RHEUMATOLOGY NURSE
PRACTICE

Inside this Issue

ISSUE 3 | VOLUME 4

- How have the findings of recent, large systematic reviews reassured the rheumatology community regarding its current approach to treating patients with rheumatoid arthritis (RA)?
- What correlations have recently been found between the use of biologic disease modifying anti-rheumatic drugs and specific adverse events?
- How has the recent introduction of biosimilars in the United States impacted patients with RA?
- How might some of the new and late-stage agents under development offer new opportunities for the treatment of RA?

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LOOKING AT THE HORIZON

What Does the Future Hold in the Treatment of RA?

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ACTIVITY DESCRIPTION

In this issue of *Rheumatology Nurse Practice*, we will explore recent systematic reviews that provide a snapshot of the current RA evidence base supporting different treatment options at each stage of disease. We will also look ahead to new therapies, including biosimilar agents, and discuss where these new treatments may fit into evolving best practices in the care of patients with RA.

LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

- Analyze primary conclusions regarding efficacy and safety of recent systematic reviews of common treatment regimens used in patients with RA
- Assess the potential impact of the introduction of biosimilars on your clinical practice
- Determine appropriate shingles and varicella vaccination protocols in patients being introduced to tofacitinib therapy
- Discuss the complexities of dealing with parents of pediatric patients, especially when aggressive treatment options are being considered

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LOOKING AT THE HORIZON

What Does the Future Hold in the Treatment of RA?

Treatment options for rheumatoid arthritis (RA) are expanding rapidly. The U.S. Food & Drug Administration (FDA) recently approved 2 new products for the treatment of RA (the interleukin-6 receptor inhibitor sarilumab and a second adalimumab biosimilar), and several additional novel biologics and small molecule therapies may be available soon. Amid these advances, it's time to take stock of where we are and where we are going with RA treatment.

Updates on Available RA Medications

According to the American College of Rheumatology (ACR), comparative-effectiveness research (CER) is needed to better understand the relative safety, efficacy, and costs of different RA treatments.[1] Despite calls for more CER, however, few randomized clinical trials (RCTs) have included head-to-head comparisons of specific treatment choices for RA. In lieu of direct comparisons, the rheumatology community relies on meta-analyses of RCTs. Over the past year, several large-scale meta-analyses and systematic reviews have examined the enormous body of RA clinical research conducted to date. By reviewing hundreds of RCTs enrolling thousands of patients, investigators have attempted to tease out meaningful trends in RA treatment.

Treatment Approaches for Patients Naïve to Methotrexate (MTX)

One systematic review focused on patients with RA who were naïve to MTX therapy (N=6,485).[2] The review included 19 studies of patients with MTX-naïve RA who started treatment with a biologic disease-modifying antirheumatic drug (DMARD) plus MTX, single-agent MTX, or biologic monotherapy. Trial duration ranged from 6 to 24 months.

Drug Names Included Within This Supplement

GENERIC	BRAND
Adalimumab	Humira
Infliximab	Remicade
Etanercept	Enbrel
Golimumab	Simponi
Abatacept	Orencia
Rituximab	Rituxan
Certolizumab pegol	Cimzia
Tocilizumab	Actemra
Tofacitinib	Xeljanz
Anakinra	Kineret
Sarilumab	Kevzara
Sirukumab	*TBA*
Baricitinib	Olumiant
Clazakizumab	*TBA*
Olokizumab	*TBA*
Filgotinib	*TBA*
Upadacitinib	*TBA*
Peficitinib	*TBA*
Decernotinib	*TBA*
Ixekizumab	Taltz
Secukinumab	Cosentyx
Brodalumab	Siliq
Infliximab-dyyb	Inflectra
Etanercept-szzs	Erelzi
Adalimumab-atto	Amjevita
Infliximab-abda	Renflexis
BI 695501	*TBA*

Across all trials, the biologic plus MTX arms included patients treated with 4 anti-TNF therapies (adalimumab, infliximab, etanercept, and golimumab), as well as 2 non-TNF biologics (abatacept and rituximab). No trials including certolizumab pegol, tocilizumab, or tofacitinib were included. Furthermore, the biologic monotherapy trials included only anti-TNF biologics.

In general, compared with patients who started on MTX monotherapy, patients who started treatment with a biologic plus MTX were 40% more likely to achieve at ACR 50 response (defined as at least a 50% improvement in RA-related signs and symptoms based on criteria determined by the American College of Rheumatology) and 62% more likely to achieve clinical remission (Table 1). Combination biologic/MTX therapy also increased the risk of adverse events (AEs) compared with MTX monotherapy, underscoring the vital role of adverse event management in RA treatment. In trials comparing single-agent anti-TNF therapy with MTX monotherapy, there were no meaningful differences in the expected response rates, remission rates, and rates of AEs between treatment approaches.[2]

Treatment Approaches Following Conventional DMARD Failure

After a poor response to MTX or another conventional synthetic DMARD (csDMARD) such as sulfasalazine or leflunomide, patients with RA generally have 3 treatment options:

- Add a biologic DMARD or small-molecule agent to MTX
- Switch to biologic or small-molecule monotherapy
- Continue MTX (or other csDMARD) or switch to another csDMARD

To understand the evidence supporting these treatment choices after csDMARD failure, 2 recent systematic reviews examined a total of 136 randomized clinical trials enrolling more than 46,000 patients with RA (Table 2).[3,4] In these reviews, biologic agents included the 5 FDA-approved anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), 4 non-TNF biologics (abatacept, anakinra, rituximab, and tocilizumab), and the small-molecule JAK inhibitor tofacitinib. The duration of most studies in the analysis ranged from 6 to 12 months.

In the first set of studies comparing combination therapy with single-agent MTX, patients with RA achieved better clinical outcomes when treated with a biologic or small molecule agent plus MTX or another csDMARD.[3] ***Compared with MTX monotherapy, combination therapy more than doubled the likelihood of achieving an ACR50 response and achieving clinical remission.*** Although the event rates across all groups were low, combination therapy also significantly increased the risk of serious infection and treatment discontinuation due to AEs compared with MTX alone.[3]

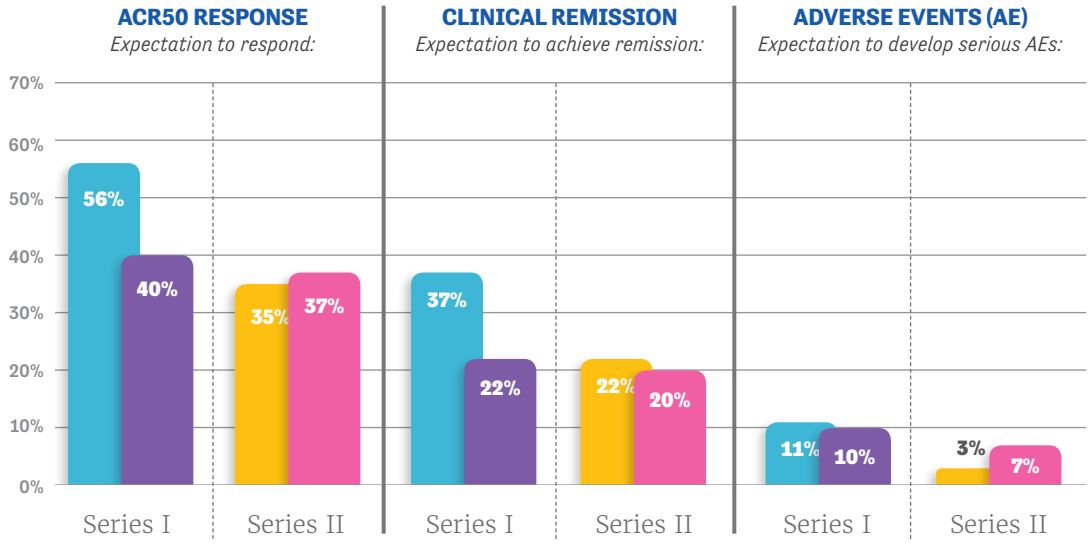
The review of monotherapy studies favored treatment with a biologic DMARD or small molecule alone over MTX monotherapy or placebo. ***Single-agent treatment with a biologic DMARD or JAK inhibitor improved the likelihood of achieving an ACR50 response by 54% compared with MTX alone.*** Although evidence on clinical remission was limited, trends favored an anti-TNF or non-TNF biologic compared with MTX alone.[4]

In several studies of biologic monotherapy vs. placebo, use of a single-agent biologic or small molecule significantly increased the likelihood of response and the likelihood of clinical remission. The rates of serious AEs and withdrawals due to AEs were higher with biologic monotherapy than with placebo, but the overall risk was low across treatment groups.[4]

These findings are consistent with another meta-analysis that showed no safety and efficacy differences between biologic DMARDs and tofacitinib, used alone or in combination with MTX, in patients who responded poorly to csDMARDs.[5] Whether treated with biologic DMARDs or tofacitinib after csDMARD failure, patients had similar rates of improvement in the signs and symptoms of RA.[5]

Table 1
Best Estimate of Treatment Response in Patients Naïve to Methotrexate[2]

Comparisons of treatment options in patients with RA who are naïve to MTX (N=6485)



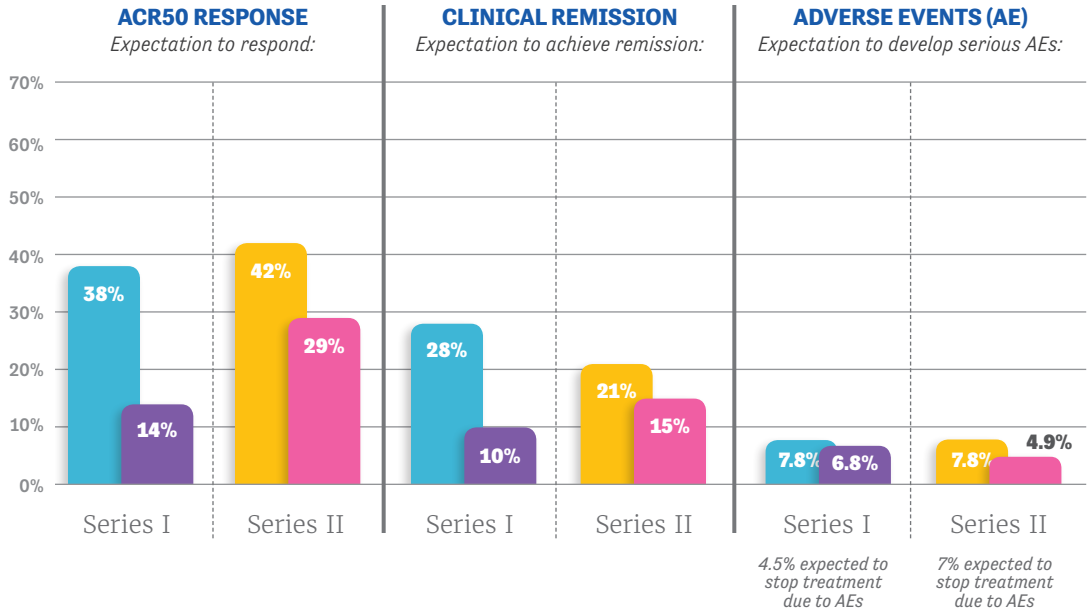
Series I
- *Biologics* + MTX*
- *MTX monotherapy*

Series II
- *Anti-TNF*
- *Anti-TNF MTX monotherapy*

*MTX, methotrexate; TNF, tumor necrosis factor / *Biologics included abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and rituximab.*

Table 2
Best Estimate of Treatment Response Following Conventional DMARD Failure[3,4]

Treatment options in patients with RA with an inadequate response to MTX



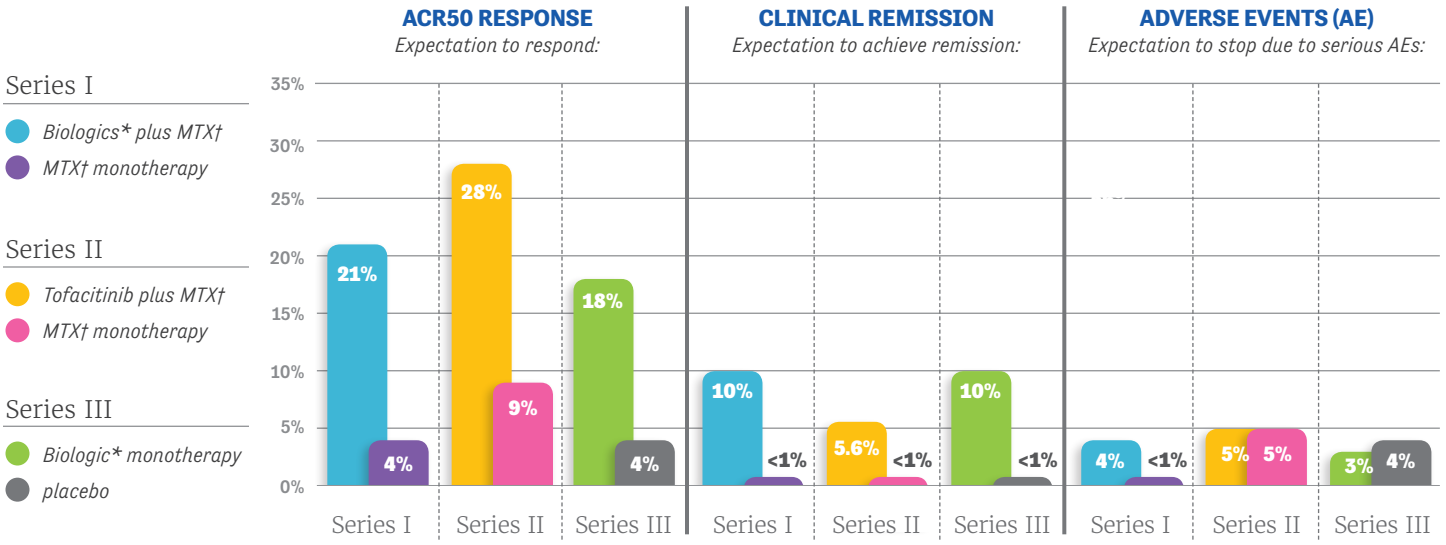
Series I
- *Biologics* plus MTX†*
- *MTX† monotherapy (N=32,874)*

Series II
- *Biologic* monotherapy*
- *MTX† monotherapy (N=14,049)*

*MTX, methotrexate. / *Biologics included abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and the small-molecule inhibitor tofacitinib. / †MTX or another conventional synthetic DMARD (csDMARD).*

Table 3
Best Estimate of Treatment Response Following Biologic DMARD Failure[6]

Comparisons of treatment options in patients with RA with a history of inadequate response to biologic therapy (N=3,364)



*MTX, methotrexate. / *Biologics included abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and rituximab. / †MTX or another conventional synthetic DMARD (csDMARD).*

Treatment Approaches Following Biologic Failure

Another systematic review evaluated treatment approaches and outcomes for patients with RA who had a history of inadequate response to prior biologic therapy (N=3,364).[6] The analysis included 12 studies spanning 3 types of comparisons: biologics plus MTX vs. MTX monotherapy; tofacitinib plus MTX vs. MTX monotherapy; and biologic monotherapy vs. placebo. The biologics included 4 anti-TNF agents (golimumab, etanercept, certolizumab pegol, and infliximab), plus 3 non-TNF biologics (rituximab, abatacept, and tocilizumab). In some cases, patients assigned to MTX therapy were given csDMARDs other than MTX. The majority of trials lasted less than 12 months.

Combination therapy with a biologic or tofacitinib plus MTX resulted in better outcomes than single-agent MTX or other csDMARD therapy (Table 3). ***In the trials of biologics plus MTX, patients were 4 times more likely to experience an ACR50 response and 20 times more likely to achieve clinical remission when treated with a biologic DMARD plus MTX compared with MTX monotherapy.*** In the tofacitinib trials, treatment with tofacitinib plus MTX increased the likelihood of an ACR50 response by more than 3-fold compared with single-agent MTX. Patients treated with tofacitinib plus MTX were also more likely to achieve clinical remission, although the difference compared with MTX monotherapy was not statistically significant.

In the biologic monotherapy trials, treatment with biologics significantly increased the likelihood of an ACR50 response and clinical remission with placebo. Across all trials, the risk of AEs increased in the more aggressive treatment arms, but the overall rates of treatment discontinuation remained low.

Reviews of RA Medication Safety

The European League Against Rheumatism (EULAR), as part of the process of developing its 2016 RA guideline update, conducted a comprehensive review of the safety of conventional and biologic DMARDs.[7] In the review, csDMARDs included azathioprine, chlorambucil, chloroquine, cyclosporine, cyclophosphamide, gold/auranofin, hydroxychloroquine, leflunomide, minocycline, MTX, mycophenolate, penicillamine, sulfasalazine, and tacrolimus. Biologic DMARDs included abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib, as well as biosimilars to the reference products.

Results from the EULAR safety review include the following major findings:[7]

- Biologic DMARDs increase the risk of **serious infection** by between 10% to 80% compared with csDMARDs, depending on the study. There are no differences between biologic DMARDs in the risk of serious infection.
- Biologic DMARDs also increase the risk of **tuberculosis** compared with csDMARDs. The magnitude of increased risk with biologics is high, ranging from more than 2-fold to 12.5-fold compared with csDMARDs. Tuberculosis screening and treatment, if needed, are cornerstones of safe use of biologic DMARDs.
- Biologics do not increase the risk of **herpes zoster** compared with csDMARDs.
- Biologic DMARDs do not increase the risk of most **cancers**, including lymphoma and non-melanoma skin cancer. However, biologics may increase the risk of melanoma compared with csDMARDs. In a single study, there was a non-statistically significant 50% increased risk of melanoma in patients treated with biologics.

Other recent analyses have found no significant correlations between cancer risk and treatment with biologic DMARDs or tofacitinib.[8] In the systematic reviews of RA therapies described in Tables 1-3, no single RA treatment regimen significantly increased the risk of cancer compared with other regimens, including placebo.[2-4,6]

New and Emerging RA Medications

On May 22, 2017, the FDA approved sarilumab for the treatment of RA.[9] Sarilumab inhibits the activity of interleukin-6 (IL-6) by blocking the IL-6 receptor (IL-6R). Sarilumab joins tocilizumab as anti-IL-6 biologics available to treat RA.[10] Several other agents in late-stage development exploit proven mechanisms of action in RA, including IL-6 and Janus kinase (JAK) (Table 4).

Sarilumab

The FDA approved sarilumab for the treatment of adults with moderate to severe RA and an inadequate response or intolerance to at least 1 conventional or biologic DMARD.[9] It can be given either as monotherapy or in combination with MTX or other csDMARDs. Sarilumab's approval was based on results from several phase 3 studies

Table 4
Newly Approved and Emerging Agents in RA

	Biologic Target	Structure	Status
IL-6 Pathway Inhibitors			
Sarilumab	IL-6R	Anti-IL-6 receptor monoclonal antibody	FDA approved May 2017
Sirukumab	IL-6	Anti-IL-6 monoclonal antibody	Under FDA review
Olokizumab	IL-6	Anti-IL-6 monoclonal antibody	Phase 3 trials ongoing
JAK Inhibitors			
Baricitinib	JAK1, JAK2	Small molecule inhibitor	Under FDA review; Approved in Europe
Filgotinib	JAK1	Small molecule inhibitor	Phase 3 trials ongoing
ABT-494	JAK1	Small molecule inhibitor	Phase 3 trials ongoing
Peficitinib	JAK1, JAK3	Small molecule inhibitor	Phase 3 trials ongoing
IL-17 Pathway Inhibitors			
Secukinumab	IL-17A	Anti-IL-17A monoclonal antibody	Phase 3 trials complete

IL-6, interleukin-6; IL-17, interleukin-17; JAK, Janus kinase.

showing its benefits after failure of conventional and biologic DMARD therapy.[11–13]

Sarilumab After MTX

The phase 3 MONARCH trial was a head-to-head comparison of sarilumab and adalimumab monotherapy in 369 patients with active RA despite treatment with MTX.[12] All patients were considered poor candidates for continued MTX treatment due to inadequate response (53%) or a history of intolerance to MTX (43%). Patients were randomly assigned to single-agent sarilumab 200 mg or adalimumab 40 mg every 2 weeks. As a superiority trial, MONARCH was designed to test whether sarilumab monotherapy was superior to adalimumab monotherapy based on the primary endpoint of mean change in Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR) score compared with baseline.

After 24 weeks, the trial met this endpoint. The mean changes in DAS28-ESR scores from baseline were -3.28 points in the sarilumab group and -2.20 points in the adalimumab group ($P<0.0001$). Several secondary endpoints also supported the superiority of sarilumab over adalimumab monotherapy. Patients treated with sarilumab monotherapy were more likely than those treated with adalimumab monotherapy to achieve ACR20, ACR50, and ACR70 responses, and more likely to reach clinical remission. The overall rate of adverse events was similar in both treatment arms. Although neutropenia was more common with sarilumab than adalimumab (13.6% vs 0.5%), the risk of serious infection was the same (1.1%) in both groups.[12]

Sarilumab After Anti-TNF Therapy

The phase 3 TARGET study demonstrated the potential clinical role of sarilumab in patients who are poor responders to or intolerant of anti-TNF therapy.[13] The trial enrolled 546 patients with moderate-to-severe RA who had a previous inadequate response (92%) or intolerance (8%) to TNF-targeted therapies. Patients were randomly assigned to treatment with subcutaneous (SC) sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks. All patients also remained on background treatment with synthetic DMARDs, which included MTX in approximately 85% of patients. After 24 weeks, the ACR20 response rates were 55.8% and 60.9% in the sarilumab 150 mg and 200 mg groups, respectively, compared with 33.7% in the placebo group. Sarilumab was well tolerated, with treatment discontinuation due to adverse events in 7.7% and 9.2% of patients in the 150 mg and 200 mg groups, respectively. The most common treatment-emergent AE was serious infection, occurring in 0.6%, 1.1%, and 1.1% of patients in the sarilumab 150 mg, sarilumab 200 mg, and placebo groups, respectively.[13]

Sirukumab

Sirukumab is an investigational monoclonal antibody that blocks the IL-6 signaling pathway by directly targeting IL-6 rather than its receptor. Sirukumab is currently under review by the FDA as well as regulatory agencies in Europe and Japan.[14]

Sirukumab in Poor Candidates for MTX

The SIRROUND-H trial was a head-to-head comparison of sirukumab and adalimumab monotherapy in 559 patients with RA who were naïve to biologic therapy.[15] All patients were considered inappropriate candidates for MTX due to inadequate response or intolerance. Therefore, patients were randomly assigned to start biologic monotherapy with sirukumab 50 mg every 4 weeks, sirukumab 100 mg every 2 weeks, or adalimumab 40 mg every 2 weeks. The co-primary endpoints were mean change in DAS28-ESR and ACR50 responses at 24 weeks. Secondary endpoints included ACR20 responses and clinical remission.

After 24 weeks, the mean change in DAS28-ESR score was significantly better in both sirukumab dosing groups compared with adalimumab. Patients treated with sirukumab were also significantly more likely than those treated with adalimumab to achieve clinical remission. Additional subgroup analyses showed that the benefits of sirukumab were consistent regardless of the reason for MTX discontinuation (inadequate response vs. intolerance). Despite the significant differences in responses based on DAS28-ESR scores, however, the ACR20 and ACR50 responses were comparable across all treatment groups. The rates of serious adverse events were 7.0%, 2.7%, and 4.3% in the sirukumab 50 mg, sirukumab 100 mg, and adalimumab 40 mg groups, respectively.

Sirukumab After Anti-TNF Failure

On the other end of the biologic treatment spectrum, the SIRROUND-T trial demonstrated the benefits of IL-6 inhibition with sirukumab in 878 patients with RA who had an inadequate response to anti-TNF therapy.[16] At enrollment, patients had an average disease duration of 12.5 years. In this heavily pretreated population, 90% of patients had at least 3 prior lines of biologic therapy, including non-TNF biologics in 39% of patients. Most patients (81%) were also taking conventional synthetic DMARDs at baseline, and were permitted to continue these agents as background therapy during the study. Patients were randomly assigned to sirukumab

50 mg every 4 weeks, sirukumab 100 mg every 2 weeks, or placebo every 2 weeks. Patients in the sirukumab 50 mg group also received a placebo injection every 2 weeks to maintain study-group blinding.

After 16 weeks, 24% of patients in the placebo group achieved the primary endpoint of ACR20 response. By comparison, 40% and 45% of patients in the sirukumab 50 mg and 100 mg groups, respectively, achieved ACR20 responses ($P<0.001$ for both). In the safety analysis at 52 weeks, the most common adverse events in the sirukumab groups were injection-site reactions in 8% and 16% of patients treated every 2 and every 4 weeks, respectively. Therefore, findings from the SIRROUND-T trial illustrate the role of novel IL-6 therapy in improving the signs and symptoms of RA, even in patients with active disease despite extensive exposure to prior biologic therapies.

Baricitinib

Of the 4 proteins in the JAK family (JAK1, JAK2, JAK3, and Tyk2), JAK1 and JAK3 are particularly active in mediating the inflammatory signals of RA.[17] Blocking other JAK proteins reduces inflammation, but also increases the risk of off-target side effects.[18] Tofacitinib, the first JAK inhibitor approved by the FDA for the treatment of RA, has broad activity against JAK1 and JAK3, and to a lesser extent, JAK2. Baricitinib is an investigational small molecule JAK inhibitor with potent JAK1/JAK2 activity, moderate activity against Tyk2, and negligible activity against JAK3.[19]

In April 2017, the FDA requested additional data on baricitinib to determine optimal dosing in patients with RA and to clarify safety concerns.[20] Baricitinib is currently approved in Europe for the treatment of RA in patients who are poor responders or intolerant to csDMARDs.[21]

Baricitinib After Biologic Therapy

The phase 3 RA-BEACON trial compared baricitinib and placebo in 527 patients with moderately to severely active RA who had an inadequate response or intolerance to prior biologic therapy.[22] At enrollment, patients had a history of treatment with 1 (42%), 2 (30%), or ≥3 (27%) biologic DMARDs. Approximately 38% of patients also had a history of treatment with 1 or more non-TNF biologic DMARDs (eg, abatacept, tocilizumab, rituximab, or anakinra). These heavily pretreated patients were randomly assigned to once-daily treatment with baricitinib 2 mg (n=174), baricitinib 4 mg (n=177), or placebo (n=176).

After 3 months, patients in the baricitinib arms were significantly more likely than those in the placebo group to achieve clinically meaningful responses. In the baricitinib 4-mg group, more than half of patients achieved an ACR20 response and had meaningful improvement in physical functioning. One-third of patients treated with baricitinib 4 mg reached the threshold for low RA disease activity, and 1 in 6 achieved clinical remission.

Baricitinib After MTX

The phase 3 RA-BEAM trial was a head-to-head comparison of baricitinib vs. adalimumab in 1,305 patients who were poor responders to MTX.[23] In addition to maintaining background MTX, patients were randomly assigned to baricitinib 4 mg once daily, adalimumab 40 mg every 2 weeks, or placebo. Baricitinib demonstrated superiority to adalimumab in terms of ACR20 response and DAS28-CRP, with differences between the study groups emerging as early as 12 weeks after treatment initiation. Among patients treated with baricitinib, 74% had ACR20 responses, 52% reached low clinical disease activity, and 35% achieved remission by week 24.[23]

Baricitinib As Early or Initial Therapy

Additional phase 3 trials support the role of baricitinib early in the RA treatment continuum. In the phase 3 RA-BUILD study, baricitinib improved the signs and symptoms of RA in patients who had an inadequate response to csDMARDs but had not yet initiated biologic DMARD therapy.[24] After 12 weeks, 62% of patients treated with baricitinib achieved an ACR20 response.[24] In another phase 3 trial of patients who were just starting treatment for RA, baricitinib monotherapy demonstrated superiority over MTX monotherapy.[25] After 24 weeks, 77% of patients treated with baricitinib monotherapy achieved an ACR20 response, compared with 62% of those treated with MTX monotherapy.[25]

Other Emerging Therapies

Several additional therapies are also under development for RA, including those targeting IL-6, JAK, and other key mediators of RA disease activity. Two investigational IL-6 inhibitors—**clazakizumab** and **olokizumab**—have shown promising activity in phase 2 studies of patients with RA who failed prior treatment with conventional or biologic DMARDs.[26,27]

Among the investigational JAK-targeted therapies, **filgotinib** is the first selective JAK1 inhibitor to be

studied in RA. In the recent phase 2 DARWIN 1 and DARWIN 2 trials, filgotinib showed activity against RA as a single agent and in combination with MTX.[28,29] **Upadacitinib** is another investigational, oral, selective JAK1 inhibitor. In the phase 2 BALANCE I and BALANCE II studies, upadacitinib was active in patients with RA who had an inadequate response to MTX or anti-TNF therapy.[30,31] Filgotinib and upadacitinib are now undergoing further evaluation in phase 3 studies. Additional upcoming JAK-targeted therapies include **peficitinib** (a JAK1/JAK3 inhibitor) and **decernotinib** (a JAK3 inhibitor).[32,33]

Agents targeting other key interleukins, including IL-17 (ixekizumab, secukinumab, brodalumab), are also in development for the treatment of RA.[34] A range of other promising treatment approaches are also under evaluation, including agents that target key signaling pathways (granulocyte macrophage-colony stimulating factor, Bruton's tyrosine kinase, and phosphoinositide-3-kinase pathways), neural stimulation, and dendritic cell-based therapeutics.

Biosimilars in RA

Biosimilars represent another opportunity to target key mediators of RA disease. The ACR defines biosimilars as biological products that are highly similar to an already approved agent, with no meaningful differences in efficacy, safety, or potency. As "follow-on biologics," biosimilars can be manufactured at a lower price than the reference biologics, potentially reducing RA treatment costs for patients and health systems.[35]

Four biosimilars are currently available in the United States for the treatment of RA and other rheumatic and autoimmune diseases (Table 5). In 2016, **infliximab-dyyb** (biosimilar to infliximab; formerly CT-P13) became the first biosimilar to be FDA-approved for the treatment of RA.[36] Later that year, the FDA also approved **etanercept-szzs** (biosimilar to etanercept) and **adalimumab-atto** (biosimilar to adalimumab).[37,38] In April 2017, **infliximab-abda** became the second FDA-approved infliximab biosimilar and the fourth biosimilar anti-TNF agent available for the treatment of RA.[39] In general, biosimilars tend to share the same indications and warnings as their reference biologics.[39-42]

Another biosimilar to adalimumab (BI 695501) is currently undergoing FDA review.[43] Several additional investigational biosimilars to anti-TNF and non-TNF biologics are also under development for the treatment of RA.

Switching to Biosimilars

One of the more controversial issues related to biosimilar use in rheumatology practices involves "non-medical" switching, or switching patients to a biosimilar product when they are responding well to their current biologic therapy.[44] Two major studies recently examined the safety and efficacy of non-medical biosimilar switching in patients with RA.[45,46]

Table 5

Biosimilars Currently Available for the Treatment of RA in the United States[39-42]

Biosimilar Product	Reference Product	Indications	Warnings	FDA Approval
Infliximab-dyyb	Infliximab	RA (in combination with MTX), AS, adult and pediatric Crohn's disease, plaque psoriasis, PsA, and UC	Serious infections, malignancy (lymphoma)	April 2016
Etanercept-szzs	Etanercept	RA (alone or in combination with MTX), AS, JIA, plaque psoriasis, and PsA	Serious infections, malignancy (lymphoma)	August 2016
Adalimumab-atto	Adalimumab	RA (alone or in combination with MTX), AS, adult Crohn's disease, JIA, plaque psoriasis, PsA, and UC	Serious infections, malignancy (lymphoma)	September 2016
Infliximab-abda	Infliximab	RA (in combination with MTX), AS, adult and pediatric Crohn's disease, plaque psoriasis, PsA, and US	Serious infections, malignancy (lymphoma)	April 2017

AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; MTX, methotrexate; PsA; psoriatic arthritis; UC, ulcerative colitis

DANBIO: A National Switch to Biosimilars

In 2015, the Danish health system implemented a nationwide switch from infliximab to an infliximab biosimilar as a cost-saving measure. A recent observational study from the DANBIO registry, which collects data on nearly all patients in Denmark who are being treated with biologic therapy, focused on the safety and efficacy of switching from reference to biosimilar products.[45] The DANBIO registry study included 802 patients either with RA, axial spondyloarthritis, or psoriatic arthritis who had been treated with infliximab for a median duration of 6.8 years before switching to CT-P13. The median follow-up after the switch was 413 days.

Patients showed no change in disease activity, as measured 3 months before and after the switch to CT-P13. Drug continuation rates after 1 year were slightly lower after the switch to the biosimilar (83.4%) compared with historic retention rates during treatment with infliximab (86.2%). After the switch, 132 patients (16.4%) discontinued treatment with CT-P13. Of these, approximately half stopped therapy due to lack of efficacy, and 28% stopped due to adverse events. Patients who had been treated with infliximab for more than 5 years were less likely than those with a shorter treatment history to discontinue CT-P13. No new safety signals were detected for CT-P13. Overall, the DANBIO observational data show that switching from infliximab to an infliximab biosimilar does not adversely affect disease activity in inflammatory arthritis, including RA.[45]

NOR-SWITCH: Randomized Trial of Biosimilar Switching

The NOR-SWITCH trial was the first prospective, randomized, double-blind trial designed to evaluate the safety and efficacy of switching patients who are stable on biologic therapy to a biosimilar.[46] The trial recruited 482 patients from 40 infusion centers in Norway. At the time of enrollment, all patients had been stable for at least 6 months on treatment with infliximab for Crohn's disease, ulcerative colitis, spondyloarthritis, RA, psoriasis, or psoriatic arthritis. Patients were randomly assigned to continue infliximab or switch to an infliximab biosimilar (CT-P13; infliximab-dyyb), with no change in their dosing regimen.

The primary endpoint was disease worsening after 52 weeks, as assessed by multiple standard disease activity measures for each diagnosis. Among patients with RA, the severity of RA disease activity was measured using the DAS28 score, the Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and ACR/EULAR remission criteria.

After 52 weeks, all safety and efficacy outcomes were similar between patients who continued treatment with infliximab and those who switched to an infliximab biosimilar (Table 6). The safety and efficacy outcomes were consistent across all 6 diagnoses, including the subgroup of patients with RA. These findings suggest that patients can be switched from reference infliximab to biosimilar infliximab without compromising treatment efficacy or safety.

Outcomes at 52 Weeks	Patients Continued on Infliximab (n=241)	Patients Switched to Infliximab Biosimilar (n=241)
Efficacy endpoints		
Worsening disease	26%	30%
Clinical remission	61%	61%
Safety endpoints		
Any adverse events	70%	68%
Serious adverse events	10%	9%
Adverse events leading to treatment discontinuation	4%	3%

Table 6
NOR-SWITCH: Safety and Efficacy of Continuing Infliximab or Switching to an Infliximab Biosimilar[46]

ACR Position on Biosimilars

The ACR has been a vocal advocate of regulations that ensure the safe and effective use of biosimilars. In 2016, the ACR published a position statement outlining several precautions on biosimilar use in patients with RA and other rheumatic diseases, including the following:[35]

- Patients who are stable on biologic therapy should not be switched automatically to a biosimilar agent as a cost-saving measure (ie, non-medical switching) 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 (ie, not pooled with other biosimilars) to ensure that unique safety risks are identified

As real-world experience with biosimilars grows, the FDA is refining its standards for biosimilar approval and product labeling. In 2017, the FDA issued draft guidelines that would establish rigorous clinical testing before biosimilars can be considered "interchangeable" with the reference product. Under the new criteria, clinical trials would have to include 2-way switching between products—from the originator to the biosimilar and back again—to establish interchangeability.[47] In response, the ACR issued a statement endorsing the FDA draft guidance on biosimilar interchangeability.[48] The ACR noted that the 2-way product switching reflects real-world rheumatology practice, where patients often move across health plans, payers, and formularies during treatment.[48]

Summary

The outlook for patients with RA has improved dramatically in recent years thanks primarily to the introductory of biologics and small molecule therapies. Yet as more and more treatment options with diverse mechanisms of action are introduced for patients with RA, decisions about the right and wrong choices are becoming increasingly difficult. Nevertheless, goals should always focus on controlling and hopefully reversing the progression of disease and limiting the impact of medication-related side effects.

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THE SHINGLES VACCINE:

You Don't Know What You Don't Know

by Elizabeth Kirchner, CNP, RN-BC

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So this is new and fancy. Just when I thought I had the whole "shingles vaccine thing" covered, along come the JAK inhibitors to throw a monkey wrench into the whole shebang.

Let's start with what I thought I knew: Shingles are bad, patients with autoimmune inflammatory diseases are at higher risk for shingles, there's a vaccine available (Zostavax®), and the timing of the vaccine can get tricky in patients being treated with high-dose prednisone and/or biologics because, you know, it's a live vaccine. Grossly oversimplified, sure, but that's the crux of the matter.

Then tofacitinib came along and made my brain hurt.

Tofacitinib is a JAK inhibitor approved for use in patients with moderate-to-severe rheumatoid arthritis (RA) who have an inadequate response or intolerance to methotrexate.[1] The one glaring safety signal that came out of the tofacitinib clinical trials and subsequent real-world studies involved shingles. A study by Dr. Jeff Curtis and colleagues found that the risk of shingles in patients on tofacitinib is approximately double compared to the rates seen in patients on biologics.[2] The same seems to be true for baricitinib, another JAK inhibitor that is not yet approved in the United States.[3]

So then what's the logical next step for providers when we find out that a medication puts patients at higher risk for shingles? More vaccine please.

But wait! Safety first! Remember, we are super-duper careful about giving the shingles vaccine to patients on biologics.

But wait! Are the JAK inhibitors biologics? No, they are not. They are "targeted synthetic disease modifying antirheumatic drugs," aka tsDMARDs (thank you ever so much, that's just what I needed—another acronym to remember). So we should theoretically be able to give patients on JAK inhibitors the shingles vaccine, right?

But wait! Dr. Kevin Winthrop at Oregon Health & Sciences University says it's not that easy. Dr. Winthrop is über smart—he gets studies conceived, approved, enrolled,

completed, and published while I'm still rolling out of bed and lamenting the fact that I'm not allowed to wear my pajamas to work.

In 2015, Dr. Winthrop presented a late-breaking abstract at the annual American College of Rheumatology meeting entitled "Assessment of immunogenicity of live zoster vaccination (Zostavax®) in rheumatoid arthritis patients on background methotrexate before and after initiating tofacitinib or placebo" (apparently, being ūber smart doesn't always equate to an ability to write a catchy abstract title).[4]

The major point of the study was to show that patients given the live zoster vaccine and then started on tofacitinib were able to mount an adequate immune response (i.e., the vaccine "took"). But what Dr. Winthrop and his co-authors also found was that one patient developed disseminated shingles from the vaccine. When they went back and looked, they realized that that particular patient did not have varicella antibodies before being vaccinated.

Let that sink in a moment. Perhaps reread those sentences again. Don't worry, it took me a while to get it, too.

What the study findings mean from a clinical perspective—and this is giving me palpitations as I write it because the LAST thing a Vaccine Queen like me wants to do is complicate the vaccination process—is that we should probably check varicella zoster virus immunoglobulin G levels (VZV IgG) on all of our patients before they start a JAK inhibitor. If they don't have evidence of previous infection, they need VARICELLA vaccination, not ZOSTER vaccination.

The live zoster vaccine is 14x stronger than the varicella vaccine,[5] which is why, in an immunocompromised person, the zoster vaccine can cause disseminated illness. Like the zoster vaccine, the varicella vaccine is live, so the same precautions apply. Unlike the zoster vaccine, the varicella vaccine requires two doses, given at least 28 days apart.

I suspect a good many of you are now thinking to yourself, "Holy Moly! What are we going to do about our patients born after 1980 who should therefore have received the varicella vaccine series, but VZV IgG won't show up because the commercially-available tests don't pick up IgG from vaccine, only from actual chicken pox disease?"

Right? Am I right? ***Amiright?*** Of course I am. You're smart, almost as smart as Dr. Kevin Winthrop.

Bad news: I don't really have an answer for you here. This would be an excellent time to consult with your good friends over in Infectious Disease.

Good news: This whole headache will theoretically go away once the new subunit shingles vaccine is approved (which will hopefully happen later this year or maybe in 2018). It's not live, so we won't have to perform all these mental acrobatics just to protect our patients. Stay tuned for more on that, because when that vaccine comes out, I can assure you that I will be waiting with baited breath for Dr. Kevin Winthrop to tell us all about it!

(With apologies to Dr. Kevin Winthrop, who really doesn't deserve this kind of abuse.)

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My Initial Experience with Biosimilars

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Jacqueline Fritz, RN, MSN, CNS, RN-BC, is Owner and Coordinator of Education at the Medical Advancement Center in Cypress, CA. Her primary responsibility is working as an advanced practice nurse for a large rheumatology practice where she is involved in patient visits, research programs, and infusion center coordination. In addition, she enjoys speaking, teaching, and learning about immunology.

Not long after the U.S. Food and Drug Administration approved its first biosimilar agent for use in patients with rheumatoid arthritis (RA), our office undertook its initial journey to become better educated about what this meant for ourselves and our patients.

We started with infliximab-dyyb (Inflectra), a biosimilar to infliximab (Remicade), as that was the first biosimilar available in California.[1] Our first step was to review the product insert. What are the differences between the biosimilar and the reference product? What do our patients need to be made aware of?

The FDA defines a biosimilar as follows:

> *"A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an already-approved biological product, known as a reference product. The biosimilar also must show it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products."*[1]

As our team started doing its research, our first concern involved patient safety. What constitutes a "minor difference"? In the case of Inflectra, the difference is in the fragment crystallizable (FC) region of the antibody, which is why it is not considered to be bioidentical to Remicade. According to a report from the European Medicines Agency, there is a "small difference in the amount of affucosylated infliximab, which translates to lower binding affinity towards the FC receptors."[2] Remember that communication to the immune system is mediated through the Y portion of the antibody. The top portion of the Y (the antigen-binding site) serves as "the lock" that traps the harmful antibody while the bottom portion communicates the message to the B and T cells for further immune mediation.

While Inflectra is approved as a biosimilar to Remicade, it is not an interchangeable product as defined by the FDA. An interchangeable biological product, in addition to meeting the standard for biosimilarity, is expected to produce the same clinical result as the reference product in any given patient.[1] This is an important distinction, and one that has been emphasized by patient advocacy groups such as the Patients for Biological Safety & Access, which says on its website that "the choice of products should not be determined by pharmacist, regulator, or insurer, but by the prescriber in consultation with their patient."[3]

Inflectra first became available in our practice this spring. Its wholesale acquisition cost is approximately 15% less than Remicade. So if you do the math (understanding that each pharmacy has a different actual sale price), this is what the cost savings might look like: Remicade is approximately $1,113 per 100 mg vial and Inflectra $946 per 100 mg vial. That is a savings of $167 per vial, which can be pretty significant over the course of a patient's full year of therapy.[4]

In June 2013, the European Medicines Agency published a 105-page Assessment Report on Inflectra that thoroughly reviewed the clinical trials and studies completed before Inflectra was approved by the FDA. While there was a numerically higher number of serious infections, including active tuberculosis, in the patients treated with Inflectra compared to Remicade, the report authors concluded that "the observed difference was most likely a chance finding" due to the low numbers of patients with serious infections. There were no new safety signals that were identified.[2]

When we were initially compelled to use Inflectra earlier this year, we proceeded with caution. One of our initial experiences was with JT, an RA patient who had done

well with 5 previous Remicade treatments. She had no previous tolerance issues and demonstrated notable improvements in swollen and tender joints, as well as Health Assessment Questionnaire scores, with Remicade. When the switch was made to Inflectra, we had JT come in during her usual appointment slot. She was given 3 mg/kg of Inflectra at her first infusion.

About 20 minutes into the infusion, JT developed chest pain, shortness of breath, and erythema, which is not uncommon in patients receiving an initial infusion of a new biologic. We stopped the infusion, immediately began a normal saline flush, and pushed an additional 25 mg of diphenhydramine. JT's reaction abated to a degree with these interventions, but she still reported some chest tightness. We gave her an additional 6 mg of intravenous dexamethasone, which mitigated her symptoms, but JT refused to have us restart the infusion.

So now we were faced with a dilemma. JT had been stable and was doing well on Remicade. Is she now considered a TNF non-responder after her reaction to Inflectra? Should we (and could we) go back to Remicade? Typically, if a patient develops antibodies to Remicade, we try another TNF inhibitor, but would JT's failure on Inflectra mean that she had failed two TNF inhibitors and would benefit more from a biologic with a different mechanism of action?

For safety reasons, we decided to transition JT to a non-TNF biologic—abatacept. Early results are mixed—her tender and swollen joint counts have increased, but she has not any tolerance issues.

Since our experience with JT, we have changed our protocol for infusion of Inflectra. Patients now receive pre-infusion hydration, dexathamethsone 6 mg IV (unless they are diabetic), and diphenhydramine 50 mg. We have also lengthened the infusion time from 2 to 3 hours. There have been no further serious adverse events (SAEs) since JT.

It is important to note that, after our report of JT's SAE to the Inflectra manufacturer, I received a phone call and met with a representative to complete a full report within 24 hours. There have been two follow-up calls to check on JT's condition. Clearly, this is not something being taken lightly, which is comforting.

Our office is admittedly a bit perplexed by the changes being forced upon us in regard to biosimilars. For some patients currently taking Remicade, we have written "Please use brand name" or "Dispense as written" on the prescription, but it seems to make little difference at the pharmacy.

If you haven't yet had to navigate patients onto biosimilars, I am confident that you soon will. Our office is currently involved in phase III clinical trials for 7 different biosimilars, and none of our patients in the trials have suffered an SAE. Nonetheless, we remain on high alert, knowing that severe reactions, including anaphylaxis, can occur in patients receiving any infusible biologic or biosimilar.

Undoubtedly, biologics are both life-altering and expensive. Making any sort of change in a patient who is doing well on any therapy is nerve wracking, and perhaps with time, we'll learn that the switch from a biologic reference product to a biosimilar will be "no big deal." For now, I will remain hopeful yet vigilant, doing what I believe is best for my patients and helping them navigate through the many hurdles put in front of them by their disease as they seek to return to work, regain their self-esteem, and recapture their quality of life.

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Managing Our Colorful Array of Patients

by Iris Zink, MSN, NP, RN-BC

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Sometimes as rheumatology nurses, we walk into a room and our heart sinks as we're faced with a patient who we know is going to challenge every nursing skill that we possess.

Other times, we brighten up as we see a patient who is like an old friend and has become an extension of our own family.

Then there are those patients who can set us back an hour by bringing in scores of articles and information to review together, whether it be wisdom from Dr. Oz or Dr. Google.

Wouldn't it be great to know exactly what we are walking into when we open the door to every one of our patients? What if we gave every patient a 5-minute personality test that told us the best way to approach them and care for their needs? If we knew in advance what a patient desired, perhaps we could better meet those needs and make more efficient use of our time.

These tools certainly exist. One of my favorites is the Competing Values Framework that was developed at the University of Michigan's Ross School of Business to help build work teams (Figure 1). This model identifies four personality types that are linked to specific colors.[1] While not everyone fits into one clear personality type, many of us have dominant traits that can be grouped into specific quadrants.

Yellow people are social and community focused. They crave collaboration, social support, and a feeling of belonging. In our offices, yellow patients tend to be very social and chatty. These are the patients who might be best suited to be prescribed the same medication regimen as a friend or family member, or to meet other patients who are taking their same medication so that they can talk to them about how the drug made them feel. Yellow patients crave support and like to have someone that they can call and ask questions of. You might get a clue that your patient is yellow when you hear their life story and how their disease is impacting their social and family life.

Blue people are very bottom-line. They want results, and they want them fast. The blue patient will ask your opinion about the treatment being recommended for them, and they will likely expect it to work quickly so that they can get back to their usual daily regimen. They may want you to employ a quantitative measurement tool to concretely prove or disprove that their regimen is working. For blue patients, it's our job to provide them with realistic timeframes of expected improvement from a specific treatment regimen. Blue patients can be difficult to deal with at times if they believe that things are not being done properly or fast enough.

Red people are the managers of the world. They are all about the process and gathering data to support the process. These are the patients who bring in folders of data and articles to review. Red patients need to discuss the importance of Treat to Target goals and be reassured that treatment will be adjusted or changed every 12 weeks (or less) if they have not met the goal of either remission or low disease activity.[2] Red patients like structure and punctuality (don't keep them in the waiting room too long!) and appreciate being provided with relevant resources to advance their knowledge base. They are the patients who will call the office in advance of their appointment to see if there are labs, tests, or forms they can fill out to ensure a more efficient visit.

Green people are our "idea" patients. They are the ones most likely to experiment with alternative treatments or have creative ideas about managing their RA. They like to be the first to get the newest and greatest gadget or technology. The green patient is willing to take risks on treatment regimens that perhaps don't have a significant evidence base behind them to feel better fast. Green patients rapidly embrace change and adjustments to therapy, but they still need understanding and compassion when discussing how their disease impacts their lives.

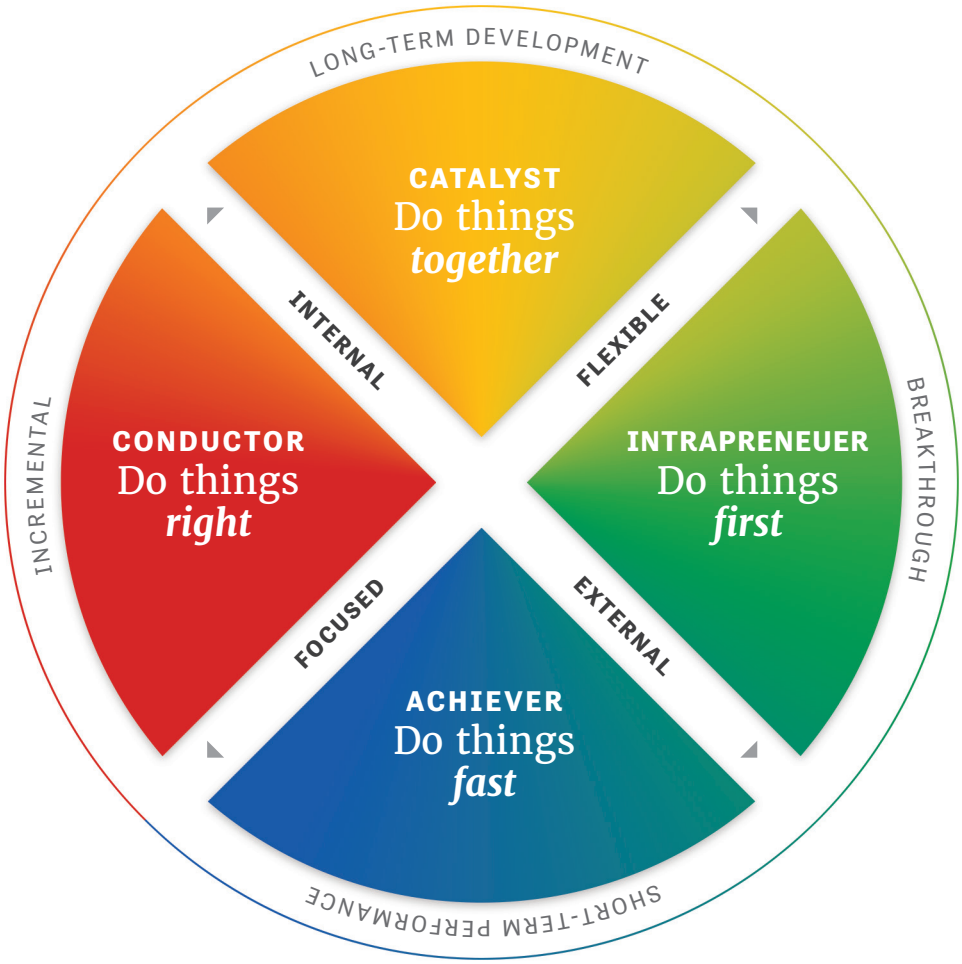

Table 1
Competing Values Framework

YELLOW PATIENTS need social time and want you to listen to their personal story

RED PATIENTS need to understand things and require intellectual explanations of disease state and process

BLUE PATIENTS are bottom line and want to know how fast they will get better

GREEN PATIENTS want to know what is new and in the near-term pipeline, and they may challenge you to find creative solutions to treat their RA.

Personally, I am mostly yellow and blue. I love the social connection I have with my patients and their families (that's the yellow), but I am also deadline-oriented when I have a new idea or something needs to be done (that's the blue).

As you are reading this, I'll bet you are categorizing some of your more challenging patients and perhaps gaining a greater understanding of how and why they are the way they are. That's what I did with one of my most challenging patients, DQ, who first came to me 3 years ago with joint pain. We quickly diagnosed him with RA.

DQ is both very red and very blue. He is bottom line and wants to get better fast, but he also wants to understand the process, the disease, and the outcomes to expect. At every visit, DQ seemed to take endless amounts of time talking through every aspect of his disease with me, what the long-term implications were, and what each step of treatment would include. He wanted to know about the mechanism of action of every medication as well as all of the potential side effects and ways in which his progress would be measured. Because his personal needs often swallowed up a lot of appointment time that I could not always afford, I enrolled DQ into a manufacturer's nurse program. DQ's assigned nurse was able to spend the needed time on the phone with him explaining how his drug regimen worked, the potential risks and benefits, and expected outcomes.

Of course, each patient is an individual, and some may straddle multiple colors/quadrants, but being proactive in thinking about what to expect before you open the exam room door may help maximize the quality of your time with each patient.

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Giving Parents Time to Think

by Cathy Patty-Resk, MSN, RN, CPNP-PC

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As a pediatric rheumatology nurse, my visits typically involve more than just the patient. Including mom and/or dad in the discussion often requires a variety of communication and negotiation tools as we try to do what is best for our patient while making sure that all parties buy into important decisions.

One of our more interesting recent cases involved TP, a 10-year-old male who initially was referred to our office complaining that his right shoulder hurt. He thought it was possibly as a result of "throwing around a football too much with my dad."

TP had a recent episode of left hip pain and a slight fever 3 months before we first saw him, during which time he claimed he "couldn't walk." At that time, he was seen in a local hospital Emergency Department (ED), where he was diagnosed with toxic synovitis based on labs and X-rays. He was treated with an IV dose of an anti-inflammatory and instructed to take ibuprofen as needed. According to TP's parents, this episode was preceded about a week before with a viral illness accompanied by diarrhea.

After his ED visit, TP's hip pain improved within a few days and his fever subsided. A week later, however, he complained of intermittent left wrist pain, although that lasted only a day or two before resolving.

TP's only other notable history was an episode of left ankle pain with swelling and warmth during the fall soccer season, which his parents attributed to a possible on-field injury.

Our initial evaluation revealed tenderness at the right bicep tendon insertion site, but no tenderness or warmth in any joints. TP had full range of motion, and X-rays of his right shoulder did not indicate a fracture or any other abnormalities. Results of a basic laboratory panel, including acute phase reactants, were unremarkable.

Finding nothing of significance in our workup, we suggested that TP continue with the ibuprofen as needed and follow up with an orthopedic surgeon if his shoulder pain did not improve within a week.

Three months later, TP was back in our office for further evaluation after conservative treatment suggested by the orthopedic surgeon failed to resolve his shoulder pain. At this visit, TP also complained of intermittent wrist pain and demonstrated decreased range of motion with irritability on rotation. We performed an MRI, which showed fluid distention of the biceps tendon sheath, large glenohumeral joint effusion, and extensive synovitis. More targeted lab testing showed highly elevated rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), and C-reactive protein levels.

Based on these results, we diagnosed TP with rheumatoid factor-positive, CCP-positive polyarticular juvenile idiopathic arthritis (JIA), also known as JRA.

Rheumatoid factor-positive polyarthritis is classified as a JIA, representing the pediatric version of rheumatoid polyarthritis. It has an estimated prevalence of between 1-30 per 300,000 children. Approximately 70% of cases of rheumatoid factor-positive polyarthritis occur in females, with typical onset between ages 10 and 12. It is generally a bilateral and symmetrical joint disease, with a distal prominence involving the joints of the hands (wrists and fingers) and the feet (ankles and metatarsophalangeal joints).[1] It is the most aggressive type of arthritis in children and carries the highest risk of joint damage.

"...parents often need a little more time to work through some of their own feelings before helping their child cope with their diagnosis. A parent who is not able to cope well with the diagnosis will often see some of their anxiety transfer to their child."

After making our diagnosis, we began treatment of TP with a combination of naproxen 10 mg/kg BID, sulfasalazine 500 mg PO BID, and prednisone 5 mg PO daily. We also referred TP to an ophthalmologist for evaluation of possible uveitis, which was negative.

Six weeks later, seeing no improvement, we introduced weekly methotrexate (MTX) 25 mg SC and increased the prednisone to 7.5 mg PO daily. This too was ineffective and we suggested the introduction of etanercept. TP's parents were initially hesitant about escalating to use of a biologic therapy, so we sat down as a group to go over the pros and cons of our suggestion.

When evaluating and treating any patient with JIA, it is important to recognize that children do not always present with abrupt onset of RA, as is often the case in adults. Making the proper diagnosis can often take a series of visits due to possible viruses, sports injuries, and lack of clear physical findings. Once a diagnosis is made, however, the approach to treating JRA is similar to adults – intervening quickly and aggressively to give the patient the best chance of achieving a rapid remission and preserving joint function.

Certainly, there is added complexity when dealing with parents of pediatric patients, especially when more unfamiliar medications such as biologics are being suggested. As when dealing with any chronic condition, parents often need a little more time to work through some of their own feelings before helping their child cope with their diagnosis. A parent who is not able to cope well with the diagnosis will often see some of their anxiety transfer to their child, possibly resulting in acting out toward medication and blood draws, nonadherence to medication plans, and poorer overall outcomes.

In TP's case, we could sense the apprehension and fear of his parents when we suggested the addition of etanercept to his regimen and agreed to give them time to think about our suggestion while seeing if a longer trial of MTX would be effective. This is often when parents will ask, "If this was your child, what would you do?" Parents are looking for validation and approval for the tough decision to start a treatment that can lead to serious health sequelae.

Use of a biologic therapy in a pediatric patient is not a decision that should be taken lightly due to safety risks and the support that is often needed from parents to help the child cope with their treatment. Eventually, TP's parents acquiesced to the use of etanercept due to their son's rapidly worsening pain. We will know in a few weeks whether it is effective in reducing TP's symptoms and allow us to discontinue his steroid.

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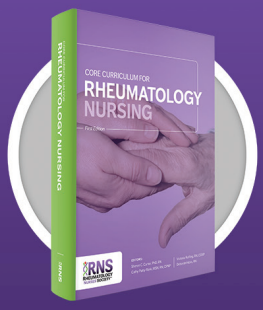

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