



RHEUMATOLOGY NURSE PRACTICE

NEWSLETTER

Inside this Issue

ISSUE 4 | VOLUME 1

- » What does the latest evidence say about the real-world benefits of a treat-to-target strategy in the management of patients with rheumatoid arthritis (RA)?
- » Is drug tapering or discontinuation a viable strategy in patients with RA who achieve clinical remission on specific drug regimens?
- » What are some of the new therapeutic targets being explored through the current drug development process in RA?
- » What impact are biosimilars expected to have for patients with RA in the United States?

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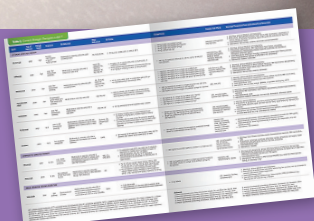
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BONUS CONTENT! Within this issue of *Rheumatology Nurse Practice*, you can find a comprehensive pull-out chart of all approved agents for the treatment of RA, along with indications, dosages, and safety information for your personal use.



Learning Objectives

1. Identify key steps in the treat-to-target algorithm that are intended to more tightly control RA patients' disease activity
2. Determine which RA patient cohorts, if any, would benefit from drug tapering or discontinuation of specific treatment regimens
3. Select new therapeutic targets under investigation in late-stage clinical trials of biologic therapies being developed for possible use in patients with RA
4. Discuss current concerns surrounding the potential introduction of biosimilars for RA patients in the United States

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PRACTICE
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Treatment Trends in Rheumatoid Arthritis

B iologic agents that target specific molecules involved in inflammatory and immune system responses have revolutionized treatment of rheumatoid arthritis (RA). Best practices in RA management have evolved to now favor early and intensive therapy, often involving a combination of a biologic agent with methotrexate (MTX), to achieve clinical remission. The treatment of RA is again poised to undergo another shift with the introduction of additional biologic therapies and biosimilar products.

Update on RA Therapies

Rheumatology providers have a growing number of options for initiating therapy and adjusting treatment in patients with RA. To date, comparative effectiveness studies have found no major differences in the efficacy of current RA therapies for most patients.^{1,2,3} With no clear differences in efficacy, treatment decisions rely on factors such as mechanism of action, ease of use, side effect profile, and patient preference.⁴

The mechanisms of action of current biologic therapies fall into three general

categories: agents that target tumor necrosis factor (TNF) and other cytokines; agents that target lymphocytes, including T cells and B cells; and small-molecule inhibitors of other key molecular pathways in RA. Most traditional disease-modifying antirheumatic drugs (DMARDs) work by suppressing the body's immune response and/or inflammatory systems, although the exact mechanisms of action are in some cases unknown. MTX and other common DMARDs used in RA can be distinguished by route of administration, dosing schedule, side effects, and other factors.⁴

NEWSLETTER SUMMARY

This issue of Rheumatology Nurse Practice will examine the latest updates shaping the use of biologic therapy in RA, including an update on the Treat to Target (T2T) algorithm, new options for drug tapering, and an overview of emerging biologic agents, including biosimilars.

BONUS CONTENT!

As an added bonus, within this issue of Rheumatology Nurse Practice, you can find a comprehensive pull-out chart of all approved agents for the treatment of RA, along with indications, dosages, and safety information for your personal use.

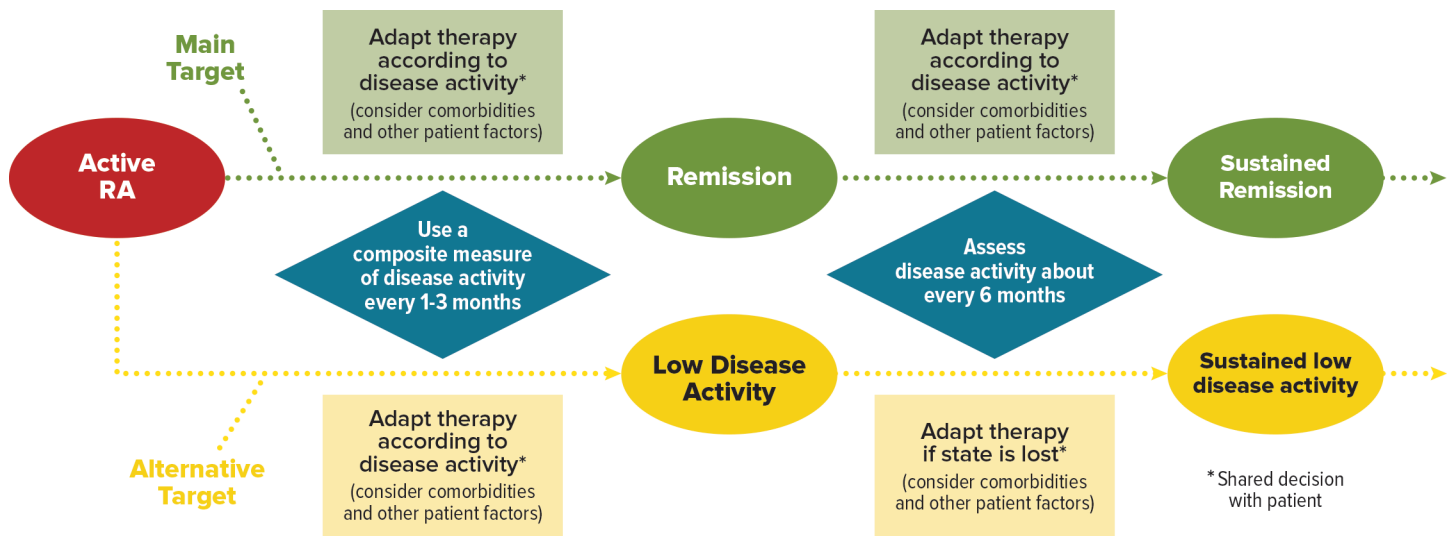


Figure 1
Treat-to-Target
Algorithm for
Active RA⁵

Treat to Target (T2T) Algorithm

Optimal RA treatment involves much more than selecting the right agent or combination of therapies. The T2T approach was introduced to the rheumatology community in 2010 as a framework for RA management. In 2015, the T2T Task Force developed an updated algorithm that reinforces the core principles of treatment initiation, monitoring, and adjustment, with the goal of achieving timely and persistent control of RA disease activity (Figure 1).⁵

According to the updated algorithm, the T2T approach includes several key steps. Each RA management choice should be based on shared decision-making between the patient and the rheumatology provider:

- Determine the goal of therapy.** Ideally, most patients with early RA should aim to achieve clinical remission. As an alternative, low disease activity is an appropriate goal to reduce RA symptoms and improve functional status and quality of life for patients with advanced disease.
- Select a composite measure of disease activity.** Clinicians should select from several validated disease activity measures that incorporate joint counts, such as the clinical disease activity index (CDAI) and the disease activity score with 28 joint counts (DAS28). Each composite measure has a specific threshold for defining the targets of clinical remission and low disease activity. For example, DAS28 clinical remission is defined as a score <2.6.

- Measure disease activity.** After starting RA treatment or switching to a new regimen, clinicians should measure RA disease activity every 1 to 3 months. Patients who are responding to treatment should see a corresponding decrease in their disease activity scores.
- Adjust treatment.** If necessary, adjust the treatment regimen every 3 to 6 months until the goal of clinical remission (or low disease activity) is reached.
- Maintain the treatment goal.** Once the patient has achieved clinical remission, the long-term treatment goal is to maintain this state to prevent further joint damage, control symptoms, and preserve physical functioning.
- Adjust treatment again as needed.** If disease activity ever increases beyond the threshold of remission—suggesting a loss of treatment effect—RA therapy should again be adjusted until the patient returns to a state of clinical remission.

New studies are highlighting the real-world benefits of adhering to a T2T strategy. The CORRONA (Consortium of Rheumatology Researchers of North America) database is part of an ongoing initiative designed to collect and analyze real-world data on patients with RA and other rheumatologic diseases. At the 2015 American College of Rheumatology (ACR) annual meeting, researchers presented findings from a new study of the CORRONA database demonstrating the range of benefits of achieving tight disease control.⁶

The analysis included 1,627 RA patients who had moderate or high disease activity at baseline, defined as a CDAI score >10. Patients who met all of the following clinical, functional, and structural targets after 6 months were described as achieving comprehensive disease control (CDC):

- DAS28 using C-reactive protein (DAS28-CRP) score: <2.6
- Health Assessment Questionnaire (HAQ) score: <0.5
- Change from baseline in modified Total Sharp Score (mTSS): ≤0.5

At 6 months, 331 patients (20%) achieved CDC while 1,296 patients (80%) had 1 or more clinical, functional, or structural targets that remained above goal. Patients who achieved CDC within 6 months also experienced significant improvements in a range of other patient-reported outcomes. Compared with patients who did not achieve CDC, patients with RA who achieved CDC had significantly lower pain scores, less fatigue, and a greater reduction in morning stiffness. Patients who achieved CDC were also significantly less likely than non-achievers to report quality of life issues at 6 months. Therefore, data from the CORRONA registry support the meaningful benefits of achieving tight control of RA disease activity in the real-world clinical setting.

Drug Tapering and Disease-Free Remission

In the current era of T2T and aggressive treatment regimens, many patients with early RA are now achieving clinical remission. For patients who achieve initial disease control, drug tapering is an attractive strategy for reducing the potential long-term side effects of therapy while also lowering treatment costs.⁷ Several recent studies have explored the possibilities of drug tapering and even treatment discontinuation in patients with well-controlled RA.⁷

Drug Tapering with Etanercept

The PRIZE (Productivity and Remission in a Randomized Controlled Trial of Etanercept vs. Standard of Care in Early Rheumatoid Arthritis) study enrolled 306 patients with early, active RA

who had not previously received MTX or biologic therapy.⁸ All patients started combination treatment with subcutaneous injections of etanercept 50 mg plus oral MTX 10–25 mg weekly. After 52 weeks of full-dose combination therapy, 215 patients (70%) achieved clinical remission (DAS28 <2.6) and were eligible for tapered dosing. Within this subgroup, 193 patients were randomly assigned to 1 of 3 treatment groups for 39 additional weeks of dose-tapered therapy:

- Etanercept 25 mg injection + oral MTX weekly (n=63)
- Placebo injection + oral MTX weekly (n=65)
- Placebo injection + oral placebo weekly (n=65)

After 39 weeks, patients who continued combination therapy at a reduced dose maintained better control of RA disease activity than those who switched to either MTX alone or double placebo. Overall, 63% of patients who switched to etanercept 25 mg + MTX remained in remission after 39 weeks of tapered therapy. By comparison, only 40% of patients who switched to MTX alone remained in remission (P=0.009 vs. combination therapy). Outcomes were even worse for those who discontinued all active therapy by switching to double placebo. In this group, only 23% of patients remained in clinical remission after 39 weeks (P<0.001 vs. combination therapy).⁸ Therefore, findings from the PRIZE study support the feasibility of drug tapering in patients who achieve remission after early, aggressive therapy. In contrast, discontinuing etanercept altogether was associated with worse outcomes.

Drug Tapering with Adalimumab

The OPTIMA (Study of the Optimal Protocol for Methotrexate and Adalimumab Combination Therapy in Early Rheumatoid Arthritis) trial enrolled 1,032 patients with early RA who had not previously been treated with MTX.⁹ In the first phase of the OPTIMA trial, patients were randomly assigned to begin treatment with adalimumab 40 mg every 2 weeks plus weekly MTX 7.5–20 mg (n=515) or weekly MTX alone (n=517). After 26 weeks, 40% of patients who started treatment with combination adalimumab/MTX achieved the target of low disease activity (DAS28 <3.2). By comparison, only 22% of patients who started treatment with MTX monotherapy achieved low

Clinical Remission (DAS28-CRP <2.6)

	AFTER 12 MONTHS OF ACTIVE THERAPY	6 MONTHS AFTER TREATMENT WITHDRAWAL
Abatacept 125 mg plus MTX	60.9%	14.8%
Abatacept 125 mg monotherapy	42.5%	12.4%
MTX monotherapy	45.2%	7.8%

DAS28-CRP, 28-joint disease activity score with C-reactive protein; MTX, methotrexate.

Table 1

Drug-Free Remission in Early RA Patients¹⁰

disease activity after 26 weeks. Results of the first phase of the trial, therefore, highlight the benefit of an intensive treatment regimen for achieving low disease activity in patients with early RA.

The second phase of the OPTIMA trial evaluated treatment strategies for patients who reached the target of low disease activity within the first 6 months of treatment. Patients with low disease activity in the adalimumab/MTX group were randomly assigned to 1 of the following strategies for 52 additional weeks:

- **Adalimumab continuation:** adalimumab 40 mg every 2 weeks plus MTX 7.5–20 mg weekly
- **Adalimumab withdrawal:** placebo plus MTX 7.5–20 mg weekly

Patients who achieved low disease activity in the first phase of the trial with MTX monotherapy continued single-agent MTX for 52 additional weeks.

Among all treatment approaches, patients who began treatment with adalimumab and continued on biologic therapy had the best long-term results. After a total of 78 weeks of therapy, 91% of patients in the adalimumab continuation group maintained the treatment target of low disease activity (DAS28 <3.2) and 86% reached clinical remission (DAS28 <2.6). However, patients in the other treatment groups who were given MTX alone did nearly as well. Among patients in the adalimumab withdrawal group, 81% maintained low disease activity through week 78, and 66% achieved clinical remission. Similarly, in the MTX monotherapy group, 81% achieved low disease activity and 68% achieved clinical remission after 78 weeks. Therefore, the overall findings of the OPTIMA trial demonstrate that patients with early RA who achieve low disease activity within the first 26 weeks of therapy continue to have favorable outcomes through 78 weeks of treatment, regardless of the treatment regimen.

Drug-Free Remission in Early RA

In the AVERT (Assessing Very Early Rheumatoid Arthritis Treatment) study, 351 patients with early RA were randomly assigned to start treatment with abatacept 125 mg plus MTX, abatacept 125 mg monotherapy, or MTX monotherapy.¹⁰ After 12 months of initial treatment, patients who achieved low disease activity (DAS28-CRP <3.2) were eligible to enter a second study period during which all RA therapies were discontinued. The study endpoints measured the proportion of patients who achieved clinical remission (DAS28-CRP <2.6) at 12 months and sustained a drug-free remission at 18 months (Table 1).

Results from AVERT showed that only approximately 15% of all patients with early RA are able to achieve a sustained drug-free remission after treatment with abatacept plus MTX, and an even smaller percentage for those using alternate monotherapy regimens.¹⁰ Remission may be more likely in certain RA patients, including those with anti-citrullinated protein antibody (ACPA)-positive disease and those treated when diagnosed with very early RA (≤ 3 months' duration).^{11,12}

In the future, drug tapering regimens may become a routine approach for managing RA patients who achieve early clinical remission. However, until more evidence is available to guide drug-tapering decisions, patients should generally focus on maintaining control of their RA disease activity with approved therapies.

Emerging Agents in RA

Targeted biologic therapy is likely to remain the mainstay of RA treatment, with many new options under development for achieving patients' therapeutic goals. Several agents in phase 3 development are building on proven mechanisms of RA treatment, such as Janus Kinase (JAK) and interleukin-6 (IL-6) inhibition (Table 2). Other emerging biologic therapies are exploiting new targets in the pathophysiology of RA.

JAK Inhibitors

Proinflammatory cytokines and immune system cells use the JAK signaling pathway to coordinate the inflammatory response. The JAK family of signaling proteins has four members: JAK1, JAK2, JAK3, and Tyk2.¹³ Of these, JAK1 and JAK3 are particularly active in RA. Blocking other JAK family members reduces inflammation, but may contribute to an increased risk of side effects as well.¹⁴ Tofacitinib, the first JAK inhibitor approved for the treatment of RA, has broad activity against JAK1 and JAK3, and, to a lesser extent, JAK2.

Baricitinib is an investigational, oral inhibitor of JAK1 and JAK2. In a phase 2 study, baricitinib improved the signs and symptoms of RA in patients who had moderate to severe disease activity despite treatment with MTX.¹³ In recent phase 3 trials, baricitinib significantly improved treatment outcomes in patients with inadequate responses to synthetic DMARDs (RA-BUILD) or anti-TNF therapy (RA-BEACON).^{15,16} At the 2015 ACR annual meeting, researchers presented new data from additional phase 3 trials showing the superiority of baricitinib to MTX (RA-BEGIN) and adalimumab (RA-BEAM) in patients with RA.^{17,18}

By selectively blocking JAK1 alone, novel JAK1 inhibitors may result in fewer off-target side effects than agents that block other members of the JAK family.¹⁴ Filgotinib, the first selective JAK1 inhibitor developed for the treatment of RA, recently demonstrated efficacy as a single agent and in combination with MTX.^{19,20} Another novel JAK1 inhibitor, ABT-494, has also shown promising activity in patients with moderate-to-severe RA and an inadequate response to prior anti-TNF therapy.²¹ Phase 3 trials of filgotinib and ABT-494 are expected to launch in 2015 and 2016.^{22,23}

IL-6 Inhibitors

IL-6 is one of the key mediators of inflammation and joint destruction in patients with RA. Tocilizumab, a monoclonal antibody directed against the IL-6 receptor (IL-6R), was the first approved RA therapy to inhibit the IL-6 signaling pathway. Building on this proven mechanism of action, additional novel agents are also being developed to target the IL-6 signaling pathway in patients with RA.^{24,25}

Sarilumab is an investigational monoclonal antibody directed against IL-6R. In recent phase 3 studies, treatment with sarilumab improved disease control in RA patients with an inadequate response to MTX (RA-MOBILITY) and in RA patients who were poor responders to or intolerant of anti-TNF therapy (RA-TARGET).^{26,27} Given subcutaneously every 2 weeks, sarilumab shows similar safety and tolerability compared with tocilizumab given by IV injection every 4 weeks.²⁸

Sirukumab is an investigational monoclonal antibody that disrupts the IL-6 signaling pathway by directly targeting IL-6 rather than its receptor.²⁵ In a phase 2 study, treatment with sirukumab improved RA disease control in patients with an inadequate response to MTX.²⁵ Ongoing phase 3 trials of sirukumab include a study in patients with active RA despite anti-TNF therapy (SIRROUND-T) and a head-to-head trial comparing sirukumab monotherapy with adalimumab monotherapy (SIRROUND-H).^{29,30}

Other Emerging Therapies

Several other biological therapies are currently under development in RA. These include investigational agents targeting IL-17 (ixekizumab, secukinumab,

Table 2
Emerging Agents in Phase 3 Clinical Trials for RA

	Biologic Target	Structure
<i>JAK INHIBITORS</i>		
Baricitinib	JAK1, JAK2	Small molecule inhibitor
Filgotinib	JAK1	Small molecule inhibitor
ABT-494	JAK1	Small molecule inhibitor
<i>IL-6 PATHWAY INHIBITORS</i>		
Sarilumab	IL-6R	Anti-IL-6 receptor monoclonal antibody
Sirukumab	IL-6	Anti-IL-6 monoclonal antibody

IL-6, interleukin-6; JAK, Janus kinase

brodalumab), IL-12/23 (ustekinumab, CNTO 1959), IL-20 (NNC 109-0012), and IL-21 (NNC 114-006).³¹ Novel therapies that target B cells (ofatumumab) and granulocyte-macrophage colony-stimulating factor (GM-CSF; mavrilimumab, MOR103) are also being studied.³¹ Given the robust pipeline of targeted therapies for RA, patients may have more options for individualized treatment in the future.

Biosimilars

As patents for the earliest anti-TNF agents and other biologics begin to expire, a new class of biologic therapy is emerging.³¹ Biosimilars—also called “follow-on biologics”—are defined as biological products that are highly similar to an already approved agent, with no meaningful differences in efficacy, safety, or potency.³²

Although biosimilars are relatively new in the United States, they have been available in some foreign markets for nearly a decade. In 2006, a biosimilar form of somatotropin, a growth hormone, became the first biosimilar to gain approval in Europe. To date, the European Medicine Agency has approved 19 biosimilar products, including biosimilar forms of erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF).^{33,34} In March 2015, the U.S. Food & Drug Administration (FDA) approved its first biosimilar agent, a biosimilar to filgrastim (a G-CSF used to prevent infection in patients undergoing various cancer treatments and in patients with severe chronic neutropenia).³⁵

Biosimilars in RA

In recent years, multiple studies have demonstrated the comparable safety and efficacy between biosimilars and their reference biologics in RA, including biosimilars to infliximab, etanercept, adalimumab, and rituximab.³⁶⁻⁴³ In 2013, two infliximab biosimilars became the first biosimilar monoclonal antibodies available for the treatment of RA in Europe.^{44,45} Several biosimilar products are now being used to treat RA and other rheumatic diseases in Japan, South Korea, and other regions.⁴⁶

Clinical experience with biosimilars in RA is growing around the world.^{47,48} One recent study included 39 patients from a single infusion center in Finland who had been treated with infliximab for RA and other rheumatic diseases for an average of 4 years. All patients were switched to an infliximab biosimilar and observed for a median of 11 months. Patients experienced no changes in symptom level or disease activity following the switch, and no new safety concerns arose.⁴⁷ Another study evaluated 98 RA patients in South Korea

who started treatment with original infliximab (n=46) or biosimilar infliximab (n=52). During 20 months of follow-up, patients in both treatment groups experienced statistically equivalent rates of DAS28-ESR remission, adverse events, and drug retention.⁴⁸

Building on this positive clinical experience, biosimilars are becoming standard therapies for RA patients in Europe.^{49,50} In July 2015, the U.K.-based National Institute for Health and Care Excellence (NICE) developed a resource for rheumatology providers to encourage the use of biosimilar infliximab in appropriate patients with RA. The guidance advises clinicians on how to incorporate biosimilars into their practice and how to switch patients from infliximab to biosimilar therapy.⁴⁹

ACR Guidance

In the United States, biosimilars are being greeted with cautious optimism. In February 2015, the ACR published a position statement outlining specific considerations for the use of biosimilars in RA and other rheumatic diseases.³² To ensure the safe and effective use of these new therapies in rheumatology practice, the ACR recommends a range of precautions:

- Biosimilars should have names that are distinct from the reference medications to avoid confusion and facilitate easy reporting of postmarketing safety data
- Patients who are stable on biologic therapy should not be switched automatically to a biosimilar agent as a cost-saving measure without prior consent of the prescribing clinician
- Clinicians should have the ability to specify “dispense as written” on all prescription medications
- Safety data for each biosimilar should be collected and analyzed separately (i.e., not pooled with other biosimilars) to ensure that unique safety risks are identified

The safety of biosimilars is of special concern. The ACR position statement includes a cautionary tale from Europe in the 1990s, when a biosimilar form of EPO increased the risk of a potentially fatal adverse event called pure red cell aplasia by 95%.^{32,51} The safety problem was traced to a change in the manufacturing process that altered the molecular structure of the biosimilar, increasing the likelihood that patients produced anti-EPO antibodies.^{32,51} This experience underscores the

importance of examining the safety of biosimilars, including any interactions between the biosimilar product and the immune system.³²

Patient education will be important for easing the transition to biosimilars, as survey data suggests that patients have a limited understanding of these products. In a North American survey of patients with RA who had been taking biologic therapy for 1-to-5 years, only 26% correctly identified the definition of a biosimilar. When asked to rate their interest in using a biosimilar product, 40% were somewhat or very interested, while 30% of patients were neutral. By comparison, 30% of patients were somewhat or completely opposed to using a biosimilar product.⁵²

Biosimilar Naming Guidelines

In preparation for biosimilar approvals, the FDA issued draft guidelines for naming biosimilar products in August 2015.⁵³ The proposed rules, which align with the ACR recommendations, are designed to minimize confusion as new biological products become available for clinical use.^{32,53} According to the FDA guidance, biosimilars cannot have “proprietary” names, or names that are totally separate from their reference products. Instead, all biosimilars must use nonproprietary names that follow a strict construction:

- **Core name:** all biosimilar names must contain the name of the reference product (e.g., etanercept or certolizumab pegol).
- **4-letter suffix:** to differentiate between products, all biosimilars must also contain a 4-letter, lowercase suffix that otherwise carries no meaning. As examples, acceptable etanercept biosimilar names could include etanercept-abcd or certolizumab pegol-efgh. In contrast, etanercept-PAIN or certolizumab pegol-MOVE would not meet the FDA naming criteria.

Biosimilar Pricing Trends

Similar to generic drugs, biosimilar products are expected to provide some degree of cost savings for patients and healthcare systems.⁴⁶ One study estimated the total cost savings of biosimilars to be \$44.2 billion in direct spending across

all classes of biologics between 2014 and 2024 in the United States, with anti-TNF inhibitors accounting for 21% of the total cost savings.⁵⁴ In June 2015, NICE published new RA treatment guidelines recommending that the least expensive drugs be used ahead of higher-priced alternatives. The NICE guidance stipulates a preference for biosimilars over brand-name medications, as well as a preference for generic products, such as generic MTX.⁵⁰

Compared with reference biologics, some analysts predicted that biosimilars would have price reductions of up to 35%.⁵⁴ Recent cost trends, however, suggest that biosimilars may not yield the savings anticipated. In September, the biosimilar form of filgrastim launched in the United States at a price of \$438.98 for a 480 mcg syringe, only about 3% lower than the average sales price of the reference product (\$449.81).⁵⁵ In the United Kingdom, a 100-mL vial of infliximab costs approximately \$660. By comparison, the two approved infliximab biosimilars are listed for \$593, or approximately 10% less.⁵⁰

In October 2015, the Centers for Medicare and Medicaid Services (CMS) set a single billing and payment code (J-code) for all biosimilars of a given biological product covered under Medicare Part B.⁵⁶ In practical terms, if multiple infliximab biosimilars enter the U.S. market, all will be reimbursed at the same price for Medicare recipients. According to some experts, the CMS payment rule removes the ability of biosimilars to compete on price, thereby limiting one of the potential advantages of this novel type of biologic therapy.⁵⁷

Future Perspectives

Since the introduction of TNF inhibitors more than 15 years ago, options for biologic therapy have grown to include 10 agents with diverse mechanisms of action. The next generation of RA biologics may be available soon, accompanied by a wave of biosimilar products. Additional trends include a renewed emphasis on RA treatment goals and drug tapering for patients who achieve early disease control. As best practices in RA management continue to evolve, new opportunities are expected to emerge that improve treatment outcomes for patients with RA.



See references for this article on page 10 & 15

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BONUS CONTENT!

As an added bonus, within this issue of *Rheumatology Nurse Practice*, you can find a comprehensive pull-out chart of all approved agents for the treatment of RA, along with indications, dosages, and safety information for your personal use.

Table 1. Current Biologic Therapies in RA¹⁻¹⁰

Agent	Year of Approval	Biologic Target	Structure	RA Indication	Other Indications	RA Dosing
CYTOKINE-DIRECTED THERAPY						
Etanercept	1998	TNF	Soluble TNF receptor 2-IgG Fc fusion protein	Moderately to severely active RA, with or without MTX	JIA, PsA, AS, Ps	<ul style="list-style-type: none"> 50 mg once weekly with or without MTX
Infliximab	1998	TNF	Anti-TNF monoclonal antibody	Moderately to severely active RA in conjunction with MTX	Adult CD, pediatric CD, adult UC, pediatric UC, AS, PsA, Ps	<ul style="list-style-type: none"> 3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks, in conjunction with MTX Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks
Adalimumab	2002	TNF	Anti-TNF monoclonal antibody	Moderately to severely active RA with or without MTX	JIA, PsA, AS, adult CD, pediatric CD, UC, Ps, HS	<ul style="list-style-type: none"> 40 mg every other week in combination with MTX (or 40 mg/week without concomitant MTX)
Certolizumab pegol	2008	TNF	Polyethylene glycol-linked anti-TNF monoclonal antibody	Moderately to severely active RA	CD, PsA, AS	<ul style="list-style-type: none"> 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered
Golimumab	2009	TNF	Anti-TNF monoclonal antibody	Moderately to severely active RA in combination with MTX	PsA, AS, UC	<ul style="list-style-type: none"> 50 mg administered by SQ injection once a month
Tocilizumab	2010	IL-6	Anti-IL-6R monoclonal antibody	Moderately to severely active RA and an inadequate response to one or more DMARDs; with or without MTX or other DMARDs	Systemic JIA, polyarticular JIA	<ul style="list-style-type: none"> IV dosing: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response SQ dosing: 162 mg every week; for patients weighing <100 kg, SC dosing should begin at 162 mg every other week and can increase to weekly based on clinical response
Anakinra	2001	IL-1	IL-1 receptor antagonist	Moderately to severely active RA in patients who have failed one or more DMARDs	CAPS	<ul style="list-style-type: none"> 100 mg/day by SQ injection; 100 mg every other day for patients with severe renal insufficiency or ESRD
LYMPHOCYTE-DIRECTED THERAPY						
Rituximab	1997	B cells	Anti-CD20 monoclonal antibody	Moderately to severely active RA in combination with MTX in patients with an inadequate response to one more anti-TNF therapies	NHL, CLL, GPA, MPA	<ul style="list-style-type: none"> In combination with MTX, two 1000 mg IV infusions separated by 2 weeks every 24 weeks (or based on clinical evaluation, but not <16 weeks) Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion
Abatacept	2005	T cells	Recombinant CTLA-4 and IgG1 fusion	Moderately to severely active RA, with or without MTX or other DMARDs (except TNF inhibitors)	JIA	<ul style="list-style-type: none"> For IV infusion: weight-based dosing (<60 kg, 500 mg; 60-100 kg, 750 mg; >100 kg, 1000 mg) given over 30 minutes at 0, 2, and 4 weeks, then every 4 weeks For SQ injection: optional single IV loading dose (weight-based dosing), followed by 125 mg injection within 1 day; continue with weekly injections of 125 mg
SMALL-MOLECULE KINASE INHIBITORS						
Tofacitinib	2012	JAK pathway	Small-molecule inhibitor	Moderately to severely active RA in patients with Inadequate response or intolerance to MTX, alone or in combination with MTX or other DMARDs	None	<ul style="list-style-type: none"> 5 mg twice daily Dose reduction to 5 mg once daily in patients with moderate hepatic or moderate/severe renal impairment

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AS = ankylosing spondylitis; CAPS = cryopyrin-associated periodic syndromes; CD = Crohn's disease; CLL = chronic lymphocytic leukemia; COPD = chronic obstructive pulmonary disease; CTLA-4 = cytotoxic T lymphocyte antigen 4; DMARD = disease-modifying antirheumatic drug; ESRD = end-stage renal disease; GI = gastrointestinal; GPA = granulomatosis with polyangiitis; HBV = hepatitis B virus; HS = hidradenitis suppurativa; IL-1 = interleukin-1; IL-6 = interleukin-6; IL-6R = IL-6 receptor; IV = intravenous; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; MPA = microscopic polyangiitis; MTX = methotrexate; NHL = non-Hodgkin's lymphoma; PML = progressive multifocal leukoencephalopathy; Ps = plaque psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SQ = subcutaneous; TNF = tumor necrosis factor; UC = ulcerative colitis; URI = upper respiratory tract infection; UTI = urinary tract infection.

Dosage Forms	Common Side Effects	Warnings/Precautions/Contraindications/Drug Interactions
<ul style="list-style-type: none"> • 50 mg single-use prefilled syringe • 50 mg single-use prefilled auto-injector • 25 mg single-use prefilled syringe • 25 mg multiple-use vial 	Infections and injection-site reactions	<ul style="list-style-type: none"> • Warnings: serious infections and malignancy • Precautions: demyelinating disease, heart failure, HBV reactivation, anaphylaxis or serious allergic reactions, cytopenias, lupus-like syndrome, autoimmune hepatitis • Contraindications: sepsis • Interactions: live vaccines, anakinra, abatacept, cyclophosphamide
<ul style="list-style-type: none"> • 100 mg of lyophilized infliximab in a 20 mL vial for IV infusion over ≥2 hours 	Infections (e.g., URI, sinusitis, pharyngitis), infusion-related reactions, headache, abdominal pain	<ul style="list-style-type: none"> • Warnings: serious infections and malignancy • Precautions: hepatotoxicity, HBV reactivation, heart failure, cytopenias, hypersensitivity, demyelinating disease, lupus-like syndrome, live vaccines or therapeutic infectious agents • Contraindications: infliximab >5 mg/kg in moderate to severe heart failure; previous severe hypersensitivity reaction to infliximab or its components • Interactions: anakinra, abatacept
<ul style="list-style-type: none"> • Injection: 40 mg/0.8 mL in a single-use prefilled pen • Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe • Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe • Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe • Injection: 40 mg/0.8 mL in a single-use glass vial (institutional use only) 	Infections (e.g. URI, sinusitis), injection site reactions, headache, rash	<ul style="list-style-type: none"> • Warnings: serious infections and malignancy • Precautions: anaphylaxis or serious allergic reactions, HBV reactivation, demyelinating disease, cytopenias, heart failure, lupus-like syndrome • Contraindications: none • Interactions: live vaccines, anakinra, abatacept
<ul style="list-style-type: none"> • 200 mg lyophilized powder in a single-use glass vial, with 1 mL sterile water for reconstitution and injection • 200 mg/mL solution in a single-use prefilled syringe for injection 	URI, rash, UTI	<ul style="list-style-type: none"> • Warning: serious infections and malignancy • Precautions: heart failure, anaphylaxis or serious allergic reactions, HBV reactivation, demyelinating disease, cytopenias, lupus-like syndrome • Contraindications: none • Interactions: live vaccines, biologic DMARDs, coagulation testing (e.g., aPTT)
<ul style="list-style-type: none"> • 50 mg/0.5 mL in a single dose prefilled auto-injector • 50 mg/0.5 mL in a single dose prefilled syringe • 100 mg/1 mL in a single dose prefilled auto-injector • 100 mg/1 mL in a single dose prefilled syringe 	URI, nasopharyngitis, injection-site reactions	<ul style="list-style-type: none"> • Warnings: serious infections and malignancy • Precautions: HBV reactivation, heart failure, demyelinating disease, hypersensitivity reactions • Contraindications: none • Interactions: anakinra, abatacept, live vaccines, therapeutic infectious agents
<ul style="list-style-type: none"> • Single-use vials (20 mg per mL) for IV administration: 80 mg per 4 mL; 200 mg per 10 mL; 400 mg per 20 mL • Single-use prefilled syringe for SQ administration: 162 mg/0.9 mL 	URI, nasopharyngitis, headache, hypertension, increased ALT, injection-site reactions	<ul style="list-style-type: none"> • Warning: serious infections • Precautions: GI perforation, laboratory monitoring due to treatment-related changes in neutrophils, platelets, lipids, and liver function tests, hypersensitivity reactions, live vaccines • Contraindications: known hypersensitivity to tocilizumab • Interactions: live vaccines, CYP450 substrates (e.g., warfarin, cyclophosphamide), CYP3A4 substrates (e.g., oral contraceptives, statins)
<ul style="list-style-type: none"> • 100 mg/0.67 mL solution for SQ injection; graduated syringe allows for doses between 20 and 100 mg 	Injection site reaction, worsening of RA, URI, headache, nausea, diarrhea, sinusitis, arthralgia, flu like-symptoms, abdominal pain	<ul style="list-style-type: none"> • Warnings and precautions: serious infection, concomitant use with anti-TNF agents, hypersensitivity reactions, neutrophil monitoring, live vaccines • Contraindications: known hypersensitivity to anakinra, its components, or E. coli-derived proteins • Interactions: TNF inhibitors
<ul style="list-style-type: none"> • 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial 	URI, nasopharyngitis, UTI, bronchitis, infusion reactions, serious infections, cardiovascular events	<ul style="list-style-type: none"> • Warnings: fatal infusion reactions, severe mucocutaneous reactions, HBV reactivation, PML • Precautions: tumor lysis syndrome, infections, cardiac arrhythmias and angina, bowel obstruction and perforation, live virus vaccines, cytopenias • Contraindications: none • Interactions: cisplatin
<ul style="list-style-type: none"> • 250 mg lyophilized powder in a single-use vial for IV infusion • 125 mg/mL solution in a single-dose prefilled syringe for SQ injection 	Headache, URI, nasopharyngitis, nausea	<ul style="list-style-type: none"> • Warnings and precautions: serious infections, history of infections, live vaccines, hypersensitivity, anaphylaxis and anaphylactoid reactions, increased risk of respiratory infections, concomitant use with anti-TNF agents • Contraindications: None • Interactions: TNF inhibitors, other biologic DMARDs (e.g., anakinra), blood glucose testing (IV abatacept only)
<ul style="list-style-type: none"> • 5 mg tablets 	URI, headache, diarrhea, nasopharyngitis	<ul style="list-style-type: none"> • Warnings: serious infections and malignancy • Precautions: GI perforations, laboratory monitoring, live vaccines; not recommended in patients with severe hepatic impairment • Contraindications: none • Interactions: CYP3A4 inhibitors (e.g., ketoconazole), CYP2C19 inhibitors (e.g., fluconazole), CYP inducers (e.g., rifampin)

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Table 2. Common DMARDs in RA¹ (Continued)

Agent	Year of Approval	Mechanism of action	Use in RA	Other Rheumatology Uses*	Dosing
Methotrexate	1953 for cancer 1988 for RA	<ul style="list-style-type: none"> • Antiinflammatory effects • Interruption of the TNF pathway • Immune system suppression via inhibition of folic acid metabolism 	<p>First-line therapy for RA</p> <p>Used alone and in combination with synthetic and biologic DMARDs</p>	PsA, SLE, JIA, polymyositis	<ul style="list-style-type: none"> • Oral: 7.5-25 mg once weekly • SQ: can be used in those on the
Hydroxychloroquine	1955 for SLE	<ul style="list-style-type: none"> • Anti-inflammatory effects via immune cell pH imbalance • Cytokine disruption, causing decreased autoantibody production and reduced lymphocyte activation 	Off label	SLE, DLE, Sjögren's syndrome	<ul style="list-style-type: none"> • Oral: 200-400 mg daily • Dosing using • Risk of retinal doses
Sulfasalazine	1950 for RA and UC	<ul style="list-style-type: none"> • Immune system suppression via inhibition of lymphocyte and leukocyte cell function • Inhibits absorption of folic acid 	Commonly used as part of triple therapy regimen for RA in conjunction with MTX and HCQ	UC	<ul style="list-style-type: none"> • Oral: 1-3 g daily in 4 doses • Not recommended in young years
Leflunomide	1998 for RA	<ul style="list-style-type: none"> • Inhibits pyrimidine synthesis and exhibits anti-proliferative properties, thereby reducing joint pain, edema, and structural joint damage 	Active RA	None	<ul style="list-style-type: none"> • Oral: 1-3 g once daily
Azathioprine	1968 as immunosuppressant following renal transplant	<ul style="list-style-type: none"> • Unknown mechanisms of immunosuppression 	Extraarticular manifestations of RA	Systemic vasculitis, Behçet's disease	<ul style="list-style-type: none"> • Oral: 2-4 mg/kg daily • IV: available
Cyclosporine	1983 as immunosuppressant following organ transplant	<ul style="list-style-type: none"> • Reduces T-cell activity by inhibiting immune response to IL-2 	Refractory RA	Psoriasis, severe atopic dermatitis, pyoderma gangrenosum, chronic autoimmune urticaria	<ul style="list-style-type: none"> • Oral: 1-4 mg/kg divided into 2-4 doses • Average dose into 2-4 doses • Maximum 4 mg/kg/day • Available in capsules
Cyclophosphamide	1959 for cancer	<ul style="list-style-type: none"> • Interferes with DNA structure leading to cell death • Immunomodulatory effects via unknown mechanisms 	Severe RA	Lupus nephritis, JIA, vasculopathies	<ul style="list-style-type: none"> • IV doses: 1-2 g/m² weekly • Available in reconstituted mg, 1 g

*Including common off-label uses.

ACE, angiotensin converting enzyme; AZA, azathioprine; CBC, complete blood count; DLE, discoid lupus erythematosus; GI, gastrointestinal; HCQ, hydroxychloroquine; IL, interleukin; IV, intravenous; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus; SQ, subcutaneous; SSZ, sulfasalazine; UC, ulcerative colitis.

Common Side Effects	Nursing Considerations
<p>7.5 to 25 mg taken on the same day weekly can consider higher doses than given orally; injection also given same day once weekly</p>	<p>GI upset (nausea, vomiting, diarrhea, loss of appetite), mouth sores, increased risk of infection</p> <ul style="list-style-type: none"> • Rapid onset of action (3-8 weeks) • Ease of administration via oral or SQ injection • Relatively low cost • MXT may be taken in combination with other medications • Requires frequent lab monitoring of liver function and blood count • Requires folic acid supplementation • Alcohol should be avoided due to risk of liver toxicity • Pregnancy category X: contraindicated in pregnancy or while breast feeding • May decrease effects of digoxin therapy
<p>200 mg/day to 400 mg/day should not exceed 6.5 mg/kg/day patient's ideal body weight if renal toxicity with cumulative >1000 g</p>	<p>GI upset (nausea, vomiting, diarrhea, loss of appetite), skin rash, hyperpigmentation, sun sensitivity, hair loss and change in hair color, tinnitus, loss of hearing, unusual bleeding, bruising, chest pain, palpitations, blurred vision, seeing spots</p> <ul style="list-style-type: none"> • May be taken with food or milk to reduce risk of GI symptoms • Baseline eye exam by an ophthalmologist recommended prior to starting therapy and every 6 to 12 months while on medication • Dose reduction may be required in patients with renal insufficiency • Slower onset of action (6 months) • May be taken in combination with other medications • Pregnancy category C: use with caution if benefits outweigh risks • Concentrated in breast milk but not contraindicated during breast feeding
<p>total dose of 2 g/day divided in 2 to 4 doses per day, preferably with food recommended for patients < 2000 g</p>	<p>GI upset (nausea, vomiting, diarrhea, loss of appetite), headache, skin rash, sun sensitivity, reversible decrease in sperm count</p> <ul style="list-style-type: none"> • Should not be given to patients with sulfonamide or salicylate allergy • Requires regular lab monitoring of CBC • Protective clothing recommended with sun exposure • Proper hydration recommended to reduce the risk of kidney stones • Pregnancy category C: use with caution if benefits outweigh risks • Nursing mothers should discontinue either nursing or the medication, as SSZ crosses into the breast milk • Male patients may need to discontinue therapy in cases of infertility • Increases the effectiveness of oral anticoagulants and oral hypoglycemic agents • Decreases the effectiveness of digoxin, folic acid, and iron
<p>10 mg or 20 mg tablets taken daily</p>	<p>GI upset (abdominal pain, nausea, diarrhea), increased risk of infections, reversible alopecia, elevated liver function tests</p> <ul style="list-style-type: none"> • Requires regular lab monitoring of liver function • Contraindicated in women of childbearing potential • Pregnancy category X: not for use during pregnancy • Women who wish to "wash out" from the drug in preparation for pregnancy will need to take an 11-day course of cholestyramine to remove leflunomide from the system; blood testing is required to confirm that the drug has been eliminated • Men who wish to father a child should consider discontinuing leflunomide and taking an 11-day course of cholestyramine to eliminate the drug from their bodies • Increases the effectiveness of NSAIDs
<p>available in 50 mg tablets; 3-5 mg/kg/day initial dose; 1-2 mg/kg/day maintenance dose available in 100 mg/20 mL vials</p>	<p>GI upset (nausea, vomiting, diarrhea), blood count abnormalities, leukopenia, cytopenia, macrocytic anemia, unusual bleeding or bruising, increased risk of infection</p> <ul style="list-style-type: none"> • Requires regular lab monitoring of CBC and liver function • Numerous drug interactions, including ACE inhibitors, anticonvulsants, allopurinol • Requires AZA dose reduction of 50% to 75% if concurrent treatment with allopurinol is necessary • Pregnancy category D: use in life-threatening emergencies when no safer drug is available • Not recommended during breast feeding, as AZA is excreted in low levels into breast milk
<p>initial dose of 1.25 mg/kg/day divided into 2 doses per day; titrated to target dose of 2.5 mg/kg/day in divided doses per day maximum dose should not exceed 4 mg/kg/day available in 25 mg, 50 mg, 100 mg tablets</p>	<p>Myelosuppression (leukopenia, thrombocytopenia), hypertension, tremors, increased risk of infection, GI upset (nausea, abdominal pain, diarrhea, dyspepsia), elevated triglyceride levels, photosensitivity</p> <ul style="list-style-type: none"> • Different formulations are not dose equivalent; switching between branded and generic versions requires caution • Slower onset of action (4 to 8 weeks in RA) • Requires regular lab monitoring of liver function, blood count, blood chemistry • Can be taken in combination with salicylates, NSAIDs, oral corticosteroids, and MTX • Pregnancy category C: use with caution if benefits outweigh risks • Not recommended during breast feeding; excreted into breast milk
<p>starting for RA: 10 mg/kg every 2 weeks available in powder form for intravenous substitution at 100 mg, 200 mg, 500 mg, and 2 g doses</p>	<p>Myelosuppression (leukopenia, thrombocytopenia), GI upset (nausea, vomiting, diarrhea, abdominal pain), lethargy, joint pain, hair loss and color/texture change, hemorrhagic cystitis, increased risk of infection, slow wound healing, mouth sores, hematuria, unusual bleeding and/or bruising</p> <ul style="list-style-type: none"> • Requires regular lab monitoring of CBC and urinalysis • Adequate fluid intake and hydration required to reduce the risk of hemorrhagic cystitis • Pregnancy category D: use in life-threatening emergencies when no safer drug is available • Excreted in breast milk and not recommended while breast feeding

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References: Treatment Trends... (continued from page 10)

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Don't Forget Our Old Friends

by Jacqueline Fritz, RN, MSN, CNS

We are fortunate in rheumatology that we are blessed with so many new options to care for and treat our patients that we sometimes forget some of our older friends. Every now and then, though, we get a reminder that old friends can sometimes be just the ones we need for some of our patients.

Meet Uncle Harry, a crusty, independent and stubborn 80-year-old. He presented to our clinic after a referral by his primary care physician with positive rheumatoid factor, arthralgia, and 2 hours of morning stiffness. A pack-a-day smoker with a history of congestive heart failure (CHF), Harry lives alone and assured me that he was “perfectly fine with that.” Upon initial questioning, Harry said that his joint pain improved when he takes “them little white pills” (eg, prednisone), and he was really hopeful that he could resume his normal life schedule when his recent exacerbation of joint pain was resolved.

While Harry was dressed reasonably neatly, it was clear to me that his shoes were a real stumbling block. Between his swollen and stiff fingers, pitting edema, general shortness of breath and dyspnea on exertion, and widespread generalized pain, the best Harry could do was walk in with his shoes open and not exactly on his feet. Nonetheless, Harry assured me that, “I am fine. I don’t need any help. I am 80! I got here by myself and I can take care of this too!”

On physical exam, Harry had 14 tender and 12 swollen joints. His erythrocyte sedimentation rate was 109 and his C-reactive protein level was extremely elevated at 15.46. His renal and liver function levels were within normal limits. Harry’s health activity questionnaire score (HAQ) was 2.0, indicating moderate limitations to performing daily activities.

At presentation, Harry was taking three medications as a result of his CHF. He had also increased his prednisone to 40 mg BID as “they seem to really help!” (although they increase water retention and are contraindicated due to his CHF).

After the initial exam, we started Harry on a prednisone taper, 10 mg of methotrexate, sulfasalazine, and hydrocodone bitartrate/acetaminophen 4 times a day. We also ordered an ETA 14-3-3 diagnostic panel as well as hepatitis and tuberculosis assays. We advised Harry to get a pneumonia vaccine and flu shot 2 weeks apart.

Six weeks later, Harry returned to our clinic for his initial follow-up. The number of tender and swollen joints had not changed. His HAQ score remained stuck at 2.0. Both his ETA 14-3-3 and tuberculosis tests came back positive. Hepatitis serologies were negative.

Clearly, Harry still had very active disease, and not surprisingly, he was angry at me for putting him on a regimen that did not work. He told me he had stopped taking all the medications except the prednisone a few weeks ago because “nothing you gave me was working.” He could not say how long he tried the “other pills” before stopping them. He also complained that the sulfasalazine made his urine too yellow. To further complicate matters, Harry developed a nodule under his left clavicle that was being evaluated by an oncologist. He also did not get either vaccine that was recommended.

With his daughter in the room at this visit, we managed to get Harry to agree that perhaps a tiny bit of adherence would really benefit his condition. I promised him that we would try something else if he would increase his methotrexate as ordered, taper his prednisone use, start hydroxychloroquine 200 BID and return to our office in three weeks.

At Harry's next visit, his x-rays came back with no erosive disease. Terrific! But now the BIG question—what next? With a history of CHF, possible cancer, a positive tuberculosis test, and a pattern of medication non-compliance, the risk/benefit calculation was complicated.

As rheumatology nurses, there are many times we are quick to jump to some of our more aggressive therapies when we have a patient who we can't help right away...

While we considered our next option, I got a call from Harry's daughter who was excited to report her dad was much better with the "miracle drug" on which we started him.

Certainly, I was happy to hear that, although I know that there is nothing miraculous

about hydroxychloroquine (HCQ), one of our old friends in rheumatology. While HCQ's mechanism of action is not well understood, it may in part be due to the fact that the drug concentrates inside the cells, principally within the acidic cytoplasmic vesicle. In lysosomes, accumulation of HCQ raises the intravesicular pH and thereby inhibits autoimmune peptides.¹ While HCQ's effects on RA typically take approximately 3–6 months to surface in most patients,² they had a near-immediate impact for Harry.

The combination of sulfasalazine and HCQ often work synergistically, but since Harry declined to continue on sulfasalazine, we are currently treating him with methotrexate and HCQ alone. We will see when Harry completes his next HAQ if his functional assessment mirrors the objective opinion of Harry and his daughter.

As rheumatology nurses, there are many times we are quick to jump to some of our more aggressive therapies when we have a patient who we can't help right away—and often rightly so—but there are instances when our old standbys can be useful in patients like Harry with so many complicating factors.

And so on Harry's behalf, let me say, "Thank you old friend!"



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Patients Who Don't Fit the

Profile

by Iris Zink, MSN, NP

Like baseball, many things about medicine revolve around statistics. For instance...

- Patients with rheumatoid arthritis (RA) present most commonly between the fourth and sixth decades of life¹
- RA is 2.5 times more common in women than men¹
- Concomitant RA and ankylosing spondylitis (AS) is extremely rare, with less than 100 cases reported in the medical literature

Of course, our patients aren't numbers on a page and many of them don't fit nicely into classification boxes. Take R.R. for example, a 78-year-old patient of mine who had been a very active man slowed only by a history of spinal stenosis.

After successful back surgery in 2012, R.R. quickly returned to walking four miles a day. Everything was fine for the next 2 years before he began complaining of hand pain and an inability to make a fist or hold a rake. To get to the bottom of his issues, we ordered x-rays of his hands and a full lab workup.

R.R.'s anti-cyclic citrullinated peptide, C-reactive protein, and erythrocyte sedimentation rate results were all normal, but his rheumatoid factor was elevated at 25 IU/mL (normal is 14 IU/mL at our lab). Perhaps a decade or two ago—when the medical literature indicated an elevated RF in an elderly patient was generally meaningless³—we would have discounted this finding. Today, we're not so quick to discount its importance.

Due to R.R.'s worsening MCP pain, which did not improve after initial use of an NSAID, we ordered an MRI of his left hand. It revealed erosions of the distal metacarpophalangeal (MCP) joints consistent with a diagnosis of RA. At this point, we began discussing more aggressive treatment options. We also initiated more serious discussions about R.R.'s drinking habit.

He consumed "several" alcoholic beverages each day, which obviously was not helping his overall condition.

We began R.R. on a daily regimen of 20 mg of leflunomide and 10 mg of prednisone, tapering the prednisone over the course of several weeks as the leflunomide began to work. R.R. was also advised to cut his alcohol intake down to no more than 2-3 drinks a week, and we began closely monitoring his liver enzymes.

Unfortunately, R.R.'s disease continued to progress over the next 6 months, and we began looking for more aggressive treatment options. Prior to initiating biologic therapy, we ordered a chest x-ray, which appeared abnormal. Consequently, a thoracic spine x-ray was ordered. It showed bamboo spine and calcification of the anterior longitudinal ligaments consistent with AS.

As an elderly male, R.R. didn't fit into the usual bucket for a new diagnosis of either RA or AS. Confused, I met with one of our rheumatologists to discuss this case. R.R. had had a long history of lower back pain but had never reported nocturnal inflammatory awakening due to pain. His MRI showed erosions over the MCP joints consistent with RA and yet his thoracic spine x-ray suggested a diagnosis of AS. I looked at our rheumatologist with a confused look. She told me, "He has both RA and AS."

After reaching this dual diagnosis, R.R. was weaned off of prednisone and started on infliximab. Unfortunately, he fell down an embankment not long after his first dose of infliximab and fractured 2 vertebrae. After kyphoplasty, we re-started R.R. on infliximab. After his second dose of infliximab, R.R. reported some improvement in the pain and stiffness in his hands, although his back pain has worsened due to his fractures, and more surgery may be necessary. We continue to search for long-term answers.



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It's Our Time for Rheumatology Nurses to Shine

by Sheree C. Carter, PhD, RN



This issue of *Rheumatology Nurse Practice* is focused on the medical treatment options available to patients with rheumatoid arthritis (RA). It provides an excellent bookend to our 3 previous issues that have focused on, in chronological order, the current meaningful use indicators in RA, the pathophysiology of RA, and interpretation of laboratory data in RA. We understand this is a “medical model approach” to the care of RA, and we hope that you all gained valuable insights to help your own practice and improve the lives of your patients. However, we also understand that nurses are not often educated via the medical model approach in nursing school, specifically in regards to rheumatology, and depend on rheumatologists and peers to supplement their medical knowledge and understanding.¹

Treatment options available to our patients with rheumatic diseases have given great hope to those working in our field, and our options continue to expand thanks to advances in genetics and identification of pathways at a microscopic cellular level. Kudos to the bench scientists and researchers for making the complex and fascinating discoveries that lead to new medications in our armamentarium to treat rheumatologic diseases. With the growth of our pharmacologic toolbox, our roles and responsibilities as rheumatology nurses have grown as well.

In the medical literature, rheumatology nurses from around the world have demonstrated how we are distinctively positioned to more comprehensively serve patient needs by providing education about treatment, drug administration, product storage, and self-injection technique; determining readiness for and understanding of treatment; monitoring safety and progress; and coordinating overall care.² When we talk to others about our role as a rheumatology nurse, the first words out of our mouth should be “complex” and “mandatory to successful patient outcomes.”

In the last 5 years, the medical literature has been replete with recommendations and changes regarding approaches to treatment for many of our major rheumatologic disease states. In RA, for instance, we recently saw the release of the second recent update to treatment guidelines.^{3,4} Our patient goals now focus on inhibiting disease progression, achieving clinical remission, and relieving symptoms. Never have rheumatology nurses been more essential in helping to implement these evidence-based guidelines and giving patients their best chance at living successfully with a chronic disease.

In a 2013 study by Cottrell et al, rheumatology nurses from around the world were found to spend more time with patients not responding well to biologic treatment than physicians. I doubt that comes as a surprise to many of us. By establishing a therapeutic

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relationship, the rheumatology nurse and patient are able to establish the hidden link regarding quality of life, educational needs, and emotional concerns that are critical in care and treatment of rheumatic diseases.

Throughout the past 12 months, we have done our best within the pages of *Rheumatology Nurse Practice* and through our corresponding live broadcasts to provide you with a variety of materials and stories to help educate yourself, and we hope that you have been able to apply some of this knowledge to the core skill that make us nurses—assessment, diagnosis, outcome identification and planning, implementation, and evaluation.

As nurses, what we are taught and instinctually develop is the ability to critically examine whether our patients are telling us the truth or just what they think we want to hear.² Along with our more basic assessment of treatment response, we must also monitor our patients for things such as depression, sexual problems, fears of dependence, and chronicity of the progression of RA, even when our patients do not initiate the discussion.^{2,5}

It has been our distinct pleasure and honor to help shape and deliver this year's *Rheumatology Nurse Practice*. We invite your comments and suggestions of topics for future issues. But most importantly, we applaud you as rheumatology nurses—now get out there and publish!



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My Most Memorable Patient

by Elizabeth Kirchner, CNP

My most memorable patient thinks of herself as a bother. She calls herself my “problem patient” and apologizes every time she contacts me, which often happens 2 or 3 times a week. But to me, she is neither a bother nor a problem patient, and I tell her every time I talk to her that there is no need to apologize for calling. Instead, I feel like I should be apologizing to her.

I have been part of the team caring for “Sophia” (not her real name) for more than 15 years. In that time Sophia has gone through 18 joint surgeries—mostly total joint replacements—and every non-biologic and biologic DMARD available for the treatment of rheumatoid arthritis (RA). We check her labs assiduously and monitor her carefully. And yet, 15+ years into this journey, we still don't know exactly what disease she has.

For the sake of convenience, we call Sophia's disease seronegative RA, yet everyone on Sophia's team—her husband, her children, her hand orthopedist, her foot orthopedist, her hip and knee surgeon, her shoulder surgeon, her general internist, her rheumatologist, her infectious disease physician, her physician assistant, and I—all know she has something much, much worse. On multiple occasions, we have seen Sophia come in with a warm tender joint, and 3 weeks later, the joint has completely dissolved. All we can do is watch helplessly and call a surgeon for another joint replacement.

Without a doubt, Sophia does not have classic RA that you'll read about in any guideline or textbook. There is no known septic process that influences her disease.

All we have been able to conclude about Sophia is that her disease is not a lot of things. The problem is we don't know what it is or, more importantly, the best way to treat it.

So what makes Sophia my most memorable patient? I admit part of it is purely intellectual. Someday, somehow, we are going to solve this puzzle. The clue might come in a new diagnostic test, or in a pathology report from one of her (inevitable) future surgeries, or maybe one of the dozens of cultures we send will finally come back positive for a previously-unknown organism. I do not enjoy the mystery and what it means for Sophia and her family, but it does bring out the tenacity in me.

But what really makes Sophia my most memorable patient is everything we have learned from each other over the years. She has taught me how to be grateful for the health we do have instead of focusing on what we've lost, how to let others love us and how to love others more deeply, and how to remain hopeful when things are looking pretty bleak. I have also learned that there is something to be said for toughness. While family support and having a shoulder to cry on are essential to face life's difficult challenges, especially ones as daunting as Sophia's, sometimes you just have to say, “I gotta do this,” grit your teeth, and get to work.

Despite not knowing exactly what disease Sophia has, and knowing (at least on some level) that whatever she has is not going to go away anytime soon, there have been many bright spots in her disease course. When she first came to us in her early 50s, Sophia was wheelchair-bound. Now, except for when she has recently undergone lower extremity surgery, she is ambulatory. Even though we have never been able to achieve full remission, we have seen her symptoms go into near-remission for months at a time. This, and the fact that she is able to enjoy spending time with her 2 young grandchildren, gives Sophia hope. I honestly think that it is the hope, and not the medications, that have benefitted her most over the years. She has a loving, supportive family, a network of friends, and an amazing sense of humor.

Sophia's story is not a slam-dunk victory of modern medicine over ancient disease. It is not one of those shining examples we can all hold up and say, “See how I solved this problem and made this patient better!” But her story is memorable because despite not knowing what Sophia has, how to treat it, or what her future holds, I know Sophia is going to keep fighting, living life to the fullest, and laughing a lot. And I hope to have the honor of being with her every step of the way.



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Commercial Support

Supported by an educational grant from Pfizer.

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