RHEUMATOLOGY NURSE
PRACTICE
Accredited education for registered nurses and advanced practice providers

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ISSUE 3 / VOLUME 4

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DROP THE ANCHOR?

DMARD Monotherapy for the Treatment of RA

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ACTIVITY DESCRIPTION

In this issue of *Rheumatology Nurse Practice*, we will explore the current body of evidence addressing the use of DMARD monotherapy, specifically biologic and targeted synthetic small molecule therapies, in patients with RA. What do the guidelines say about when to prescribe biologics or small molecules, and is monotherapy with these medications ever recommended? What do real-world practice patterns reflect? What does the data say about the efficacy and safety of biologics and small molecules, both as monotherapy and in combination with conventional DMARDs? Lastly, what are the current approaches to tapering regimens in patients who have achieved clinical remission?

LEARNING OBJECTIVES

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

- Identify situations when biologic and small molecule monotherapy might be appropriate in patients with RA
- List at least three reasons why patients with RA may discontinue use of methotrexate
- Discuss efficacy and safety data from clinical trials looking at the use of specific biologics and small molecules as monotherapy in patients with RA
- Review the role of methotrexate in the prevention of antidrug antibodies and as a preventative measure for cardiovascular disease

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This newsletter was reviewed by **Tiffany Clark, CNP**. Ms. Clark has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

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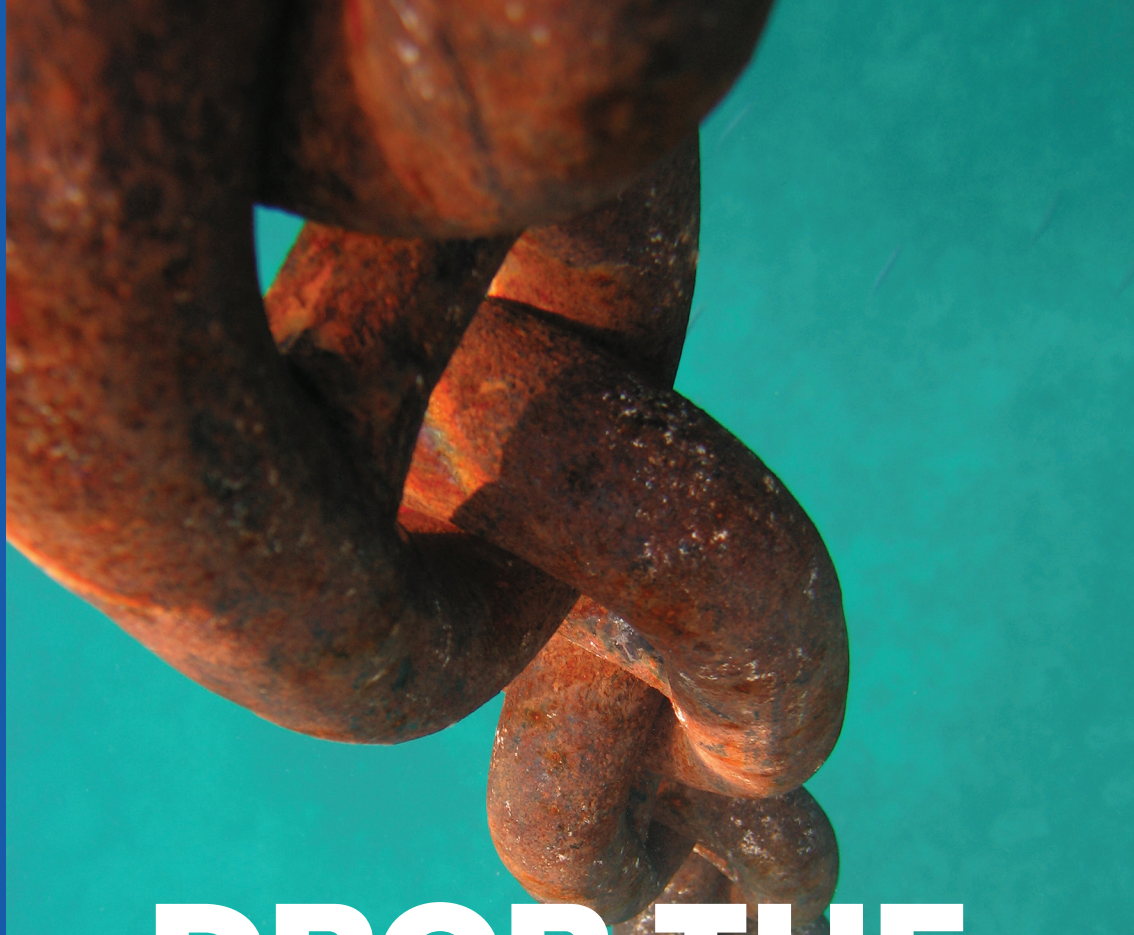


DROP THE ANCHOR?

DMARD Monotherapy for the Treatment of RA

For years, conventional synthetic disease-modifying antirheumatic drugs (DMARDs) have formed the backbone of treatment for patients with rheumatoid arthritis (RA). While several different DMARDs may be used—including sulfasalazine, leflunomide, and hydroxychloroquine—methotrexate (MTX) is the most commonly prescribed "anchor" drug.[1] Across practice guidelines, MTX monotherapy is typically recommended as the initial treatment of choice in DMARD-naïve patients with RA, assuming the absence of contraindications to its use.[2,3] This recommendation is based upon a wide body of literature supporting MTX as an effective, well-tolerated, and low-cost treatment option.[1]

Drug Names Included Within This Issue

GENERIC	BRAND
Leflunomide	Arava
Hydroxychloroquine	Plaquenil
Sulfasalazine	Azulfidine
Tofacitinib	Xeljanz
Baricitinib	Olumiant
Tocilizumab	Actemra
Adalimumab	Humira
Infliximab	Remicade
Etanercept	Enbrel
Golimumab	Simponi
Abatacept	Orencia
Anakinra	Kineret
Rituximab	Rituxan

However, for a substantial number of patients, MTX monotherapy is not the optimal initial treatment approach for a variety of reasons, such as aggressive disease and family planning. For these patients, optimal initial treatment choices may include using MTX in combination with other agents as well as prescribing monotherapy with different medications.[2] Over the last two decades, a number of new options, including injectable biologics, oral synthetic small molecules, and biosimilars, have become available to help clinicians and patients with RA attain clinical treatment goals, provide relief, and improve quality of life.[3] In the United States, a number of these medications have been approved for use as both monotherapy and in combination with conventional DMARDs (Table 1).

A Look at Treatment Guidelines

The 2015 American College of Rheumatology (ACR) guideline for the treatment of RA provides treatment recommendations as well as separate algorithms geared to patients with early (<6 months) and established (≥6 months) disease.[2] In 2017, the European League Against Rheumatism (EULAR) released its updated recommendations for the management of RA with synthetic DMARDs and biologics. In contrast to the ACR guidelines' use of disease duration to stratify treatment pathways, the EULAR guidelines use the presence or absence of unfavorable prognostic factors.[3]

While there are some differences between the two, both guidelines are built around the guiding principles of achieving early disease control, utilizing a treat-to-target (T2T) approach, providing individualized care, and promoting shared decision-making. Each guideline provides treatment recommendations for when to introduce or switch to a new class of medication. Of course, it is important to note that these guidelines only provide recommendations and that the optimal treatment for an individual patient may differ from the option listed in the treatment algorithms.

Initial Therapy

Both the ACR and EULAR guidelines recommend DMARD monotherapy ± short-term, low-dose glucocorticoids (GCs) as the preferred initial therapy for most DMARD-naïve patients with RA. In the event MTX is contraindicated (or early intolerance is apparent), other DMARDs (eg, sulfasalazine, leflunomide, and hydroxychloroquine) may be used. Based upon the T2T approach, therapy should be adjusted until the goal of clinical remission or low disease activity is reached. In the event that disease activity remains moderate or high despite optimized DMARD monotherapy (with or without GCs) or if patients develop side effects, intolerance, or adherence issues to MTX, additional treatment options should be considered.[2,3]

Subsequent Therapy

It is at this point that biologics and small molecules typically enter the picture. Treatment guidelines provide a variety of additional options and pathways, giving providers and patients the flexibility to individualize and optimize their care.

According to the ACR guidelines, recommended treatment options for patients with early RA who have moderate or high disease activity despite DMARD monotherapy (with or without GCs) expand to include the following:

- Combination conventional DMARDs
- Tumor necrosis factor (TNF) inhibitor ± MTX
- Non-TNF biologic (ie, rituximab, abatacept, sariliumab, tocilizumab, anakinra) ± MTX

For patients with established disease, tofacitinib ± MTX is a treatment option in addition to the above choices. Short-term, low-dose GCs may also be added to any treatment regimen.[2]

In contrast, EULAR treatment recommendations for patients who do not achieve improvement or experience side effects with initial DMARD monotherapy are stratified by the presence or absence of unfavorable

Table 1 *Biologic and Small Molecule Therapies Approved for Use in the Treatment of RA in the United States*[56-66]

Biologic DMARDs and biosimilars		
Medication	**Class**	**Use**
Adalimumab (Humira)	TNFi	Monotherapy or in combination with methotrexate or other non-biologic DMARDs
Adalimumab-atto* (Amjevita)		
Adalimumab-adbm* (Cyltezo)		
Certolizumab pegol (Cimzia)	TNFi	Monotherapy or in combination with methotrexate or other non-biologic DMARDs
Etanercept (Enbrel)	TNFi	Monotherapy or in combination with methotrexate
Etanercept-szzs* (Erizi)		
Golimumab (Simponi)	TNFi	In combination with methotrexate
Infliximab (Remicade)	TNFi	In combination with methotrexate
Infliximab-dyyb* (Inflectra)		
Infliximab-abda* (Renflexis)		
Sarilumab (Kevzara)	IL-6 receptor inhibitor mAb	Monotherapy or in combination with methotrexate or other non-biologic DMARDs
Tocilizumab (Actemra)	IL-6 receptor inhibitor mAb	Monotherapy or in combination with methotrexate or other non-biologic DMARDs
Anakinra (Kineret)	IL-1 receptor inhibitor mAb	Monotherapy or in combination with DMARDs other than TNF blocking agents
Abatacept (Orencia)	Co-stimulation inhibitor (T cell inhib)	Monotherapy or in combination with DMARDs other than TNF blocking agents
Rituximab (Rituxan)	Anti-B-cell agent	In combination with methotrexate
Small molecule DMARD		
Tofacitinib (Xeljanz)	JAK inhibitor	Monotherapy or in combination with methotrexate or other non-biologic DMARDs
Baricitinib	JAK inhibitor	Monotherapy or in combination with methotrexate or other non-biologic DMARDs

DMARD = disease-modifying antirheumatic drug; JAK inhibitor = Janus kinase inhibitor; mAb = monoclonal antibody; MTX = methotrexate; TNFi = tumor necrosis factor inhibitor

prognostic factors such as moderate to high disease activity following DMARD therapy, high swollen joint counts, and/or high levels of acute phase reactants. For those patients without unfavorable prognostic factors, treatment includes switching to or adding another conventional DMARD, preferably with the addition of short-term GCs. For patients with unfavorable prognostic factors, EULAR guidelines recommend combination therapy by adding a biologic or Janus kinase (JAK) inhibitor such as tofacitinib or baricitinib (approved in Europe for several years but only recently approved in the United States) to the existing DMARD.[3]

When selecting a biologic or small molecule, consideration should be given to factors such as cost, comorbidities, contraindications, side effect profile, and burden of taking the medication.[2,4] Neither ACR nor EULAR guidelines provide recommendations for individual medications within a medication class, and both indicate that all biologics may be used without hierarchal positioning.

Due to the availability of long-term registry data, biologics are given slight preference over JAK inhibitors.[2,3] Biosimilars, if available, may be used as a substitution for originator biologics.[3]

Depending on treatment response, further treatment options include optimizing the dose of a biologic, cycling to another medication with the same mechanism of action (MOA), or switching to a medication with a different MOA.[2-5]

Is Initial Biologic or Small Molecule Monotherapy Ever Appropriate?

At this time, neither guideline recommends biologic monotherapy as first-line therapy over DMARD monotherapy.[2,3] While some studies have shown that early biologic monotherapy is superior to MTX monotherapy, none of these studies used GCs in combination with MTX. Furthermore, other studies comparing a biologic + MTX against MTX + GCs have not demonstrated a clear clinical or structural advantage of early biologics in the frontline setting. Thus, there is a lack of compelling evidence for this strategy compared with MTX + GC as first-line therapy.

In terms of treatment approaches after initial DMARD failure, the ACR guidelines provide flexibility for biologics (TNFi, non-TNF biologics) and tofacitinib to be used with or without MTX; however, they do note the superior efficacy of combination therapy.[2] In comparison, the EULAR guidelines recommend that biologics and JAK inhibitors be used in conjunction with a conventional DMARD. These recommendations reflect data showing that most biologics and small molecules combined with MTX demonstrate superior efficacy compared with respective monotherapy.[2,3]

In the event combination therapy with a conventional DMARD is not an option, the EULAR guidelines suggest monotherapy with either an interleukin (IL)-6 pathway inhibitor such as tocilizumab or tofacitinib.[3] This is based upon data indicating tocilizumab and tofacitinib monotherapy exhibit somewhat better efficacy compared with MTX monotherapy. Monotherapy with other biologics, meanwhile, has not been found to be clinically superior to MTX monotherapy.[3,6]

Real-World Use of Biologic and Small Molecule Monotherapy

While expert guidelines generally don't recommend biologic monotherapy for patients with RA, studies suggest that monotherapy regimens are popular in real-life clinical practice.[7-9] Data derived from 2 analyses of Medicare plans in the early biologic era (1999-2005 and 2006-2009) indicate that more than 25% of patients with RA have a biologic incorporated into their treatment plan; of those, nearly one-third who initiated or switched to a biologic received it as monotherapy. Consistent with guideline

Figure 1 RNS Survey Cohort Data

In 2017, participants in a dedicated RNS survey cohort were asked the following: "In your clinical practice, please rank the most common next step for a patient with RA who fails to respond to MTX monotherapy." Nearly 50% of respondents (26/57) indicated that their practice would most commonly add a biologic or small molecule to MTX therapy. Approximately an equal amount said their practice would most commonly add a conventional DMARD to MTX. The least common second-line option was switching to biologic or small molecule monotherapy.

In your clinical practice, please rank the most common next step for a patient with RA who fails to respond to methotrexate monotherapy (1=most common step, 2=next most common step, and so on)?

	1	2	3	4	Average Score
Add a conventional DMARD such as sulfasalazine or leflunomide to methotrexate	27	16	7	7	1.86
Switch to a conventional DMARD such as sulfasalazine or leflunomide (discontinuing methotrexate)	3	12	20	22	3.02
Add a biologic DMARD or small molecule biologic to methotrexate	26	17	13	1	1.78
Switch to a biologic or small molecule monotherapy (discontinuing methotrexate)	1	12	17	27	3.17

recommendations, the vast majority of these patients (>85%) had been treated with a conventional DMARD prior to receipt of their first biologic, usually MTX.[8,9]

Similar results were reported in a more recent analysis of patient data in the CORRONA registry. Between 2001 and 2012, amongst biologic-naïve patients with RA who initiated therapy with a biologic agent, 19.1% initiated the biologic (most commonly an anti-TNF) as monotherapy. The vast majority (95%) of patients had received treatment with a conventional DMARD, most commonly MTX, prior to biologic initiation. The most common reasons for discontinuing any prior DMARD and initiating biologic monotherapy were unacceptable toxicity, lack of efficacy, and physician preference.[7]

Pathways to Monotherapy with Biologics and Small Molecules

Patients taking biologics and small molecules as monotherapy may arrive to that point via several different pathways. Some patients never initiate MTX monotherapy (or another conventional DMARD), while others discontinue MTX monotherapy for a number of reasons.

Examples of patients who typically never initiate treatment with MTX include those with a contraindication to MTX such as pregnant or breastfeeding women; alcohol users or patients with liver disease; pre-existing blood dyscrasias; known hypersensitivity; lung disease; chronic/acute infection; significantly impaired hepatic and/or renal function; and/or other comorbidities. MTX is also subject to a number of drug-drug interactions; consequently, caution is warranted with its use in elderly patients due to the renal excretion of MTX.[11,12]

Patients that do start MTX monotherapy may discontinue treatment due to drug-induced intolerance/adverse events or patient/physician preference.

While many RA patients experience mild or moderate side effects while taking MTX, the drug has a long history of generally favorable long-term safety. MTX is associated with a relatively low treatment discontinuation rate of 16% due to adverse events.[1,14] Intolerance to MTX can involve physical symptoms (e.g., abdominal pain, nausea, vomiting, fatigue) that become anticipatory or associated with MTX intake as well as behavioral symptoms (e.g., irritability, crying, drug refusal). Intolerance may also contribute to reduced adherence to therapy.[15]

Some data suggest that patients who experience an inadequate response or develop intolerable adverse events to oral MTX may benefit from switching to the subcutaneous version of the drug. Taken at the same dosage as the oral formulation, subcutaneous MTX has been associated with greater clinical response as well as improved gastrointestinal tolerability compared with oral MTX.[16,17]

Other patients may decline or discontinue treatment with MTX due to personal preference. For example, some patients may not want to abstain from alcohol, while other patients may decide MTX is the wrong treatment choice due to family planning decisions or not wishing to use effective contraceptives during the treatment course.[12]

When Is It Appropriate to Prescribe Biologic or Small Molecule Monotherapy?

As mentioned earlier, neither the ACR nor EULAR guideline recommends prescribing biologic or small molecule monotherapy over conventional DMARD monotherapy as first-line treatment for most DMARD-naïve patients, and both indicate biologic and small molecule therapies are best used later in the treatment landscape in combination with MTX or another conventional DMARD, when possible.[2,3]

However, treatment recommendations do not necessarily preclude the decision to use biologic or small molecule monotherapy as part of an individualized treatment approach. For some patients, including MTX or another conventional DMARD into the treatment regimen may not be appropriate for a multitude of reasons (see Table 2). For these patients, initiating or switching to

Table 2

Potential Reasons for Initiating Biologic or Small Molecule Monotherapy[7,15]

- Contraindications to MTX
- Lack of or suboptimal efficacy with MTX
- Adverse events associated with MTX
- MTX intolerance
- Suboptimal adherence to MTX monotherapy or combination therapy
- Patient unwillingness to take MTX
- Simplify treatment regimen
- Insufficient pharmacological clearance (e.g., elderly, impaired renal function)
- Treatment goals reached and desire to reduce number of medications

monotherapy with a biologic or small molecule may provide clinical benefit, improve adherence, and help patients reach treatment goals.

Biologic or Small Molecule Monotherapy: What Does the Data Say?

For a substantial number of patients with RA, it is highly likely they will receive treatment with a biologic or small molecule, either as monotherapy or in combination with MTX or another conventional DMARD, at some point during their disease course.

Unfortunately, extrapolating data from clinical studies and applying it to clinical practice is complicated because head-to-head comparative data is limited, and available information is often the result of indirect comparative studies, meta-analyses, and systematic literature reviews. This section will discuss some of the overall efficacy and safety trends observed with biologic and small molecule therapies.

While numerous studies have been conducted evaluating biologics and small molecules as monotherapy or in combination with MTX/DMARDs against MTX/other DMARD monotherapy and/or placebo, substantially fewer studies have directly compared the safety and efficacy of biologic or small molecule monotherapy against itself in combination with MTX/other conventional DMARD. This section, while not exhaustive, will highlight examples of clinical trials in which the safety and efficacy of biologic or small molecule monotherapy was compared with itself in combination with MTX/other conventional DMARD (Table 3).

Overall Efficacy

Based upon the literature, several overarching themes regarding the use of biologics and small molecules can be made, including the following:[3,6,18-34]

- At this time, it is still not clear if there is an optimal choice or sequence of biologic and/or small molecule therapies following failure of MTX monotherapy
- Biologics and small molecules have demonstrated improved clinical efficacy when used in combination with MTX compared with MTX monotherapy
- Biologics and small molecules have improved efficacy when used in combination with MTX compared with monotherapy
- If combination therapy is not feasible, the literature supports the use of tocilizumab or tofacitinib monotherapy over other biologics as they have demonstrated better efficacy compared with MTX monotherapy

The greater efficacy of tocilizumab monotherapy compared with MTX was established in the AMBITION study. Patients with active RA for whom previous treatment with a DMARD/biologic had not failed were assigned to receive tocilizumab 8 mg/kg every 4 weeks or MTX 7.5 mg/week titrated to 20 mg/week.

At week 24, tocilizumab monotherapy demonstrated superior efficacy, with 69.9% of patients achieving an ACR20 response compared with 52.5% in the MTX treatment group. The incidence of severe adverse events and serious infections was similar between the 2 groups, occurring in 3.8% vs. 2.8% and 1.4% vs 0.7% of patients in the tocilizumab and MTX arms, respectively.[28]

Results from the 52-week SURPRISE study also support the use of tocilizumab monotherapy. In this study, patients with RA and moderate or high disease activity despite MTX were assigned to receive tocilizumab either as an add-on to MTX or as monotherapy. In this study, tocilizumab monotherapy was found to be superior to MTX/DMARD monotherapy. However, it should be noted that tocilizumab used in combination with MTX led to more rapid suppression of inflammation and reduction in radiographic progression compared with switching from MTX to tocilizumab monotherapy.[29]

Similarly, the greater efficacy of tofacitinib compared with MTX was established in the ORAL START trial. In this study, patients with moderate-to-severe RA who had not received MTX or were not receiving therapeutic doses of MTX were assigned to receive either 5 mg or 10 mg of tofacitinib twice daily or MTX (titrated to 20 mg/week). At month 6, 25.5% of patients in the 5 mg tofacitinib group and 37.7% in the 10 mg tofacitinib group had achieved an ACR70 response compared with 12.0% of patients in the MTX group. Infections and gastrointestinal disorders were the most common adverse events across all 3 treatments arms. Broadly speaking, MTX tended to be associated with more gastrointestinal side effects whereas tofacitinib appeared to be associated with more infections. Four percent (4.0%) of patients in the combined tofacitinib arm developed herpes zoster compared with 1.1% in the MTX arm. The incidence of bronchitis and influenza were also higher in the combined tofacitinib arms (6.1% and 2.8%, respectively) compared with MTX (2.2% and 1.6%, respectively). In the tofacitinib arm, 5 cases of cancer developed compared with 1 in the MTX arm. The incidence of severe adverse events and serious infections was similar between the 5 mg, 10 mg, and MTX arms, occurring in 10.7% vs. 10.8% vs 11.8% and 3.0% vs. 2.0% vs 2.7% of patients, respectively.[35]

Data suggest that the JAK inhibitor baricitinib, which recently received approval from the U.S. Food and Drug Administration at a 2 mg dose, may be more efficacious compared with TNFi in patients who have had an inadequate response to MTX.[36]

Table 3 *Brief Summary of Select Clinical Trials Comparing Biologic and Small Molecule Monotherapy vs. Biologics and Small Molecules in Combination with MTX*

Medication/Study	Population & Comparator Arms	Key Efficacy & Safety Outcomes
TNF Inhibitors		
Adalimumab PREMIER study[22]	MTX-naïve patients (N=799) Arm 1: Adalimumab 40 mg q2w + MTX Arm 2: Adalimumab 40 mg q2w Arm 3: MTX monotherapy	The proportion of patients achieving ACR50 at 1 year: • ADA + MTX: 62% • ADA monotherapy: 41% • MTX monotherapy: 46% (P<0.001 for combination vs both monotherapies) Radiographic progression at 1 year: • ADA + MTX: 1.3 Sharp units • ADA monotherapy: 3.0 Sharp units • MTX monotherapy: 5.7 Sharp units After 2 years of treatment, 49% of patients in the combination arm (Arm 1) achieved disease remission, approximately twice the rate seen in the monotherapy arms. In general, all 3 treatment regimens were well tolerated, with rates and types of AEs comparable across all 3 groups. Serious infections were the most common SAE.
Etanercept ADORE study[21]	Patients with active RA with inadequate response to MTX (N=315) Arm 1: Etanercept 25 mg twice weekly + MTX Arm 2: Etanercept 25 mg twice weekly monotherapy	The proportion of patients achieving an improvement of >1.2 units in DAS28 score from baseline to week 16 (P=NS): • Etanercept + MTX: 75.2% • Etanercept monotherapy: 72.8% The rates of SAEs were similar between the ENT monotherapy and ENT+MTX arms. Infections were reported in 24.5% and 32.3% of patients in the ENT and ENT+MTX arms; however, severe infections were rare, occurring in 0.6% and 0.3% of patients, respectively.
JESMR study[25]	Patients with active RA with inadequate response to MTX (N=151) Arm 1: Etanercept+MTX Arm 2: Etanercept monotherapy	The ACR20, 50, and 70 response rates at Week 52 in the ETN + MTX group (86.3%, 76.7%, and 50.7%, respectively) were significantly greater than those in the ETN monotherapy group (63.8%; 43.5%; 29.0%, respectively). The safety profile was comparable between the 2 groups. The rates of SAEs were similar between the two arms, 2.8% and 9.2% respectively. Infections were the most common AE and were reported in 26.8% and 27.6% of patients in ENT and ENT+MTX arms, respectively.
Golimumab GO-FORWARD study[26]	Patients with active RA despite MTX therapy (N=444) Arm 1: MTX Arm 2: Golimumab 100 mg Arm 3: Golimumab 50 mg + MTX Arm 4: Golimumab 100 mg + MTX	The proportion of patients who achieved ACR20 at week 14 were (P value significance relative to MTX arm): • 33.1% in the MTX arm • 44.4% in the golimumab 100 mg monotherapy arm (P=0.059) • 55.1% in the golimumab 50 mg + MTX arm (P=0.001) • 56.2% in the golimumab 100 mg + MTX arm (P<0.001) At week 24, the median improvement from baseline in HAQ-DI score was: • 0.13 in the MTX arm • 0.13 in the golimumab 100 mg monotherapy arm (P=0.24) • 0.38 in the golimumab 50 mg + MTX arm (P<0.001) • 0.50 in the golimumab 100 mg + MTX arm (P<0.001) Through week 24, SAEs occurred in 3.7%, 6.0%, 4.2% and 12.4% of patients in Arms 1-4, respectively; serious infections occurred in 0.7%, 3.0%, 0.9% and 4.8 of patients in these respective arms.

continues on next page

Table 3 *continued* *Brief Summary of Select Clinical Trials Comparing Biologic and Small Molecule Monotherapy vs. Biologics and Small Molecules in Combination with MTX*

Medication/Study	Population & Comparator Arms	Key Efficacy & Safety Outcomes
Other Biologics		
Abatacept AVERT study[24]	Patients with early RA who were either MTX-naïve or had not received MTX during the month prior to enrollment (N=351) Arm 1: Abatacept + MTX Arm 2: Abatacept monotherapy Arm 3: MTX monotherapy	At month 12, DAS28(CRP)<2.6 was achieved by: • ABA + MTX: 60.9% (P=0.10 vs MTX monotherapy) • ABA monotherapy: 42.5% • MTX monotherapy: 45.2% Of those who were in remission at month 12 and entered the withdrawal period, sustained remission at month 18 was observed in: • ABA + MTX: 24.7% • ABA monotherapy: 28% • MTX monotherapy: 17.0% Both ABA combination and monotherapy arms had a comparable safety profile compared with MTX monotherapy. SAEs were reported in 6.7%, 12.1%, and 7.8% of patients in the ABA + MTX, ABA monotherapy, and MTX monotherapy treatment arms, respectively. Serious infections occurred in 0.8% (1/119), 3.4% (4/116), and 0 patients, respectively.
Tocilizumab FUNCTION study[30]	MTX-naïve patients with early progressive RA (N=1162) Arm 1: Tocilizumab 4 mg/kg + MTX Arm 2: Tocilizumab 8 mg/kg + MTX Arm 3: Tocilizumab 8 mg/kg monotherapy Arm 4: MTX monotherapy	The proportion of patients achieving remission, defined as DAS(ESR)<2.6, at week 24 were as follows (all results were significant vs. MTX monotherapy arm): • 32% of patients in Arm 1 • 45% of patients in Arm 2 • 39% of patients in Arm 3 • 15% of patients in Arm 4 Rates of serious adverse events were similar across treatment groups, with the overall highest rate (10.7%) observed in the 8 mg/kg TCZ+MTX group (Arm 2). Infections were the most common SAEs, ranging from 2.1% to 3.4% across treatment groups. Other safety findings of interest included elevations in ALT, occurring most commonly in the TCZ + MTX groups in a dose-dependent fashion. Grade ≥2 ALT elevations were observed in 9%, 16%, 24%, and 8% of patients in Arms 1-4, respectively.
Small Molecules		
Tofacitinib ORAL STRATEGY study[32]	Patients with active RA despite MTX therapy (N=1146) Arm 1: Tofacitinib 5 mg BID monotherapy Arm 2: Tofacitinib 5 mg BID + MTX Arm 3: Adalimumab 40 mg Q2D + MTX	The proportion of patients attaining an ACR50 response at month 6 were as follows: • 38% of patients in the tofacitinib monotherapy arm • 46% of patients tofacitinib + MTX arm • 44% patients in the adalimumab + MTX arm Non-inferiority was shown for Arm 2 vs. Arm 3 but was not shown for either Arm 1 vs. Arm 3 or Arm 1 vs. Arm 2. Discontinuation due to adverse events were observed in 6%, 7%, and 9% of patients in Arm 1, Arm 2, and Arm 3, respectively.

ABA = abatacept; ADA = adalimumab; ACR = American College of Rheumatology; CI = confidence interval; DAS = Disease Activity Score; ETN = etanercept; HAQ-DI = Health Assessment Questionnaire-Disability; MTX = methotrexate; SAE = serious adverse events; TCZ = tocilizumab; ALT = alanine transaminase

Overall Safety

The overall safety of biologics, including TNFi and non-TNFi agents, was compared with conventional DMARDs in a recent review article. Patients receiving any biologic were at an increased risk of serious infection (adjusted hazard ratio [HR]: 1.1 to 1.8) and tuberculosis (HR: 2.7 to 12.5), but not herpes zoster infection. Overall, patients on biologic therapy were not at increased risk for malignancies in general, lymphoma, or non-melanoma skin cancer. The risk of melanoma was found to be slightly increased (HR: 1.5), although that was based on the results of only one study. Interestingly, the rate of serious infection on biologic therapies was lower in more recent trials compared with older studies, possibly reflecting improved screening and management of patients at risk for infection.[37]

Similarly, the overall safety of small molecules, as monotherapy and in combination with MTX, was also evaluated in a recent review. With tofacitinib, the most commonly reported laboratory abnormalities included mild decreases in lymphocyte and neutrophil counts, and mild increases in aminotransferase and creatinine levels. Baricitinib, meanwhile, was associated with reduced hemoglobin levels. Compared with placebo, the relative risks for serious AEs with tofacitinib and baricitinib were 0.8 and 1.0, respectively. However, tofacitinib was associated with a significantly increased risk of herpes infection.[31]

Adherence/Persistence to Biologics and Small Molecules

Overall, an estimated one-third of patients discontinue therapy with their first biologic within a year of the initiation of treatment. This can occur for several reasons, including primary ineffectiveness, loss of efficacy over time, or drug intolerance.[4] One series of real-world data found patient persistence—defined as continuing with an initial biologic without switching to another biologic and without a gap in therapy of 45 days or longer—at 1 year after initiating biologic therapy with etanercept, adalimumab, infliximab, or abatacept of 45.7%, 42.9%, 40.8%, and 40.5%, respectively. Across these treatment groups, on average, 34% of patients discontinued biologic therapy, 18% restarted therapy with the same biologic, and 6% switched to a different biologic.[10] A provider survey of rheumatologists found the vast majority of patients typically cycle through 2 to 3 different biologics during their disease course.[38] Other factors may influence treatment adherence and persistence as well, such as patient preferences, beliefs, and cost.

When looking at factors that may influence treatment adherence/persistence, a study assessing patient preferences for second-line therapy (biologic or small molecule) found that patients highly valued an oral treatment option that didn't need to be combined with MTX. Medications requiring IV infusion were the most strongly opposed treatment option. Interestingly, in terms of frequency of administration, patients strongly preferred twice daily intake over intake every 1-2 weeks.[39] Other data has confirmed that patients state a preference for oral treatment options.[40]

Patient beliefs and experiences with biologic therapy have also been shown to influence adherence. A longitudinal study assessing adherence to adalimumab therapy found that approximately 25% of patients reported low to moderate adherence to therapy. Factors positively associated with increased adherence included increased belief in medication necessity, lower concerns about medication use, increased treatment control, strong views of chronicity of RA, and increased professional and family support.[41]

Lastly, the cost of treatment has also been found to influence treatment adherence/persistence. An analysis of patients enrolled in the Medicare Advantage and Prescription Drug plan (N=864) found member out-of-pocket (OOP) costs significantly affected treatment initiation and adherence to biologic therapy. Overall, 18.2% of patients (157/864) had no evidence of filling initial biologic prescriptions (initial prescription abandonment). The rate of initial prescription abandonment varied with OOP costs. For example, of the 265 patients in the $0-25 OOP cost group, no patients had evidence of an abandoned biologic prescription. In contrast, initial abandonment occurred in 32.7% of patients (54/165) in the >$550 OOP cost group. Similar trends were observed for the likelihood of refilling a prescription for a biologic.[42]

Although real-world evidence evaluating small molecule persistence/adherence is scarce, a retrospective analysis comparing real-world adherence/persistence for tofacitinib vs. biologics over a 12-month period (adalimumab, etanercept, and infliximab) found persistence/adherence between the two was similar.[43]

The Role of MTX in the Formation of Antidrug Antibodies & Cardiovascular Health

Beyond improved clinical response, there are several other reasons to consider using MTX as part of a treatment plan when treating patients with biologics and small molecules. These include possible mitigation of the formation of antidrug antibodies as well as cardiovascular protective effects of MTX.

One of the concerns about the use of biologics is the potential loss of efficacy due to the formation of antidrug antibodies. Antidrug antibodies can form as a result of the body's production of an immune response to biologic therapy if it is seen as a foreign invader. Antidrug antibodies can bind and neutralize biological agents, dramatically reducing the concentration of active, unbound drug molecules in the blood.[44]

While the formation of antidrug antibodies is a phenomenon universal to all biologic agents, it appears to be especially common with TNFi drugs. Up to 30% of patients fail to respond to TNFi therapy, and 60%

of patients who initially respond to TNFi therapy subsequently experience loss of efficacy.[44,45] Antidrug antibodies are believed to play a role in this, with findings in the literature indicating the formation of antidrug antibodies in response to TNFi therapy correlates with decreased functional drug levels, loss of therapeutic response, and/or adverse events such as infusion reactions.[46-49]

A study evaluating the development of antidrug antibodies in patients with RA treated with adalimumab—either with concomitant DMARD or as monotherapy—found that 28% of patients developed antidrug antibodies over a 3-year treatment period. The incidence of antidrug antibody development was substantially higher in patients not receiving concomitant DMARD therapy. The development of anti-adalimumab antibodies was associated with lower serum adalimumab levels, reduced clinical response, and higher rates of treatment discontinuation.[50]

The picture is less clear for non-TNFi agents. The ACT-RAY study compared the number of patients who developed antidrug antibodies while receiving tocilizumab as an add-on to MTX or as part of a switch to monotherapy. At 1 year, the number of patients with antidrug antibodies was comparable between the two groups (1.5% and 2.2%, respectively), with overall data suggesting the immunogenicity of tocilizumab may be lower compared with other biologics.[51] Findings from the literature suggest that MTX, given even at low doses (7.5-10 mg/kg), is generally well tolerated and has been associated with reduced formation of antidrug antibodies as well as improving the efficacy of biologic therapy, further supporting its role in combination therapy.[3,44]

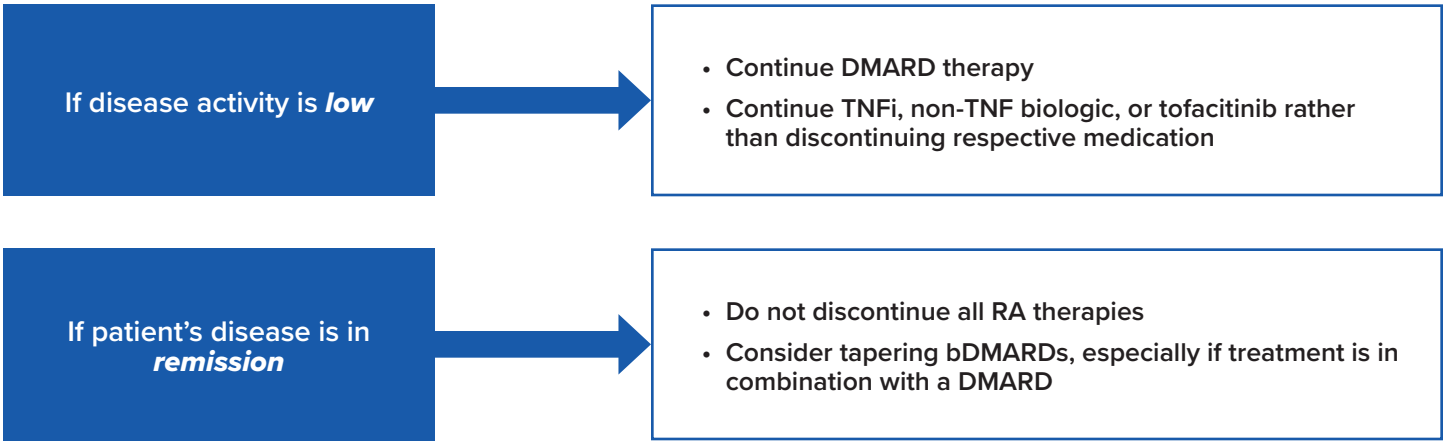
It is widely accepted that individuals with RA are at increased risk of cardiovascular events compared with the general population.[52] Evidence in the literature has found that MTX and other conventional DMARDs are associated with decreased risk of cardiovascular events.[18,53] A recent review of 28 studies found that MTX was associated with a reduced risk of all cardiovascular events in patients with RA.[53] Reductions in risk of acute myocardial infarction (MI) have also been observed in real-world practice. A large retrospective study of 107,908 commercially insured patients taking any DMARD for RA found the current use of any DMARD was significantly associated with reduced risk of acute MI.[54] These findings suggest MTX and other DMARDs may serve an important role in providing cardioprotective effects in the treatment of patients with RA.

Approaches to Tapering Biologic Treatment

With current therapies and the T2T strategy, long-term remission is now achievable in more than 50% of patients with RA.[55] When patients achieve long-term remission with biologic therapies, issues such as potential overtreatment, long-term adverse effects, economics of therapy, and patient preferences enter the conversation.[55]

So what guidance is available for patients who achieve treatment targets of either low disease activity or clinical remission when on combination therapy? The ACR and EULAR treatment guidelines both address the issue of drug tapering and recommend that tapering only be considered for patients with sustained remission on current therapy (see Figure 2). The suggested order of tapering is GCs, followed by biologics, especially if used in combination with conventional DMARDs.[3] While factors such as disease duration, degree of improvement, and duration of remission may help guide tapering decisions, more research in this area is needed.[3,19]

Figure 2 *ACR and EULAR guideline recommendations for tapering therapy in patients with RA*



When tapering is discussed, it is usually done so in the context of dose reduction or increases in intervals between drug administration.[3] Evidence supports that most patients receiving therapy with a biologic + MTX can reduce the dose of their biologic by up to 50% or increase the interval between doses accordingly and maintain their low disease activity, with little risk of flares.[19] However, the possibility of flares should be discussed when exploring the option of tapering, and a plan should be developed for monitoring and managing a flare in the event one occurs that reflects patient values and preferences.[2]

It is important to note that drug tapering is different than drug discontinuation, which in the case of a biologic therapy often leads to disease flares.[19] However, even in the event of disease flares following tapering or discontinuation, most patients will recover their previous treatment response on intensification or reinstitution of therapy.[3] EULAR guidelines reflect the view that patients with RA on conventional DMARD monotherapy, even if they have achieved sustained remission, should never fully stop treatment.[3]

Summary

As the number of treatment options has expanded for the treatment of RA, determining optimal therapeutic approaches has become increasingly complex. Clinical practice guidelines that are based upon currently available data provide support to rheumatology providers for treatment approaches. However, it is ultimately up to rheumatology providers to determine when to implement, change, or taper RA therapies, as well as decide which agents to use. This process reflects assessing the risk/benefit of various monotherapies or combination therapies based on efficacy and safety data, and balanced with patient treatment goals, values, and preferences.

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Making Deviations to the Normal Treatment Pattern

by Carrie Beach, BSN, RN-BC

When a patient is newly diagnosed with rheumatoid arthritis (RA), there are specific treatment guidelines that are typically followed. This includes the initiation of one or more non-biologic disease modifying anti-rheumatic drugs (DMARDs), most commonly methotrexate.

In my practice, it is a near-certainty that a patient who presents with minimal or mild symptoms of RA will be started on hydroxychloroquine (HCQ), at least until their diagnosis is more definitive. Once a patient moves into the "probable" or "definite" RA category, they will usually be started on methotrexate, the gold standard first-line therapy. If a patient is unable to tolerate methotrexate, we'll often move to another conventional DMARD such as leflunomide or azathioprine before breaking out the bigger guns (aka, biologic therapies). There are a number of reasons for this progression, not least of all insurance company requirements for many of our patients.

There are, however, times when it is in the best interest of our patients to deviate from this normal course and attack their disease in a different manner.

LF was one of those atypical patients who presented to our clinic early in my rheumatology career. At the time of her presentation, LF was a 35-year-old female referred to our clinic with a 7-month history of joint pain and swelling that was being treated only with over-the-counter ibuprofen. The pain had begun across the metatarsophalangeal joints in her feet before migrating to her bilateral metacarpophalangeal joints, wrists, and shoulders. She reported at least 2 hours of daily morning stiffness.

An MRI ordered by LF's primary care physician showed bursitis and joint inflammation. Her labs were notable for a positive rheumatoid factor and elevated C-reactive protein level.

Based on her presentation and workup, LF's diagnosis of RA was fairly obvious at this initial visit. While our typical pattern would have been to start LF on a conventional DMARD—likely methotrexate—there was one other significant piece of the puzzle to take into account. LF told us that she had been trying to conceive for several months without success. She had no children, and starting a family was very important both to her and her husband.

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"There are, however, times when it is in the best interest of our patients to deviate from this normal course and attack their disease in a different manner."

We therefore immediately ruled out methotrexate and leflunomide as first-line treatment options. We considered HCQ, but since LF already had significant joint pain, swelling, and potential joint damage, we decided an initial course of a biologic therapy would be the best way to go. This was around 2005, so there were only 3 biologic therapies to choose from—infliximab, adalimumab, and etanercept—and limited data regarding their use during pregnancy.

After significant discussion with LF and her husband, we decided to start her on etanercept monotherapy 50 mg weekly until she became pregnant. We also gave her a short-term prescription for prednisone 5 mg daily to get her symptoms under control.

A month later, LF was back in our office with significant improvement in pain and swelling. Seeing no reason to make any changes to her treatment plan, we set LF's next follow-up appointment for 2 months later. As if it were so easy!

A week later, LF called us with great news—she was expecting. We quickly scrambled to adjust her treatment regimen, tapering her off of prednisone and discontinuing etanercept altogether. Because biologics were so new at this time, we felt better taking her off etanercept; were this a patient in our practice today, we would likely have more seriously considered keeping her on etanercept to manage her RA symptoms during her pregnancy.

Fortunately, LF was one of the lucky ones, and her RA went into remission while she was pregnant. Even better, she delivered a healthy baby girl.

LF's first postpartum visit to our practice came 2 months after delivery while she was still breastfeeding. Her RA symptoms had unfortunately returned, and she required 20 mg of daily prednisone just to remain functional. Again, being that these were the early days of biologics, we had little experience with the use of etanercept during breastfeeding. We remained cautious and had LF remain on prednisone alone until she was done breastfeeding.

LF struggled with her RA during the next few months, but when she was finally done with breastfeeding, we started her back on etanercept. LF told us she and her husband had decided against having additional children, and she was back on an oral contraceptive. That allowed us to add methotrexate to her biologic. LF again saw rapid improvement on etanercept and was able to taper off of prednisone within a month.

After approximately 2 months on methotrexate, LF developed side effects that caused her to discontinue the medication. At that time, we decided to switch her to leflunomide 20 mg daily in addition to the etanercept. Surprisingly, LF has remained stable on that regimen for more than 10 years, quite rare in patients with RA but certainly not unwelcome.

LF's case may sound relatively straightforward to us now with our 2 decades of experience with biologics in nearly every setting, but at the time we first saw her, she was truly one of our practice's first guinea pigs with biologic monotherapy. It's still often necessary to make tweaks to our usual plan in our younger patients with RA who seek to start a family. While there are frequently insurance company hurdles to the frontline initiation of biologic therapy, it is important as nurses that we continue to advocate for these patients to get the care that they need to prevent disease progression and additional joint damage in the long run.

All Hail the Negotiator

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

I first met JY 2 weeks ago. A 35-year-old, tall, lanky male with a 2-year history of seronegative rheumatoid arthritis (RA), JY initially presented to a rheumatologist in my area with only a handful of troubling issues. His labs were all negative with the exception of an elevated C-reactive protein (50 mg/dL) and increased eosinophilia count (45%). Hepatitis and QuantiFERON-TB panels were negative. Physical exam demonstrated 3 swollen proximal interphalangeal joints but no tender joints. JY also reported regular morning stiffness of approximately 2 hours.

In essence, nothing truly remarkable.

What has made the initial management of JY unique is unraveling his convoluted treatment history and parsing the truth from the, well, untruth.

As we began discussing his medication history, we started at the beginning when JY was prescribed methotrexate 2 years ago. He recalled his initial reaction when reading through the potential side effects. "I remember seeing that it causes alopecia no matter how small the dose," he told me. A bit of an exaggeration, but I didn't push it.

I then asked JY if he was prescribed daily folic acid in addition to the methotrexate and was told, "That's just a vitamin—there wasn't any reason for me to take it." I calmly explained to him that the reality was just the contrary and that folic acid can help to reduce the toxicity of methotrexate and mitigate the risk of some side effects.[1]

As our conversation continued, I learned about some of the other reasons why methotrexate was "not for me," include the fear of liver, pulmonary, and blood toxicities. While it is true that methotrexate can cause side effects such as hepatotoxicity, asymptomatic radiographic lung damage, impairment of glomerular filtration, diminished vaccine responses, and alopecia, frequent monitoring can often identify any of these adverse events before they become significantly damaging.[2]

JY had lasted only 4 months on methotrexate before he voluntarily discontinued the medication due to all of his (exaggerated) concerns.

We kept going.

JY's medical chart stated that he was a "non-drinker." When I asked for verbal confirmation of this fact, JY admitted that it wasn't really true. He then proceeded to ask me how much daily alcohol he could drink and still be "safe" if he decided to restart methotrexate. This had the uncomfortable feel of a negotiation, as if there was some magic number of drinks I would agree was OK so that he could restart methotrexate. To JY's dismay, I assured him that no amount of daily drinking was safe or recommended while taking methotrexate.

It was starting to become clear why JY had stopped taking methotrexate—despite reporting that he had almost no morning stiffness and limited synovitis while on the drug—and had switched to cyclosporine 100 mg BID. I asked him if cyclosporine had been effective, but was told "not too much." Apparently, despite cyclosporine's possible side effects of renal toxicity and hypertension,[3] it was a lack of efficacy and not safety fears that were the overriding factor behind its discontinuance.

There was, of course, more to be said. "I couldn't take (cyclosporine) and drink or eat grapefruit, which was a nonstarter for me," JY said. On this, at least, JY's knowledge was sound. There are a group of active compounds in grapefruit known as furanocoumarins that are inhibitors of the cytochrome P-450 3A enzyme, which can increase the exposure to cyclosporine.[4] Consequently, unless specifically cleared by a clinician, patients taking cyclosporine are instructed to avoid grapefruit and grapefruit juice.

Sulfasalazine had also been a no-go. "It made my urine too yellow," JY told me.

Somehow, JY's previous rheumatologist had convinced him to give an injectable a try to

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better match his active lifestyle, and adalimumab was initiated. As with methotrexate, JY saw his symptoms improve quickly as his tender and swollen joint count reduced from 10/8 to 4/2, respectively. His C-reactive protein level also dipped to <5 mg/dL.

Again, though, success was short-lived. After 6 months of twice-monthly injections of adalimumab, JY decided that too much damage was occurring at the injection site and that he wanted to stop all medications to give a holistic approach to care a try. Fresh fruits, fresh vegetables, no meat, and no gluten, but still a "safe" amount of alcohol as determined by JY. How alcohol fits into a "holistic" diet remains a mystery a me, but again, I bit my tongue as best as I could.

Three months after the holistic diet began, JY first showed up in my office with badly progressing problems. His CRP was back up to 60 mg/dL, he had 12 tender and 10 swollen joints, 2 hours of daily morning stiffness, and was barely able to walk without pain.

It was obvious—at least to me—that JY needed an immediate steroid taper followed by an NSAID and then likely a second try at a biologic therapy. At the same time, I knew that JY would likely put up roadblocks to any medications involving a needle and perhaps would simply find potential danger with anything I suggested. Let's face it—a biologic has more potential side effects than a carrot stick, and I was likely going to hear about it if I failed to tread extremely carefully.

I started with a positive—there was no presence of erosive disease on a recent X-ray. However, I noted that, on the current road JY was on, this wasn't going to last long. No treatment—and fruits and vegetables don't count as treatment!—would eventually lead to disfiguring joint damage and disability.

I then reviewed with JY the side effect profiles and mechanisms of action of his more viable treatment options. Because it was an "unjection" in pill form, JY opted to start with tofacitinib after a brief indomethacin boost for joint pain. The fact that tofacitinib has shown efficacy as monotherapy was an added bonus—JY is a patient where I definitely felt that the less drugs he needed to take, the better.[5]

JY is an Internet-savvy young adult. It is clear that empowering him in our office with information about his disease and the treatment options available to him is vital, but it's also clear that his education isn't going to stop once he leaves our office. Giving him the tools to help differentiate fact from fantasy isn't easy—so many of our patients want to believe what they read online regarding things such as a holistic diet. It's my job to reinforce information and encourage JY to continue to be an active participant in the control of his disease at every step.

There is nothing enjoyable about those "gotcha" moments when we find out that what is in our patient's medical record doesn't necessarily reflect the truth, or that there are important details that are missing when we first meet a new patient. I have been sure to document these new details so that others who eventually will be responsible for treating JY have a better idea of what they may be up against. In the meantime, I'll continue to serve as a negotiator to get past whatever roadblocks JY throws up in the future so that we're able to quiet the impact of his disease and maintain his busy lifestyle.

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Tapping Into Our "Spidey Sense"

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

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Recently, I had a casual conversation with some nurse practitioner friends about an older adolescent I saw in clinic, and how my gut told me not to put her on methotrexate (MTX) because I wasn't sure I believed her when she told me that she was not sexually active. I'm not going to get into all the details of the actual visit, but I instead want to focus on whether this was truly a **judgment** or a **judgmental** call on my part.

Why was it that I felt so strongly that this patient wasn't telling me the truth about something so serious as her sexual activity even after I explained to her that certain medications such as MTX can cause birth defects or possibly fetal death? What was it about her, or me, that cued my skepticism?

As I have searched for a reasonable explanation of my decision, I have had to take a good, hard look at myself and introspectively ask, "What were you thinking?" What does it say about me that I didn't trust my patient about this crucial information, and what potential damage might a decision like this have on our patient/provider relationship? Would she now start judging me for judging her?

When my rheumatology nursing colleagues asked me why I believed this patient was sexually active even though she denied it, I could only come up with one good answer—it was my nurse's "Spidey sense."

Now of course, there is nothing in any clinical guideline that says any clinician should use his/her intuition to make treatment decisions. Patient care does not occur in the context of a Marvel comic, and I am not Spiderman (though it would be nice).

And yet, I clearly remember during this visit that I felt unusually confident in my decision not to prescribe MTX unless this patient agreed to birth control. In my gut, I was absolutely confident that I did the right thing at that moment.

Given time to reflect and rationalize my decision, I began by looking at what I know of adolescents. I spent more than 5 years working at a high school where I saw hundreds of teenagers in my office without the presence of their parents. I heard uncanny honesty from many of them regarding difficult issues and had many frank discussions about sexual activity. I am also very knowledgeable about the signs of high-risk behaviors among teens and vulnerable youth.

I thought about all of this when I reflected upon the factors that cued my "Spidey sense" in this case. Was it because this was a tall, pretty teenager who looked

"Self-introspection can be a valuable tool to help us understand why we make certain decisions, both personally and professionally, and help us to better serve our patients in the long run."

like she could have come from the pages of a fashion magazine? Was it because she looked like she was in her early 20s when in reality she was several years shy of turning 18? Was it because her general maturity level would make boys her age seem like middle schoolers? Was it because she was uncertain about attending prom because her father said he wasn't sure he was going to let her go?

Combine all of this information and, to me at least, it screams "vulnerable teen." And a vulnerable teen is someone who raises my fears. Fear of a young adult male thinking this patient is much older than she is. Fear that this patient will be flattered by the attention being paid to her and would put herself in a risky situation that could lead to a sexual relationship. Fear that this relationship would lead to the possibility of a sexually transmitted infection, pregnancy, or HIV, all risks highlighted in the clinical literature when teenaged girls date older men.[1,2]

Of course, none of my observations could be considered to be true risk factors. Instead, again based on my experience, I would consider them to be "soft signs," akin to soft neurological signs. You know, those abstract signs that aren't necessarily worrisome at the moment and would not help lead to a definitive diagnosis.

Based on my reflections of this patient, I am confident that my decision to withhold MTX wasn't a judgmental decision but was indeed my nurse's "Spidey sense" at work. There was something that simply didn't feel right to me and triggered my need to protect this patient no matter the potential damage to our relationship. Maybe the fact that this patient had previously been lost to follow-up for almost a year and had rejected a suggestion of MTX during a flare played a role in my decision—it's hard to say. In the moment of our visit, I couldn't have easily put that feeling into words, but I rather remember the unidentifiable uneasiness I felt in the exam room. This was a patient who I felt needed my help and protection even if she couldn't say so.

The situation with this patient continues to evolve. Fortunately, there are a number of other treatment options available to us that work just as well if not better than MTX in many patients. In our patients with RA for whom we are worried about the possibility of pregnancy, there is good data on the use of several nonbiologic and biologic therapies that can help control disease while presenting few fetal risks.

Were it not for my nursing colleagues, I likely would not have reflected—at least not to a significant degree—as to why I made the decisions I did with this patient. Self-introspection can be a valuable tool to help us understand why we make certain decisions, both personally and professionally, and help us to better serve our patients in the long run. So don't be afraid to listen to your "Spidey sense" even when logic points you in a different direction—nursing intuition is sometimes the best tool in our treatment arsenal.

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The Impact of Everyday Life on Drug Adherence… *And How You Can Help*

by Mariah Zebrowski Leach

I was diagnosed with my first chronic illness at age 5, so I've taken medication daily for basically as long as I can remember. As a result, I didn't have any trouble accepting that treatment would be necessary when I was diagnosed with rheumatoid arthritis (RA) at age 25. Learning how these medications would be administered was a bit of a shock, but I simply believed my doctor when he assured me the benefits would outweigh the risks.

However, I realize that I am not the norm. Many patients who are diagnosed with RA have been perfectly healthy their whole lives and have rarely or never taken medications. Then all of a sudden, BAM!—doctors are recommending the regular use of medications. With scary risks and side effects. With needles and IVs. With mountains of paperwork and astronomical costs. Forever.

It can be a lot to take in and accept, and it should be a surprise to no one that some patients have trouble adjusting to their "new normal." Putting and then keeping patients on the right path is something all rheumatology practices need to focus on. Based on my experience and interactions with other patients with RA, here are some of the biggest everyday issues patients face when it comes to drug adherence and how you can help.

Risks and Side Effects

Even if the chances are small, seeing words like "hospitalization" or "cancer" or "death" on our medication labels is very scary. In your eyes, the benefits may obviously outweigh the risks, but this isn't always clear to patients, particularly those who haven't yet come to terms with how serious untreated RA can be.

Side effects can also make us nervous. Laura L., a patient diagnosed with RA only a year ago, has experienced so many side effects since her diagnosis that she feels like she has to pick her poison.

"Do I skip the meds and feel good and present in the moment with my children?" she said. "Or do I take the meds and prevent long-term damage, even if it makes me miserable and causes me to lose time with my babies in the short-term?"

Weighing these pros and cons can be very difficult for patients, so please take our concerns seriously and help us understand the real risks of untreated RA. And if there is anything we can try to help minimize potential side effects, please let us know.

Getting the Medication

Once we have a prescription, getting our hands on the medication can often be easier said than done. The pharmacy location may not be convenient, our schedules may conflict with business hours, or we may struggle to even leave the house. Perhaps most frustratingly, sometimes we make it to the pharmacy only to discover they are waiting on a call or fax that is out of our hands.

AUTHOR BIO

Mariah Zebrowski Leach

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Using specialty pharmacies can also be complicated. Stefanie S., who has been living with RA for 8 years, recently had her specialty pharmacy replace a simple online refill option with the inconvenient requirement to call and speak with someone every time she needs a refill.

"Sometimes they tell me I can order a refill," she said, "but when it isn't delivered as promised, they'll tell me it was submitted too soon and my insurance denied it." These frustrations can take a real toll on patients.

You can help by making sure prescriptions, prior authorizations, and refills are dealt with as efficiently as possible. We'd also appreciate any tips or help you can offer when it comes to understanding the specialty pharmacy process.

Paying for the Medication

Prior to being diagnosed with RA, most patients never imagine needing to pay for expensive medications on a regular basis. While I'm incredibly grateful that there are so many copay assistance programs to help us, I am continually amazed by how many patients have no idea that these programs even exist.

If you recommend a medication with a hefty price tag, please give us time to process the sticker shock. Try to keep in mind that it's likely not the only increase in medical spending we are facing. There are also copays to doctors, bills for lab work, physical therapy, over the counter treatments, and more—as well as the impact RA can have on our ability to earn money. It's very overwhelming.

Please make sure we understand that there are ways to decrease this financial burden. Better yet, hand us the appropriate enrollment papers for the copay assistance program before we leave your office.

Treatment vs. Life Goals

Another important challenge for patients with RA is figuring out how to balance treatment options with long-term life goals. Whether it's finishing school, getting a promotion, or taking a dream vacation, if a recommended medication interferes significantly with what we want in our lives, we are going to be a lot less likely to take it regularly.

For me, starting a family was the most significant conflict with my RA treatment. I was lucky to have a rheumatologist who worked with me to find compatible treatment options, but if he had insisted on a treatment that was incompatible with pregnancy, I'm not sure I would have been able to comply.

"I think more time needs to be taken for counseling and partnering with patients," recommended Laurie Proulx, Vice President of the Canadian Arthritis Patient Alliance. "I think as patients, we need to buy into the treatment plan to stick with it."

Our life goals are important to us and need to be taken into consideration when making treatment decisions. If it is a topic you haven't researched extensively—like the impact of medications on pregnancy or breastfeeding—please be open to letting us share our own research.

A Final Note About Language

Medical professionals absolutely need to know whether patients are taking medications as instructed, and I certainly understand the need for brevity in a patient's chart. However, using language like "noncompliant" or "nonadherent" when actually discussing these topics with us can make us feel like we are being reprimanded or failing despite our best efforts.

Instead, we'd love it if you could spend some time trying to understand the specific challenges we are facing and brainstorming with us about how to overcome them. There's a big difference between telling us we aren't sticking to our treatment plan and asking how you can help. After all, in the end, we both want the same things—to find the best treatment option that will manage our disease, allow us to maintain our desired lifestyle, and not cause us to go broke in the process.

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