab alone
   - **D.** Significantly greater remission rates with combination therapy compared to either monotherapy

7. **Studies of routine clinical settings suggest that rates of intolerance and discontinuation with methotrexate are:**
   - **A.** Nearly zero in clinical settings
   - **B.** Similar to rates reported in clinical trials
   - **C.** Slightly lower than rates reported in clinical trials
   - **D.** Substantially higher than rates reported in clinical trials

8. **The ADACTA trial, which compared monotherapy with tocilizumab to adalimumab in patients with rheumatoid arthritis, reported which of the following findings?**
   - **A.** Significantly higher adverse event rates with tocilizumab
   - **B.** Significantly greater DAS28 remission rates with adalimumab
   - **C.** No significant differences between groups in clinical outcomes
   - **D.** Significantly greater reductions in DAS28 scores with tocilizumab

9. **The ORAL Start study, which compared tofacitinib (5 mg or 10 mg) to methotrexate in patients with rheumatoid arthritis, reported which of the following findings?**
   - **A.** Significantly greater ACR70 response rates with methotrexate
   - **B.** No differences between groups in response rates or radiographic progression
   - **C.** Significantly lower change in modified Sharp score with both tofacitinib doses
   - **D.** Significantly greater ACR70 response rates with 10 mg but not 5 mg tofacitinib

10. **In the ACT-RAY study, monotherapy with tocilizumab was associated with which of the following?**
    - **A.** No significant difference between groups in DAS28 remission rates
    - **B.** Numerically higher response rates with tocilizumab compared to combination therapy
    - **C.** Significantly lower DAS28 remission rates compared to tocilizumab plus methotrexate
    - **D.** Significantly higher adverse event rates with combination therapy compared to tocilizumab monotherapy

Issues in Rheumatoid Arthritis Treatment: Clinical Implications of Current Evidence Evaluation Form

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☐ Other; specify _____

LEARNING OBJECTIVES: *Having completed this activity, you are better able to:*	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Identify the appropriate use of newer therapies for rheumatoid arthritis (RA) management based on recent trial data	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Identify all approved first-line therapy options for patients with RA	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Apply strategies for using monotherapy as an appropriate option for managing patients with RA	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Describe pharmacologic strategies for the treatment of RA as they relate to the mechanism of action of therapeutic interventions	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Discuss the potential reasons for anti–tumor necrosis factor (TNF) failure	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Describe the benefits and limitations of anti-TNF cycling in disease control and patient outcomes	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Discuss whether biologic therapies with mechanisms of action other than TNF inhibition are appropriate when managing patients in whom anti-TNF therapy has failed	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Assess approaches to managing anti-TNF cycling and switching to an agent with a different mechanism of action	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Recognize the impact of Healthcare Effectiveness Data and Information Set (HEDIS) measures and Centers for Medicare & Medicaid Services (CMS) Five-Star Quality Rating System on reimbursement for management of patients 18 years and older who were diagnosed with RA	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

_____

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? *(check one)*

☐ Implement a change in my practice/workplace.

☐ Seek additional information on this topic.

☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.

☐ Do nothing differently as the content was not convincing.

☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

_____

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

☐ Yes. *E-mail address:* _____

☐ No. ☐ I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc).

_____

_____

OVERALL EVALUATION		Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
The information presented increased my awareness/understanding of the subject.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will influence how I practice/do my job.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will help me improve patient care/my job performance.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The program was educationally sound and scientifically balanced.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Overall, the program met my expectations.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I would recommend this program to my colleagues.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Jeffrey Curtis, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Jonathan Kay, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

_____

_____

Please provide additional comments pertaining to this activity and any suggestions for improvement.

_____

_____

Rutgers thanks you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.