

Individualizing Therapy for Rheumatoid Arthritis: New Strategies for Maximizing Treatment Outcomes

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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in the practice of rheumatology.

Activity Goal

To familiarize NPs and PAs with current principles for managing rheumatoid arthritis (RA) and the latest clinical evidence on biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs), including timing of treatment, effectiveness of combination therapies, and strategies for treatment switching.

Learning Objectives

After completing this activity, participants should be better able to:

1. Differentiate among the available biologic therapies for RA, based on their mechanisms of action, clinical uses, and safety profiles.
2. Develop treatment plans for RA based on disease severity, practice guideline recommendations, and patient-specific considerations regarding drug administration, dosing schedules, and tolerability.
3. Use clinical evidence on biologic DMARD therapy and treatment switching to formulate effective management plans for refractory RA.

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The advent of biologic therapy has revolutionized the treatment of rheumatoid arthritis (RA). Two decades ago, management of RA with disease-modifying antirheumatic drugs (DMARDs) was limited to patients with evidence of joint erosion.¹ During the 1990s, methotrexate (MTX) began to supplant older DMARDs, such as intramuscular gold and antimalarials, for treatment of RA in the United States.¹ During the late 1990s, an expanded understanding of the pathogenesis of the disease led to the advent of biologic therapy.² Today, RA management is governed by the core principles of early diagnosis and immediate treatment with conventional or biologic DMARDs, followed by frequent assessments and tailoring of treatment to patient needs, with the goal of minimizing cumulative inflammation (Table 1).^{3,4} Current research efforts focused on identifying genetic risk factors and biomarkers hold the promise of further tailoring of RA treatment at the individual patient level (personalized medicine).⁴

It is well established that combination therapy offers the promise of sustained benefits, making clinical remission a feasible goal in RA.⁵⁻⁷

Several large well-known trials (eg, BeST [Dutch acronym for *Behandel-Strategieën*, “treatment strategies”],⁸ PREMIER,⁹ and Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes [TEMPO]¹⁰) have demonstrated improved patient outcomes, including inhibition of radiographic progression or disease sequelae, when DMARD and biologic combinations are used to treat to the lowest level of disease activity. However, the heterogeneity among RA patients is well recognized, and the course of their disease and their responses to DMARD therapy can vary widely.^{7,11} What is lacking for clinicians are practical strategies for when to introduce biologics into a patient’s regimen, how to select the agent that would be most appropriate for the patient’s needs, and how to switch therapy when treatment response is inadequate.

This issue of *PCE Updates in Rheumatology* focuses on strategies for individualizing RA treatment, based on a patient’s disease status and response to therapy.

How Biologics Work

Clinicians in the United States who are

cares for patients with RA have 9 biologics available for use, including 5 tumor necrosis factor (TNF)- α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab); a T-cell costimulation modulator, abatacept; an interleukin (IL)-1 receptor blocker, anakinra; a B-cell depleting agent, rituximab; and an IL-6 receptor blocker, tocilizumab (Table 2).^{4,12} The biologic activities of these agents are directed at specific cytokine or cell surface molecules in the pathophysiologic pathway of RA (Figure 1).^{4,12}

The efficacy of biologic agents has been demonstrated in large randomized clinical trials, typically compared with placebo, with both the biologic group and the placebo group on concomitant MTX therapy. However, there are few large, randomized, controlled trials directly comparing the biologics to one another.¹³ Given the high cost of biologics, their differing routes of administration and dosing schedules, and their differing adverse event (AE) profiles, knowing their relative benefits and safety would help guide treatment decisions. In the absence of direct comparisons, analyses of data from registries and

Table 1. Current RA Management: Goal, Core Principles, and Accepted Approaches to DMARD Therapy

Goal	Minimize cumulative inflammation	
Core Principles	1. Detect RA early	
	2. Institute treatment immediately	
	3. Maintain tight control of inflammation to improve outcomes	
	4. Individualize treatment based on the risk-benefit ratio for each patient	
	Approaches to Therapy	<ol style="list-style-type: none"> 1. Use DMARDs early 2. Monitor treatment response; schedule frequent follow-up visits 3. Escalate therapy rapidly—using the maximum effective dose 4. Use combination therapy 5. Use biologic agents if response to nonbiologic DMARD therapy is inadequate 6. Use second-line biologic therapy if first-line biologic therapy fails

Adapted from Kiely PD et al³; van Vollenhoven RF.⁴

meta-analyses of placebo-controlled trials have been performed in an attempt to obtain some insights about the relative efficacy and safety of biologics.

A recent analysis of the Danish Database for Biological Therapies in Rheumatology registry data compared

3 TNF- α inhibitors—adalimumab, etanercept, and infliximab—in terms of treatment responses (American College of Rheumatology [ACR] 70 response and European League Against Rheumatism [EULAR] good response), remission rates (Disease Activity Score [DAS] 28 or Clinical Disease Activity

Index [CDAI] remission), and drug adherence. Patients with RA who had been DMARD-treated but TNF- α inhibitor-naïve ($n = 2326$) were included in this analysis.¹⁴ In this real-world study, the rates at 6 months for ACR70 treatment response, DAS28 remission, and CDAI remission were

Table 2. Biologic Agents for RA in Adults

Agent (Class)	Indication	Usual Dosage
Abatacept (T-cell costimulation modulator)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA	500-1000 mg IV, at 2 and 4 weeks after initial infusion and every 4 weeks thereafter
Adalimumab (TNF blocker)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA	40 mg SC, every other week
Anakinra (IL-1 receptor blocker)	Reducing signs and symptoms and slowing the progression of structural damage in moderately to severely active RA in patients 18 years of age or older who have failed treatment with 1 or more DMARDs	100 mg SC, daily
Certolizumab (TNF blocker)	Treatment of moderately to severely active RA in adults	200 mg SC, at weeks 2 and 4 after initial dose, and every other week thereafter; 400 mg SC every 4 weeks may be considered for maintenance
Etanercept (TNF blocker)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA	50 mg SC, weekly
Golimumab (TNF blocker)	In combination with MTX for treatment of moderately to severely active RA in adults	50 mg SC, once monthly
Infliximab (TNF blocker)	In combination with MTX for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA	3 mg/kg IV, at 2 and 6 weeks after initial infusion, and every 8 weeks thereafter; if response is incomplete, dose may be increased up to 10 mg/kg or administered every 4 weeks
Rituximab (B-cell depleting agent)	In combination with MTX for treatment of moderately to severely active RA in adults who have had an inadequate response to 1 or more TNF antagonists	1000 mg IV, 2 infusions, administered 2 weeks apart; subsequent courses should be administered every 24 weeks or based on clinical evaluation but not sooner than every 16 weeks
Tocilizumab (IL-6 receptor blocker)	Treatment of moderately to severely active RA in adults who have had an inadequate response to one or more TNF antagonists	4 mg/kg IV (60-minute infusion), once every 4 weeks; dose may be increased to 8 mg/kg thereafter, based on clinical response

IV = intravenously; SC = subcutaneously.
Data from prescribing information for each agent.

highest for adalimumab (19%, 26%, and 15%, respectively), intermediate for etanercept (17%, 21%, and 10%, respectively), and lowest for infliximab (11%, 17%, and 8%, respectively). Adherence rates, a surrogate marker for drug efficacy, at 48 months were higher for etanercept (56%; 95% confidence interval [CI], 51%-62%) and adalimumab (52%; 95% CI, 46%-57%) than for infliximab (41%; 95% CI, 37%-44%) ($P < .0001$).¹⁴

A meta-analysis of Cochrane database reviews indirectly compared the benefits and safety of 6 biologics—abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab.¹⁵ (Certolizumab, golimumab, and tocilizumab received approval from the Food and Drug Administration [FDA] too recently for inclusion in this analysis). All completed and updated Cochrane reviews on biologics for RA as well as data from all placebo-controlled trials that used standard dosing regimens of biologics

were included in this meta-analysis. Benefit of therapy was defined as patient- and physician-reported ACR50 improvement, and safety was determined by the number of withdrawals related to AEs. The results indicated that anakinra was less effective than all of the other biologics, although this difference was only statistically significant compared with adalimumab and etanercept. In terms of safety, adalimumab, anakinra, and infliximab were more likely than etanercept to lead to withdrawals.¹⁵

Commentary

Does the class of biologic affect your choice of treatment? What factors do you consider when selecting among the available biologic agents?

Martin J. Bergman: Most rheumatologists start biologic therapy with an anti-TNF agent; however, an agent's mechanism of action typically does not influence the choice. The most important factor in treatment selection

is usually the approved formulary list for the patient's insurance company. Cost to the patient is often the next decisive factor. If these factors are excluded, the next decision point is the patient's preference for medication administration—self-administration or administration by the clinician. Otherwise, the largest factor in deciding among the available agents is the experience of the rheumatology clinician. Being creatures of habit, we rheumatologists often prescribe the agent with which we are most comfortable. As no significant head-to-head trials comparing these agents have been conducted, experience and familiarity can be important factors.

Nicole Furfaro: Anti-TNF medications have been around the longest and have accumulated the greatest amount of safety and efficacy data as a class of medication. We have seen favorable risk-benefit ratios with these medications, and their side effects are well documented. As a class, TNF- α inhibitors demonstrate strong protection against erosive disease as well as rapid improvement in the signs and symptoms of RA. I feel comfortable using them when necessary. However, if a patient prefers infusion therapy to self-injections, has a family history of demyelinating disease, has congestive heart failure, or travels to places where tuberculosis is endemic, I may choose an agent with a different mechanism of action, such as T-cell costimulation modulation, B-cell depletion, or IL receptor blockade. Clinicians also have to consider each agent's FDA-approved uses. For example, rituximab and tocilizumab are approved for treatment of RA after an inadequate response to anti-TNF therapy, but abatacept could be used for initial biologic therapy. Other patient-specific factors must also be taken into account. Some patients live too far away from their clinician's office or

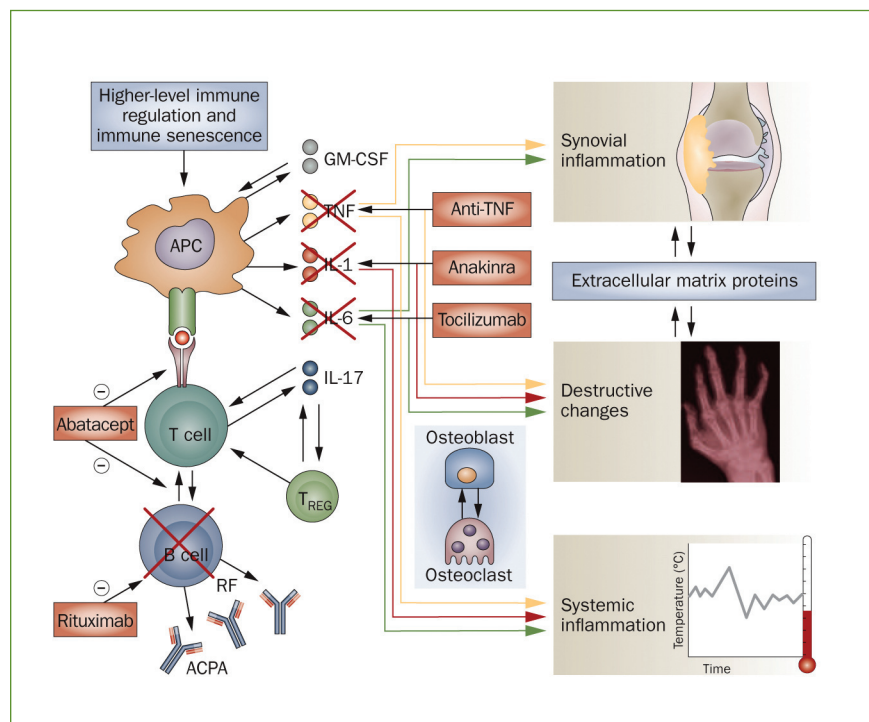


Figure 1. Biologic agents target various sites in the pathophysiologic pathways of RA, as shown in the schematic. ACPA = anti-citrullinated protein/peptide antibodies; APC = antigen presenting cell; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; RF = rheumatoid factor; T_{REG} = regulatory T cell. Reprinted by permission from Macmillan Publishers Ltd: van Vollenhoven RF. *Nat Rev Rheumatol.* 2009;5:531-541.⁴

infusion center to come for treatment, while others may cherish this experience as a therapeutic break from their routine. A patient's ability to adhere to a treatment plan may also affect the treatment choice.

When to Start Biologic Therapy

MTX has become the initial treatment of choice in RA with 15 to 20 years of therapeutic experience supported by extensive efficacy data and an acceptable tolerability profile.⁴ It is considered the anchor drug for first-line therapy in practice guidelines from the ACR and EULAR and is used as monotherapy or in combination with other nonbiologic DMARDs (hydroxychloroquine or hydroxychloroquine plus sulfasalazine) (Table 3) as well as all biologic agents.^{11,16} However, it has become increasingly clear that the efficacy of

MTX in most patients with RA is partial, with only a small proportion of patients (15%-40%) achieving disease remission.^{9,17-20}

Biologics have been recommended as first-line therapy for early RA only in patients with high disease activity. In patients with disease that is less active or of longer duration, biologics are considered as second-line therapy for patients with an inadequate response to MTX or other nonbiologic DMARDs.¹⁶ The use of biologics as first-line therapy is controversial. Recent evidence has shown better treatment responses in MTX-naïve patients with a recent diagnosis of RA (1-3 years) who received MTX plus a biologic (infliximab, adalimumab, etanercept, abatacept, or rituximab) compared with those who received MTX monotherapy.^{9,17-20} However, in these trials, 15% to 40% of patients

receiving MTX monotherapy achieved disease remission, nonprogression of radiographic changes, and functional stability. Thus, biologic plus MTX combination therapy is not necessary in all patients from the start; however, identifying these patients, or conversely, identifying those patients who would benefit from initial combination therapy, remains a key challenge in RA management.⁴

Commentary

When do you initiate biologic therapy?

MB: My primary reason for starting treatment with a biologic is failure of a patient's RA to respond to a first-line agent, such as MTX or sulfasalazine. To determine whether a treatment failure has occurred, I routinely measure disease activity, usually with the Routine Assessment of Patient Index

Table 3. Nonbiologic DMARDs for RA

Agent	Usual Dosage	Adverse Effects/Risks
Azathioprine	50-200 mg PO, daily	Hepatotoxicity, gastrointestinal toxicity, myelotoxicity
Cyclosporine	2.5-5.0 mg/kg PO, daily	Hypertension, nephrotoxicity
Gold salts	50 mg IM, weekly; or 3-6 mg PO, daily	Diarrhea (oral), fibrosing alveolitis (parenteral), hypersensitivity reactions (oral and parenteral), nephritis (parenteral)
Hydroxychloroquine	200-400 mg PO, daily	Retinopathy
Leflunomide	10-20 mg PO, daily	Hypertension, hepatotoxicity, myelotoxicity
Methotrexate	10-25 mg PO or SC, weekly	Hepatotoxicity, fibrosing alveolitis, myelotoxicity
Sulfasalazine	1000-1500 mg PO, twice daily	Hepatotoxicity, hypersensitivity reactions, myelotoxicity

IM = intramuscularly; PO = by mouth.
Adapted from van Vollenhoven RF.⁴

Examining the Safety of Biologics

Biologic therapies used in the treatment of RA are generally considered to be safe and well tolerated (Table). The most important safety concern with biologic therapies is the increased risk of infection, including upper respiratory tract infections, opportunistic infections, and reactivation of tuberculosis. Other safety concerns include increased risk of cancer (eg, lymphoma with anti-TNF therapies), lupuslike syndrome, demyelinating syndrome, and effects on vaccination. As there is an increased incidence of malignancy in RA patients, the extent to which each of the biologic therapies is associated with different types of malignancies in RA has not been clearly defined.

Khraishi M. Comparative overview of safety of the biologics in rheumatoid arthritis. *J Rheumatol.* 2009;36(suppl 82):25-32.

Table

Side Effects and Risks Associated With Biologic Agents for RA

Biologic Class (Agent)	Side Effects and Risks
B-cell depletion (rituximab)	Infusion reactions, infections
IL-1 receptor blockade (anakinra)	Injection site reactions, infections, neutropenia
IL-6 receptor blockade (tocilizumab)	Infusion reactions, infections, neutropenia, reduced platelet counts, elevated liver enzymes, elevated lipids
T-cell costimulation blockade (abatacept)	Infusion reactions, infections
TNF blockade (adalimumab, certolizumab, etanercept, golimumab, infliximab)	Injection site reactions, infections (including tuberculosis), demyelinating disease exacerbation or new onset, heart failure worsening or new onset

Adapted from van Vollenhoven RF.⁴

Data (RAPID) 3 tool or with the DAS28 or CDAI when necessary. Knowing how a patient is responding is better than guessing.

NF: The decision to start biologic therapy depends upon the severity of disease activity and how fast joint damage or limitations in functional status are progressing. In general, biologics are prescribed for patients with high disease activity despite previous

treatment with MTX or other DMARDs, those with evidence of erosive disease, or those without erosive disease but with demonstrated functional disability. Ideally, biologics are started within 3 months of RA diagnosis in patients who do not respond to MTX, demonstrate erosive disease at baseline, or have prognostic indicators of more aggressive disease (rheumatoid factor [RF] positivity, anti-cyclic citrullinated

peptide [anti-CCP] antibody titer positivity, elevated erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP]).

Do you ever use biologics as first-line therapy?

MB: I use a biologic as a first-line agent only on rare occasions. Unique situations or combinations of circumstances exist. A patient may have a sulfa allergy (which is a contraindication to sulfasalazine) and may not want to reduce alcohol intake significantly (which would increase the risk of liver toxicity with MTX). Another patient with RA may also have hepatitis C infection, and an anti-TNF agent might be considered as a first-line agent. (Evidence suggests that TNF- α inhibitors are safe in this setting^{21,22}; however, this is not an FDA indication for anti-TNF agents, nor is it a recommendation in current guidelines on biologic therapy for RA.¹⁶) Prior to starting treatment with a biologic, I determine the hepatitis B and C status of the patient and administer a tuberculin skin test.

NF: In an ideal world, clinicians would be able to use whatever treatment best meets their patients' needs at the time of assessment. In the current treatment milieu, however, insurance companies have a great deal of input regarding our treatment choices and generally will not cover expensive medications until a 3-month trial with a nonbiologic agent either ends in lack of response or unacceptable side effects. I have occasionally used biologics as first-line therapy in patients for whom insurance was not an issue, in research trials, or in patients who have a contraindication to the use of MTX or leflunomide, such as alcohol abuse or impending pregnancy. In the future, genetic markers may be able to identify patients for whom RA may be particularly devastating and provide support for the use

of rapid, aggressive treatment to achieve the best outcomes.

How to Adjust Your Treatment Strategy

Early initiation of nonbiologic DMARD therapy with rapid dose escalation to the maximum effective dose is usually considered the first step in the management of patients diagnosed with RA.^{4,16} When treatment response to monotherapy proves inadequate, the next step entails switching to combination therapy.

Combination Therapy Superior to Monotherapy

Combination therapy, including the addition of other nonbiologic DMARDs or a biologic after an inadequate response to a nonbiologic DMARD therapy, is a widely accepted strategy in managing RA.^{16,23} The superiority of combination therapies over monotherapy was demonstrated in the Tight Control of RA (TICORA),²⁴ BeST,⁸ Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo),⁵ Swedish Pharmacotherapy (SWEFOT),⁶ and Guérir la Polyarthrite Rhumatoïde Débutante (GUEPARD)²⁵ trials. These trials also demonstrated the importance of ongoing monitoring in RA management where clinical decisions based on rigorous and routine clinical measurements resulted in impressive improvements in physical function, radiographic progression, and disease activity, including remission.

Although the benefit of combination therapy is well appreciated, the order in which additional DMARDs should be used or the optimal timing of treatment switching has not been defined.⁴ In its updated recommendations, the ACR generally did not address decisions on switching or adding alternative DMARDs for patients currently receiving DMARD

therapy (whether biologic or nonbiologic). The only exception is its recommendation to switch to biologic DMARDs only after failure of nonbiologic DMARDs; ACR did not specify how many DMARD failures to allow before starting biologics.¹⁶

Switching Among Anti-TNF- α Agents

Anti-TNF- α therapies were the first RA-specific biologics that were developed for the management of moderate to severe RA and represent an important advance in the management of the disease. Nonetheless, in clinical practice, anti-TNF- α therapies are withdrawn in approximately 30% of patients during the first year of treatment because of lack of efficacy or AEs.²⁶ Options for further treatment in these patients include switching from one TNF- α inhibitor to a second TNF- α inhibitor or switching from TNF- α inhibitor therapy to treatment with another class of biologics.⁴ However, there is no clear consensus on how many TNF- α inhibitor therapies need to be tried before abandoning this class of agents or whether it is more effective to switch to a different class of biologics after the first TNF- α inhibitor failure.

Growing evidence suggests that patients who do not respond to the first anti-TNF- α agent, regardless of the reason for discontinuation, may respond well to treatment with a second anti-TNF- α agent. A Dutch registry study divided RA patients into 3 groups based on the reason for discontinuation of their first anti-TNF- α agent—nonresponse ($n = 49$), loss of response ($n = 75$), or AEs ($n = 73$)—and investigated whether the reason for discontinuation influences the effect of a second anti-TNF- α agent. At 6 months after switching therapy, patients in each group had similar improvements in DAS28 from baseline

and similar EULAR moderate/good response rates.²⁷ A second observational study also found that RA can be successfully treated with a second TNF- α inhibitor after withdrawal of the first agent because of lack of efficacy, loss of efficacy, or AEs. This study, however, showed that the probability of achieving a clinical response after switching is higher in patients discontinuing the first treatment for secondary failure (loss of efficacy) or AEs than in switchers for primary failure (lack of efficacy). Of the patients who switched because of lack of efficacy, loss of efficacy, or AEs, a moderate/good EULAR response was achieved in 38.4%, 66.6%, and 88.8% of patients, respectively.²⁸

Although patients who switch anti-TNF- α therapy do better or equally well on their second agent, a percentage go on to discontinue the second agent for the same reasons that they had discontinued the first agent.^{29,30} In patients who fail a second anti-TNF- α agent, the question is whether there is a role for a third anti-TNF- α agent or whether it is better to move on to a different class of biologic agent.

A prospective, observational study from Sweden attempted to answer this question by monitoring response rates (ACR20, ACR50, ACR70, EULAR overall and good, DAS28 <3.2, and DAS28 <2.6) in 337 first-time switchers and 36 second-time switchers and compared these to response rates of first-time anti-TNF- α agent users.³¹ The study found that the responses of first-time switchers were somewhat lower, but not markedly lower, than those of first-time anti-TNF- α agent users. The responses of second-time switchers, however, were markedly lower than those of first-time users or first-time switchers. Of first-time users, first-time switchers, and second-time switchers, 13%, 7%, and 3%

achieved ACR70 response; 34%, 25%, and 9% achieved EULAR good response; and 23%, 16%, and 6% achieved DAS28 remission, respectively. Thus, in patients who fail a second anti-TNF- α agent, perhaps other therapeutic options should be considered.³¹

In contrast to the Swedish study, a multicenter, randomized, double-blind, placebo-controlled study showed that patients who had failed 2 anti-TNF- α agents may still obtain benefit from switching to a third anti-TNF- α agent, golimumab.³² In this study, 461 patients with active

RA were randomized to placebo (n = 155) or golimumab (50 mg: n = 153 or 100 mg: n = 153). Concomitant DMARD treatment with MTX, sulfasalazine, and hydroxychloroquine (alone or in combination) was permitted, but not required, in the study. Before study enrollment, 66% of the patients had received 1 TNF- α inhibitor, 25% had received 2, and 9% had received 3 TNF- α inhibitor agents (adalimumab, etanercept, and/or infliximab). Of patients who had received 1 or 2 previous TNF- α inhibitors, significantly more patients in the combined golimumab groups

achieved ACR20 response than did those on placebo. In patients who had received 3 previous TNF- α inhibitors, there was no difference in the ACR20 response rate between the golimumab and placebo groups, although the subgroup size was small.³²

Switching to a Biologic With a Different Mechanism of Action

With the approval of biologic agents with novel mechanisms of action for use in patients with RA, the number of therapeutic options for patients with inadequate response or intolerance to a first TNF- α inhibitor has increased.

CASE STUDY: Managing RA in a 45-Year-Old College Professor

Nicole M. Furfaro, MSN, ARNP

Presentation and History

Lena, a 45-year-old community college professor, presents with complaints of increasing fatigue and pain and stiffness in her hands, wrists, feet, and ankles during the past 8 weeks. She initially thought she was “overdoing it” by staying up late to correct term papers and wrote off her morning joint stiffness to overuse injury. However, the severity of symptoms had increased dramatically over the past 2 weeks, and because her mother had been diagnosed with RA at the same age, Lena suspected something was “really wrong” when the use of over-the-counter nonsteroidal anti-inflammatory drugs did little to alleviate the pain and swelling. She had been in good health previously, with only mild anemia and exercise-induced asthma.

Physical Findings

- Height: 5 ft 6 in; weight: 130 lb; body mass index: 21.0 kg/m²
- Blood pressure 116/70 mm Hg; pulse: 80 beats/min
- Joint evaluation: swelling in wrists and ankles, bilaterally; tenderness with swelling in the first, second, and third metacarpophalangeal (MCP) and proximal interphalangeal joints, bilaterally
 - Swollen joint count (SJC): 16
 - Tender joint count (TJC): 28

Laboratory Findings

- RF: 90 IU/mL (positive) (normal value: <60 IU/mL)
- Anti-CCP antibody titer: >160 (elevated)
- ESR: 50 mm/h (elevated) (normal value: 0-20 mm/h)
- CRP: 3.1 mg/dL (elevated) (normal value: \leq 0.5 mg/dL)
- Comprehensive metabolic panel: normal; complete blood cell count: normal, except for mild anemia with a hematocrit of 32%

Radiographic Findings

Hands and wrists: diffuse osteopenia in the carpal bones, bilaterally; early erosion of the second MCP joint of the right hand

Disease Activity Assessment

The patient's clinical findings are used to calculate her DAS28-CRP using 3 variables (DAS28-3[CRP]) with the following formula:

$$\text{DAS28-3(CRP)} = 0.56(\sqrt{\text{TJC28}}) + 0.28(\sqrt{\text{SJC28}}) + 0.36(\ln\text{CRP}+1)(1.10 + 1.15)$$

(Note: DAS calculators are available online at: <http://www.das-score.nl/www.das-score.nl/index.html>)

DAS28 Score Thresholds	Disease Activity Classification
Low disease activity	\leq 3.2
Moderate disease activity	>3.2 and \leq 5.1
High disease activity	>5.1
Saag KG, et al. ¹⁶	

The patient's DAS28-3(CRP) is 7.0, correlating with high disease activity.

Currently, such options include abatacept, anakinra, rituximab, and tocilizumab.

In the Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) study, rituximab was shown to be effective in patients with an inadequate response to TNF- α inhibitors. Repeated courses of rituximab yielded sustained or improved ACR20, ACR50, and ACR70 responses as well as EULAR good response compared with original baseline values.^{32,33} However, the efficacy of rituximab was superior when used in patients who had a single TNF- α

inhibitor failure compared with patients with 2 or more TNF- α inhibitor failures,³⁴ suggesting that it would be advantageous to switch after the first TNF- α inhibitor failure.

In the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) study, abatacept plus at least 1 DMARD was shown to be superior to placebo in patients exhibiting an inadequate response to TNF- α inhibitor therapy. At 6 months, the abatacept group had significantly higher ACR20, ACR50, and ACR70 response rates (50.4%, 20.3%, 10.2%, respectively) than the placebo group

(19.5%, 3.8%, 1.5%, respectively).³⁵ These improvements were shown to be sustained after 2 years of treatment with abatacept.³⁶

The Research on Actemra Determining Efficacy After Anti-TNF Failures (RADIATE) study examined the efficacy and safety of tocilizumab with MTX in patients with active RA who had failed treatment with at least 1 TNF- α antagonist. Inadequate efficacy accounted for 95% of the TNF- α antagonist failures. Irrespective of the agent (etanercept, adalimumab, or infliximab) or the number of failed TNF- α antagonists (1, 2, or 3),

Treatment Decision

Treatment is initiated with MTX 10 mg/wk, with rapid escalation to 20 mg/wk, and folic acid 1 mg/d. Lena's high anti-CCP antibody titer, RF positivity, elevated CRP and ESR, and early erosive disease make her a good candidate for combination therapy with MTX and an anti-TNF agent. At Lena's initial visit, a request to start adalimumab was sent to her insurance company based on prognostic indicators of aggressive disease.

Clinical Commentary

With a symptom duration greater than 6 weeks, polyarticular symmetric arthritis of the hands/wrists, RF positivity, and radiographic evidence of erosive disease, Lena meets the current diagnostic criteria for RA. Some clinicians argue that the current diagnostic criteria apply only to late-stage RA by requiring joint damage and laboratory evidence of established disease. The new joint EULAR/ACR criteria, once adopted for clinical use, will help to identify patients with early RA and to achieve better long-term outcomes by allowing treatment to be instituted early in the disease process before damage is irreversible. Studies demonstrate better disease control and less radiographic progression in patients treated with MTX and a biologic agent.^{8,9}

Follow-up

After using combination therapy with adalimumab and MTX for 3 months, Lena is feeling much better. Her SJC has dropped to 2 and her TJC to 2 (both wrists). Repeated laboratory testing reveals a normal CRP at 0.5 mg/dL and an ESR of 30 mm/h. Her DAS28-3(CRP) score is 3.2, indicating low disease activity. She is able to work and feels hopeful about the future.

After 2 years, Lena presents with complaints of worsening symptoms again. During the previous 6 months, her MTX dose had been increased to 25 mg/wk, and hydroxychloroquine had been added to her regimen, followed by sulfasalazine. However, this treatment approach has done little to improve her symptoms. Furthermore, she is experiencing nausea and says she "hates taking all these pills every day." We discuss the possibility of switching to a second anti-TNF medication or changing to another agent with a different mechanism of action. Because Lena's schedule permits her easy access to clinic visits for monthly infusions, we decide that she should try abatacept.

At her next 6-month follow-up, Lena has no swollen or tender joints and reports no functional limitations. She enjoys the ease of monthly treatments.

Clinical Commentary

At this point in the course of Lena's disease, options for therapy included changing to a second anti-TNF agent or to an agent with a different mechanism of action, such as abatacept, rituximab, or tocilizumab. Many options are now available for patients whose disease does not respond to a therapy, whose treatment loses effectiveness, or who cannot tolerate an agent's side effects. Patients need to be educated on the benefits and side effects of each agent so they can share in the treatment decision and feel part of the health-care team. By discussing with us the specifics about each medication's administration, timing, and dose schedule and the expected length of time before experiencing benefit, our patients will have realistic expectations for their RA therapies and take more responsibility for treatment outcomes.

tocilizumab plus MTX was shown to be superior to placebo in ACR responses.³⁷

The results of the REFLEX, ATTAIN, and RADIATE studies suggest that switching to a biologic agent with a different mode of action is a viable therapeutic option in patients with an inadequate response to an anti-TNF- α agent; but whether this option should be considered early after the first inadequate response to TNF- α inhibitor therapy needs further evaluation.³⁸

Is Remission Universally Feasible?

Early, aggressive therapy is essential to controlling the symptoms of RA and achieving remission of the disease. Remission is important to prevent joint destruction, preserve adequate quality of life, and prevent disability. Although remission is the objective, it may not be feasible for all patients.^{4,7,39} The advent of biologic agents has made this objective feasible in about 50% of patients. In the other 50%, failure to achieve remission has been attributed to lack of response, contraindications, and treatment intolerance.⁷ In patients who fail currently available biologic therapy, new compounds are awaited.

Commentary

When do you consider switching treatment?

MB: It is important to recognize when a chosen therapy is no longer effective. While this may be obvious in some patients, in others the symptoms and findings may be more subtle. Again, it is in such patients that use of a quantitative measurement tool, such as RAPID3 or CDAI, will help to determine whether an adequate level of disease control has been reached.

NF: In an ideal world, all rheumatology clinicians would use a standardized

assessment tool to assess disease activity over time. By doing so, adherence to the goal of tight control of RA could be the gold standard of therapy, whether that means achieving remission or the lowest disease activity level possible. We have seen in trials the value of better long-term outcomes when rheumatologists are forced to change therapy to achieve low disease activity. Personally, I change therapy after 3 to 6 months if the current agent is not improving the disease activity in an individual patient. The timing depends, in part, on how often the patient is assessed. Frequent assessments may be a problem in busy rheumatology practices where providers are seeing as many patients as they can accommodate. It is also important to give an agent adequate time to achieve a response before switching to another treatment.

Is treating to remission a feasible goal?

MB: I believe that remission is attainable in more patients than we may

have realized in the past. However, I do not believe it is an absolute necessity to treat to remission. It is my practice to treat to a low disease state as an absolute requirement. By doing so, I often can get my patients to remission. Failure to attain low disease activity is my decisive factor in switching from one therapy to another, whether a conventional DMARD or a biologic. However, if a patient is doing well by all measures but still has 1 or 2 joints that are problematic or if a patient is doing well but has subtle imaging changes, I do not necessarily change medications for the sake of attaining remission. My practice is to follow the recommendations of the Swedish study³¹ described previously and to use 2 anti-TNF agents before switching to a different class. Clearly, more work on identifying which medications will work in individual patients needs to be done.

NF: The concept of treating to disease remission or lowest possible disease activity level is the accepted goal of therapy today.

PCE Takeaways

- ▶ The goal of RA management is to minimize cumulative inflammation through early diagnosis and aggressive treatment with DMARDs.
- ▶ Biologic agents are usually reserved as second-line therapy for RA that has not responded adequately to treatment with MTX alone or in combination with nonbiologic DMARDs; first-line biologic therapy may be used for patients with high disease activity at diagnosis.
- ▶ Combination therapy with MTX and a biologic has been shown to achieve better treatment responses than MTX monotherapy; however, 15% to 40% of patients achieve disease remission, nonprogression of radiographic changes, and functional stability with MTX monotherapy. Determining which patients would benefit from the more aggressive regimen remains a key challenge in RA management.
- ▶ Patients whose RA does not respond to the first anti-TNF- α agent may respond well to treatment with a second anti-TNF- α agent; however, there is no clear consensus on how many TNF- α inhibitor therapies need to be tried before abandoning this class of agents or whether it is more effective to switch to a different class of biologics after the first TNF- α inhibitor failure.

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