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# RHEUMATOLOGY NURSE NEWSLETTER

*Practical information and tools you  
can apply to your everyday practice!*

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## LEARNING OBJECTIVES

- Discuss the mechanism of action of biologic agents commonly used to treat rheumatoid arthritis (RA)
- Determine the safety of commonly used disease-modifying antirheumatic drugs (DMARDs) for the treatment of RA in women of childbearing age
- Develop strategies to help overcome common barriers that limit patient adherence to treatment regimens
- Identify current patient groups who should receive a recommendation to receive influenza vaccination, including vaccination for H1N1

## STATEMENT OF EDUCATIONAL NEED

An increasing number of pharmacologic agents are available to assist in the management of RA. Growing experience with these agents has led to key changes in the principles of RA treatment, including the early use of DMARD therapy, the use of DMARD combination therapy, and the use of biologic agents in patients who fail to respond to traditional DMARDs. Healthcare providers must also carefully consider other aspects of RA care, including pretreatment screening, ongoing safety monitoring, and treatment modification in pregnancy. Recently, efforts to improve adherence to RA medications have improved clinical outcomes associated with RA treatment. When patients follow treatment regimens as prescribed, early treatment with therapeutic regimens can significantly improve clinical outcomes, including reducing the signs and symptoms of RA, maintaining physical function, and preventing the radiographic progression associated with this debilitating disease.

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**Ann Marie MacIsaac, MSN, NP, APRN-BC**, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

There are no off-label and/or investigational uses discussed within the literature of this enduring activity.



## CONTENT AND VALIDATION TEAM

**Anne Jacobson, MPH**, Medical Writer, 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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## PEER REVIEWER

This newsletter was reviewed and approved by Regimol Chacko, RNC, MSN, CNL, IBCLC, a member of the Institute for Continuing Healthcare Education Nurse Planner Advisory Board. Ms. Chacko has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content included in this educational activity.

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Nicole M. Furfaro, MSN, ARNP, is the nurse planner for this activity.

*Any relationships faculty members have with commercial entities have been reviewed and any potential conflict(s) have been resolved.*

# CLINICAL IMPLEMENTATION OF PHARMACOLOGIC THERAPIES FOR THE TREATMENT OF RA

*As a result of improvements in the understanding of the pathophysiology of rheumatoid arthritis (RA), a wide variety of nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs) with distinct mechanisms of action are now available for the management of RA. The development of better strategies for use of these agents, including pretreatment screening for opportunistic infections, ongoing adverse event surveillance, and treatment adjustments related to pregnancy planning, has contributed to significant short- and long-term benefits for RA patients.*

## NONBIOLOGIC DMARDs

DMARDs involve a class of agents that appear to reduce inflammation and inflammation-related tissue destruction. Traditional DMARDs used in the management of RA include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Other DMARDs have shown efficacy in the treatment of RA but are generally reserved for select patients who have failed, cannot tolerate, or have contraindications to conventional RA medications. These include agents such as azathioprine, cyclosporin A, gold salts, and penicillamine.

### METHOTREXATE

Methotrexate (MTX) is a folate antagonist with potent anti-inflammatory properties.<sup>1</sup> Given its favorable efficacy and safety profile, in addition to its relative low cost and long history of use in RA, MTX has become the cornerstone of standard RA therapy.<sup>2</sup> In a 1990 meta-analysis of DMARD therapies, MTX was shown to be superior to placebo and hydroxychloroquine, and comparable to sulfasalazine, in the management of RA symptoms.<sup>3</sup> Due in part to these results, most clinicians select MTX for first-line DMARD therapy in patients with RA, particularly in patients with active RA.<sup>4</sup> MTX improves clinical and radiographic measures in patients with RA and provides a duration of effect that is superior to other DMARDs.<sup>5</sup> MTX is well tolerated, especially when given in combination with folic acid supplementation (1–3 mg/day).<sup>6</sup>

Importantly, the U.S. Food & Drug Administration (FDA) has designated MTX as a pregnancy category X drug, meaning that it is a proven teratogen (see page 10). Accordingly, MTX should be used with great caution in women of childbearing age and only after extensive counseling. In addition, because of its long half-life, women who wish to become pregnant should discontinue MTX at least 3 months before trying to conceive.<sup>7</sup>

### SULFASALAZINE

Sulfasalazine was first manufactured in the 1940s for the purpose of treating rheumatic inflammation. It combines an anti-inflammatory agent (5-aminosalicylic acid) with an antibacterial drug (sulfapyridine).<sup>8</sup> Several trials have shown the superiority of sulfasalazine over placebo in alleviating the symptoms of RA, but long-term studies have shown that it is less potent than leflunomide and MTX.<sup>9-11</sup> Sulfasalazine remains a reasonable alternative to other DMARDs, particularly in patients who have contraindications to leflunomide or MTX.<sup>8</sup> Sulfasalazine should be avoided in patients who are allergic to sulfonamides and in

those with glucose 6-phosphate dehydrogenase (G6PD) deficiency, a genetic condition that interferes with the metabolism of some drugs.

## HYDROXYCHLOROQUINE

Antimalarial agents have immunomodulatory and anti-inflammatory properties that are useful in the management of RA. Hydroxychloroquine is less potent than other antimalarials, but also less toxic, and therefore it is the most frequently used antimalarial agent used in the management of RA. Typically, hydroxychloroquine is used in the treatment of early, mild disease or in combination with other RA therapies. Although hydroxychloroquine effectively controls the signs and symptoms of RA, it has not been shown to slow the progression of RA when used as a single agent.<sup>4</sup> Retinal toxicity is the most significant adverse effect of most antimalarial therapy, but this occurs very rarely with hydroxychloroquine when appropriate dosing and routine eye exams are employed.<sup>12</sup>



## WHAT OUR PATIENTS ARE ASKING US

### “How much is this going to cost?”

**Ann Marie MacIsaac:** As with any chronic disease, RA poses a number of significant challenges for both patients and healthcare providers. As a nurse, I often find myself focusing on ways to ensure that my patients enjoy both a long and quality life (as far as either of these is within my control). I believe that all nurses have similar goals in mind. Personally, though, I wonder how many times I have provided care to my patients without asking about the potential financial burden it imposes on them.

I recently had a discussion with “Sue,” a former patient of mine who has had RA for 8 years. Candidly, she confided in me that, for the past year, her out-of-pocket costs have become overwhelming. She said she had been forced to choose between paying for treatment to adhere to the treatment plan set forth by her rheumatology care team or “putting bread on the table” for her family.

Sue’s new medications require frequent follow-up and diagnostic monitoring. She is also seeing a pain management specialist, who has prescribed various modalities, all costing an additional co-payment beyond her office visit. What’s worse is that Sue was hospitalized for an orthopedic procedure to address an ankle problem earlier this year. Consequently, she was forced to take an extended leave from her job, leaving her family 50% short of their usual income. To complete the vicious cycle, Sue was recently referred to a mental health professional for her worsening depressive symptoms. And on top of it all, because Sue lives in rural America, she must travel long distances and purchase gas just to get to her medical appointments. Sometimes, she feels so poorly that her husband has to accompany her to these appointments, requiring time away from his job too. Needless to say, it’s a devastating combination of circumstances.

During our recent conversation, Sue told me, *“I just had to get up the courage to be more forthright and honest with my healthcare providers regarding my financial situation.”* Once Sue confided in her nurse practitioner about her financial situation, she immediately received a compassionate response. Her healthcare team offered to connect her to local services that could provide her with financial help and perhaps help find ways to ease the money crunch. Sue said she was overwhelmed with gratitude at the response she received. She said she hadn’t previously spoken up because she did not think anything could be done to assist her financially and she was embarrassed by her dilemma. Once she finally did speak up, she told her nurse practitioner in a frustrated tone, *“Actually, if something was available to help me pay for things, I would have thought someone would have told me so.”*

Before another individual like Sue suffers while waiting to get up the courage to ask for help, perhaps we, as nurses, could be a bit more proactive. It might be as simple as incorporating a regular question into each patient interview about the financial burden of medical care. This question should be designed to respect each individual’s dignity and be open-ended enough to allow for further dialogue. It could be something as simple as, “Taking care of yourself and your family while dealing with a chronic condition must be difficult. Tell me, how are you managing to keep up with all of the costs related to your care?” Hopefully, the elicited response would provide you with sufficient information to take the next step in finding appropriate resources aimed at decreasing out-of-pocket expenses and alleviating a common stressor.

# BIOLOGIC DMARDs

*Biologic response modifiers (BRMs) are important tools in the management of RA. In the last decade, agents have been developed that inhibit proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), deplete B cells, and inhibit signals required for T-cell activation. Although BRMs are often used in combination with DMARDs such as methotrexate, they should not be used in combination with other BRMs.*

## TNF INHIBITORS

In patients with RA, inhibition of TNF has been shown to improve the signs and symptoms of RA, inhibit radiographic progression, and improve quality of life. Currently, five TNF inhibitors are approved for the treatment of RA: infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol.

**INFLIXIMAB** is a chimeric monoclonal antibody directed against TNF that is administered by intravenous infusion, usually at 4- to 6-week intervals.<sup>13</sup> Compared with placebo, patients on single-agent infliximab therapy are significantly more likely to achieve an ACR20 response, enjoy improved quality of life and functional status, and have less radiographic progression.<sup>14,15</sup> As with other TNF inhibitors, infliximab is often used in combination with MTX. When given concurrently with infliximab, MTX appears to boost serum levels of infliximab and reduce its immunogenicity, a potential source of reduced efficacy.<sup>16</sup> The combination of infliximab and MTX also improves radiographic outcomes compared with MTX alone.<sup>17</sup> In clinical trials, patients treated with infliximab and MTX are significantly more likely to achieve ACR20, ACR50, and ACR70 response rates than those taking MTX alone, with no significant increase in adverse effects.<sup>18</sup>

**ADALIMUMAB** is a fully human anti-TNF monoclonal antibody administered by subcutaneous injection, usually every other week. As a human antibody, adalimumab avoids common antibody-related problems, such as antibody reactions, that are associated with the chimeric construction of infliximab. Similar to infliximab, serum levels of adalimumab are increased when used in combination with MTX. Compared with placebo, patients on adalimumab therapy are more likely to achieve ACR20, ACR50, and ACR70 responses between 6 months and 2 years of therapy, regardless of whether they are concomitantly taking MTX.<sup>19</sup> In clinical trials, the combination of adalimumab and MTX has been shown to be superior to either drug used alone in slowing radiographic progression and controlling the clinical manifestations of RA for up to 3 years.<sup>20,21</sup> Patients treated with adalimumab also demonstrate improvements in quality of life relative to placebo.<sup>22</sup>

**ETANERCEPT** is comprised of portions of the human TNF receptor bound to a soluble immunoglobulin G (IgG) base. Acting as a soluble, fully human TNF receptor, etanercept reduces the amount of circulating TNF available to bind to TNF receptors on the surfaces of immune cells. Etanercept is administered by subcutaneous



injection once or twice weekly. Treatment with etanercept has been shown to improve clinical measures of RA, functional status, and quality of life.<sup>23,24</sup> The combination of etanercept and MTX is superior to MTX alone in slowing radiographic progression in patients with early RA.<sup>24</sup> In a recent meta-analysis of etanercept trials, patients treated with etanercept with or without MTX were significantly more likely to achieve ACR20, ACR50, and ACR70 responses relative to placebo, without a significant increase in adverse events.<sup>25</sup> Patients with early, active RA who receive combination therapy with etanercept and MTX can achieve sustained remission for up to 2 years.<sup>26</sup>

**GOLIMUMAB** was approved by the FDA on April 24, 2009, for the treatment of adult patients with moderately to severely active RA.<sup>27</sup> Golimumab is the first fully human monoclonal antibody against TNF available for monthly subcutaneous injection with a novel autoinjector or a standard prefilled syringe. Several recent studies have explored the optimal use of golimumab within the RA treatment spectrum. In patients who were never previously treated with MTX, initiating combination therapy with golimumab and MTX was more effective than MTX alone in reducing the signs and symptoms of RA.<sup>28</sup> The GO-FORWARD

study showed that adding golimumab to MTX improves physical functioning and other clinical parameters for up to 1 year in patients who have active RA despite MTX therapy.<sup>29,30</sup> In the GO-AFTER study, golimumab reduced the signs and symptoms of RA for up to 1 year in patients who have active RA despite previous treatment with one or more TNF inhibitors.<sup>29,31</sup> An updated safety analysis showed a favorable tolerability profile, including a relatively low rate of injection-site reactions: 8.2% with golimumab 50 mg and 12.4% with golimumab 100 mg.<sup>32</sup>

**CERTOLIZUMAB PEGOL** was approved by the FDA on May 14, 2009, for the treatment of moderately to severely active RA. Certolizumab combines a humanized monoclonal anti-TNF antibody with polyethylene glycol to form apegylated molecule that lasts longer in the bloodstream than other TNF inhibitors and selectively accumulates in inflamed joints. Certolizumab is administered by subcutaneous injection every 2 weeks for the first month of therapy and every 4 weeks thereafter. Recent follow-up data from the RAPID 1 trial showed that certolizumab pegol, when used in combination with MTX, provides improvements in ACR20 response, physical function, pain, and fatigue in patients with RA within one week and lasting for up to 2 years.<sup>33</sup> Certolizumab also inhibits the progression of joint damage when added to MTX in patients with active RA despite previous single-agent use of MTX.<sup>27</sup> In the FAST4WARD trial, single-agent certolizumab improved the signs and symptoms of RA compared with placebo in patients with active disease despite previous treatment with one or more DMARDs.<sup>34</sup> According to a recent safety analysis, approximately 7.9% of patients report injection site reactions following treatment with certolizumab. Other adverse events are mild to moderate, and together support a favorable benefit-to-risk ratio for certolizumab in the treatment of RA.<sup>35</sup>



## OTHER BIOLOGIC DMARDs

**RITUXIMAB** is a chimeric monoclonal antibody against CD20, a cell marker expressed on B cells. Rituximab has long been used in the management of non-Hodgkin lymphoma (NHL), a B-cell malignancy. Its use for the treatment of RA began when patients with both NHL and RA showed improvement in RA symptoms after treatment with rituximab.<sup>36</sup> Rituximab is FDA-approved for use in combination with MTX for the treatment of RA in patients who have failed therapy with at least one TNF inhibitor. In RA patients, rituximab is administered in two infusions 2 weeks apart, with repeat dosing at least 6 months later. The combination of rituximab and MTX is more effective than either therapy alone in achieving ACR responses.<sup>37</sup> Although up to 40% of patients with RA develop mild to moderate infusion reactions following the first dose of rituximab, the incidence and severity of these reactions decreases with subsequent infusions.<sup>38</sup> The long-term risks of extended B-cell depletion with rituximab therapy are unknown.<sup>38</sup>

**ABATACEPT** is a genetically engineered protein that acts against T cells by blocking a key step in T-cell activation.<sup>39</sup> It is administered by weight-based dosing and intravenous infusion at 0, 2 and 4 weeks, and then every 4 weeks thereafter. This form and frequency of administration has

been shown to increase the risk of infection relative to other biologic DMARDs.<sup>40</sup> Abatacept is FDA-approved for reducing signs and symptoms of RA in adult patients with moderately to severely active RA. Compared with placebo, abatacept has been shown to significantly improve physical function, reduce disease activity and pain, and slow radiographic progression of joint damage for up to 4 years after initial treatment.<sup>41-43</sup> In combination with MTX, abatacept has been found to be more effective than MTX monotherapy in achieving clinical response.<sup>41</sup>

**ANAKINRA** is the only therapy currently available for RA that targets IL-1, a proinflammatory cytokine implicated in synovial inflammation and joint destruction.<sup>44</sup> Anakinra is a humanized recombinant IL-1 receptor antagonist that is given by daily subcutaneous injection. Treatment with anakinra increases the likelihood of achieving an ACR20, ACR50, and ACR70 response relative to placebo. Anakinra also improves other measures, such as health-related quality of life, pain, radiographic progression, and erythrocyte sedimentation rate compared with placebo. Injection-site reactions occur in approximately 70% of patients treated with anakinra.<sup>45</sup>

## WHAT OUR PATIENTS ARE ASKING US

# Considerations for Drug Therapy in RA

## PRESCREENING TESTS

Treatment with TNF inhibitors and other biologic DMARDs increases the risk of new opportunistic infections as well as the reactivation of latent infections.

Before initiating therapy, patients should be screened for the presence of latent viral, bacterial, and fungal infections that may be reactivated in the presence of immune suppression.

## HEPATITIS B AND C SCREENING

Use of immunosuppressive therapy can impair the normal antiviral response by interfering with viral clearance and promoting viral infection.<sup>46,47</sup> Because hepatitis B virus (HBV) persists in the body even after serological recovery from acute hepatitis B, patients who have been exposed to HBV are at risk for reactivation of infection when the immune response is suppressed. Immunosuppressive therapy may also cause flares of hepatitis in patients with HBV or hepatitis C virus (HCV) infection. To address these risks, the ACR recommends HBV and HCV screening before starting immunosuppressive therapy in patients with defined risk factors for hepatitis, such as elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels.<sup>48</sup> The Centers for Disease Control and Prevention (CDC) also recommends screening for HBV markers before initiating immunosuppressive therapy for rheumatologic disorders.<sup>49</sup>

“I have been reading a lot about flu vaccinations, especially with everything that is going on with H1N1 right now. Should I be getting these vaccinations?”

**Joyce Kortan:** In June 2008, the American College of Rheumatology Guidelines Taskforce Panel concluded that patients with RA receiving leflunomide, methotrexate, or sulfasalazine can be immunized with inactive viral vaccines (eg, influenza and pneumococcal) in accordance with Centers for Disease Control and Prevention (CDC) recommendations. The taskforce recommended avoiding live viral vaccine preparations with “all biologic agents,” but provided no directives on whether live vaccines are safe with methotrexate or corticosteroid use.<sup>1</sup>

Seasonal influenza occurs in the United States during the late fall to early spring, and associated morbidity and mortality has led the ACR Hotline to recommend immunization of high-risk groups (children under 2 years of age, adults 50 years or older, patients with a serious medical condition, and compromised immune systems, including people with inflammatory arthritis).<sup>2</sup>

In early 2009, the general public first began to hear widespread reports about the influenza A (H1N1) virus. A trivalent, inactivated vaccine and live, attenuated vaccine are both currently available, although availability is unpredictable in many parts of the United States. According to the CDC, it is recommended that the following prioritized patient groups with inflammatory rheumatic disease receive the 2009 H1N1 vaccine:<sup>3</sup>

- Pregnant women
- People who live with or care for children younger than 6 months of age
- Healthcare and emergency medical services personnel
- Persons between the ages of 6 months and 24 years
- Persons between the ages of 25 and 64 years who are at higher risk for H1N1 because of chronic health disorders or compromised immune systems (including those with inflammatory rheumatic disease)

Individuals aged 65 years and older (including those with inflammatory rheumatic disease) are not included in these prioritized groups as recent studies indicate that the risk of infection among this age group is less than the risk for younger age groups.

Adverse reactions to the H1N1 vaccine are not anticipated to be any different from the influenza vaccine. Importantly, the CDC has indicated that individuals with inflammatory rheumatic disease should not receive the live, attenuated vaccine, which is administered via nasal spray, and should only receive the inactivated vaccine, which contains fragments of killed influenza virus and is given by an injection.

Both the live and inactivated vaccines are manufactured with chicken eggs, and are consequently contraindicated if patients have related allergies. Thimerosal is also used with both vaccines in multi-dose vials and should be avoided in those with related allergies.<sup>1</sup>

Most of our patients should be advised to receive both a seasonal flu shot and the H1N1 flu shot. It is important for rheumatology nurses to remain abreast of CDC updates regarding influenza vaccination, especially as H1N1 spreads and more information on its prevention becomes available.

### REFERENCES

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3. 2009 H1N1 Flu (referred to as “swine flu” early on) and Seasonal Flu Information for Rheumatology Health Professionals. Available at [www.cdc.gov/h1n1flu/arthritis\\_clinicians.htm](http://www.cdc.gov/h1n1flu/arthritis_clinicians.htm). Accessed October 28, 2009.

However, despite these recommendations, screening rates for HBV or HCV are low in many rheumatology clinics. In a study of the Veterans Affairs Rheumatoid Arthritis (VARA) Registry, only 21% of patients were tested for HBV serology and 44% patients were screened for HCV markers.<sup>50</sup>

## TUBERCULOSIS (TB) SCREENING

Treatment with TNF inhibitors is a risk factor for the reactivation of latent TB infection. Among the TNF inhibitors, the risk of TB appears to be higher with monoclonal antibodies (eg, infliximab and adalimumab) than with soluble TNF receptor therapy (eg, etanercept).<sup>51</sup> Although the FDA currently recommends tuberculin screening only for select biologic DMARDs such as infliximab, it is good clinical practice to employ PPD testing before beginning any biologic DMARD therapy.<sup>52</sup> Before initiating TNF inhibitor therapy, all patients should undergo a TB skin test using a standard purified protein derivative (PPD) intradermal injection. Patients with a positive skin test should be treated with daily isoniazid for 9 months concomitantly with TNF inhibitor therapy under the care of a clinician with expertise in TB.<sup>53</sup>

## HISTOPLASMOSIS SCREENING

Histoplasmosis is a disease that primarily affects the lungs and is caused by infection with the *Histoplasma capsulatum* fungus. As with tuberculosis, the majority of individuals exposed to histoplasmosis will develop latent asymptomatic disease, which can be activated by the use of immunosuppressant medications. Currently, no reliable screening tests are available to detect latent histoplasmosis infection. Instead, clinicians in areas endemic for histoplasmosis (eg, places with warm humid soil such as the Ohio River and Mississippi River valleys) should review potential exposures in patients who are candidates for biologic therapy.<sup>52</sup>

Active histoplasmosis infections in patients undergoing treatment with biologic therapy for RA are infrequent, but individual cases have been reported in association with adalimumab,<sup>54</sup> etanercept,<sup>55</sup> and infliximab,<sup>56</sup> and fatal cases do occur.<sup>57</sup> In 2008, the FDA reviewed 241 cases of histoplasmosis among patients taking etanercept, adalimumab, infliximab, or certolizumab. Diagnosis of histoplasmosis was delayed in 21 of the 241 cases, leading to prolonged hospitalizations and 12 deaths. As a result of these findings, the FDA advised makers of these TNF inhibitors to strengthen boxed warnings about the risk of invasive fungal infections, including histoplasmosis.<sup>58</sup> In addition, it is important to be aware of possible signs of disseminated histoplasmosis, such as thrombocytopenia, abnormal liver function, persistent fever, cough, shortness of breath, and fatigue in patients undergoing biologic therapy.<sup>57,58</sup>

## ONGOING SAFETY MONITORING

According to the ACR, ongoing risk surveillance and safety monitoring are important features of RA management.<sup>48</sup> To reduce the risk of contracting new

opportunistic infections, providers should encourage preventive immunizations in patients with RA (Table 1). Influenza and pneumococcal vaccine status should be updated before starting RA therapy, and all live vaccines (eg, varicella-zoster vaccine, oral polio, rabies) are contraindicated during treatment with biologic therapy.<sup>48</sup>

When starting or resuming DMARD therapy, baseline tests should include a complete blood count, liver transaminase levels, and serum creatinine levels. Elevated liver transaminase levels ( $\geq 2$  times higher than normal) are a contraindication to treatment with MTX, leflunomide, and sulfasalazine. Patients receiving these DMARDs should undergo repeated testing every 2–4 weeks for 3 months after the initiation of treatment or dose escalation.<sup>48</sup> Given the risk of retinal toxicity with antimalarial therapy, patients starting treatment with hydroxychloroquine should have a complete ophthalmologic examination within the first year of therapy. Ophthalmologic exams should then be repeated annually for high-risk patients and every 5 years for low-risk patients.<sup>48</sup> Patients may also be referred to an eye expert for follow-up screening during treatment with hydroxychloroquine.

TABLE 1

RECOMMENDATIONS FOR VACCINATIONS IN PATIENTS RECEIVING NONBIOLOGIC AND BIOLOGIC DMARDs FOR RA<sup>48</sup>

AGENT	PNEUMOCOCCUS*	INFLUENZA*	HEPATITIS B†	AVOID LIVE VACCINATIONS
HYDROXY-CHLOROQUINE		X		
LEFLUNOMIDE	X	X	X	
METHOTREXATE	X	X	X	
MINOCYCLINE		X		
SULFASALAZINE	X	X		
ALL BIOLOGIC AGENTS	X	X	X	X

\*Vaccination should be considered in accordance with recommendations of the Centers for Disease Control and Prevention (CDC).  
 †If hepatitis risk factors are present.

## ADHERENCE TO

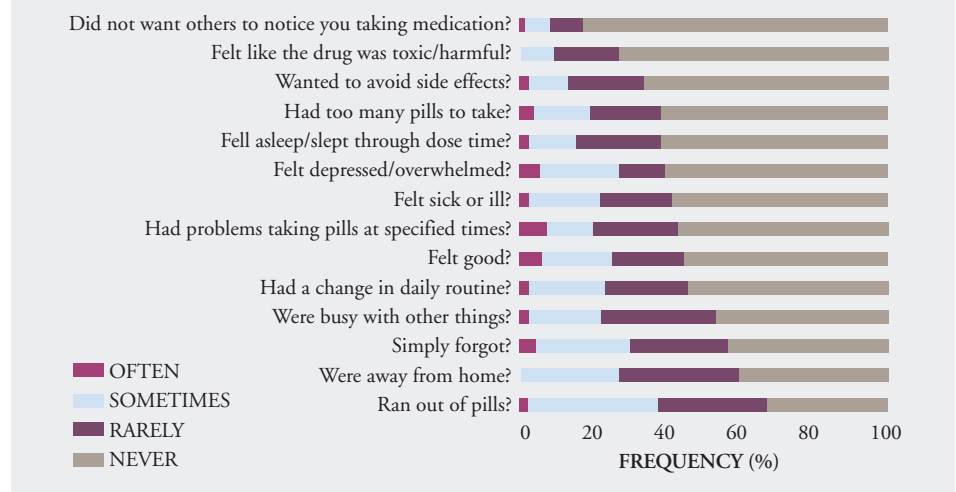
# RA MEDICATIONS

Adherence describes the extent to which patients take medications as prescribed. Many healthcare providers use compliance as an interchangeable term although it is important to recognize that compliance and adherence are not equivalent terms. While adherence indicates the active involvement of a patient in collaborating with a provider to plan and manage a treatment regimen, the connotation of compliance is that a patient is being forced to follow the regime.

Medication adherence is notoriously low in chronic diseases,<sup>59</sup> and RA is no exception. Studies have shown that while RA patients often adhere to treatment plans in the first few months of treatment, adherence rates fall to 60% or lower by the end of the first year of therapy.<sup>60,61</sup> Often, nonadherence to therapy results in unnecessarily high levels of disease activity and loss of function.

Predictors of RA adherence are subtle. One recent study examined several possible reasons for nonadherence to RA medications. In this trial, only one-third of patients reported consistently taking their medications as prescribed. The remaining two-thirds of patients provided a variety of reasons for missing medications, including running out of pills (37%), forgetting (30%), feeling depressed (27%), being away from home (27%), and feeling good (25%) (Figure 1).<sup>61</sup>

In another large study, approximately 40% of RA patients were found to be nonadherent with their DMARD therapy. Longer disease duration, a greater number of perceived side effects, and negative beliefs about the necessity of medication were weakly associated with nonadherence.<sup>60</sup> In some studies, older patients were more

FIGURE 1 REASONS FOR MISSING RA MEDICATIONS<sup>74</sup>

likely than younger patients to stop taking RA medications as prescribed, although in other studies, older age was associated with better medication adherence.<sup>62-64</sup>

Only a few studies have compared adherence with specific agents in RA. In one study of 3,829 patients with RA who were prescribed subcutaneous TNF inhibitors, overall adherence rates ranged from 63% to 73% during the first year of treatment. Patients were more likely to remain adherent to etanercept therapy than adalimumab, in part, perhaps, because of the lower pharmacy and overall costs of etanercept relative to adalimumab.<sup>65</sup>

Cost was also identified as a predictor of long-term adherence to RA therapy in another study of 2,285 patients taking TNF inhibitors. During the first year of treatment, lower out-of-pocket cost (<\$50/week) was associated with better adherence than higher out-of-pocket cost (>\$50/week).<sup>66</sup> Adherence fell over time regardless of cost, but fell more sharply in the group with higher out-of-pocket expenses.<sup>66</sup>

Adherence is particularly important in patients with early RA, when adequate therapy can have a major long-term impact on the natural history of disease. Unfortunately, adherence rates have been shown to be no better in early RA than in other stages of disease. In a study of patients

with early RA, adherence to DMARD therapy dropped from 98% at 2 months to 34% at 2 years. Patients who took their DMARD therapy as prescribed showed lower disease-activity scores, had greater improvements in physical functioning, and had earlier rates of remission than those who were not adherent with their DMARD therapy.<sup>62</sup> The link between adherence and clinical outcomes has also been seen elsewhere. In the VARA registry, patients with RA who were adherent with MTX therapy had lower disease activity, as shown by significantly lower DAS28 scores and erythrocyte sedimentation rates, compared with those who did not take their MTX as prescribed.<sup>67</sup>

Treatment algorithms in RA suggest adding additional medications or switching to new therapies in patients who do not appear to respond to prescribed treatment. However, findings from adherence studies reinforce the importance of evaluating whether patients are taking their current medications as prescribed before regimens are modified. Since reasons for nonadherence vary from patient to patient, rheumatology nurses may want to consider openly discussing adherence, including beliefs about therapeutic effectiveness, concerns about side effects, and other potential barriers, to encourage patients to continue therapy as prescribed.

# RA MEDICATIONS & PREGNANCY

Women are twice as likely as men to develop RA, and, in both sexes, the incidence of RA steadily increases after age 18.<sup>8</sup> As more women in the United States postpone pregnancy until the third or fourth decade of life, a greater proportion of women with RA will become pregnant after the onset of disease. Interestingly, the physiological changes of pregnancy are associated with an improvement in disease activity for many women.<sup>68</sup> Still, as many as 50% of pregnant RA patients will require some form of drug therapy to control their RA symptoms during pregnancy.<sup>69</sup>

Women with RA do become pregnant and they do successfully give birth to healthy children. It is important for rheumatology nurses to talk with their patients taking RA medications to weigh the risks and benefits of becoming pregnant. Drugs that have not been proven safe for the fetus (teratogens) should be discontinued before pregnancy. The FDA requires that all medications be categorized by risk to assist with pregnancy decisions. Medications are characterized as follows:<sup>70</sup>

- **CATEGORY A.** Controlled clinical studies in humans have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and no evidence exists suggesting risk in later trimesters.
- **CATEGORY B.** Reproduction studies in animals have failed to demonstrate evidence of impaired fertility or harm to the fetus. However, no controlled clinical studies have been conducted in humans.
- **CATEGORY C.** Reproduction studies in animals have either not been performed or have demonstrated evidence of impaired fertility or harm to the fetus. However, the benefit of the drug may still outweigh its risk.
- **CATEGORY D.** Adverse reaction data in human investigational trials or marketing experience has been demonstrated. However, the benefit of the drug may still outweigh its risk, especially in emergency presentations.
- **CATEGORY X.** Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both. The risk of using the drug clearly outweighs any possible benefit. MTX is an example of a Category X drug.

Recently, an expert consensus panel developed an algorithm for the management of women with RA who are interested in becoming pregnant (Figure 2).<sup>69</sup> In patients with stable or mild-to-moderate disease activity, therapy should be adjusted from drugs that are incompatible with pregnancy to compatible drugs (Table 2). For women with early RA or with active and uncontrolled disease, pregnancy should preferably be postponed until patients achieve remission or substantial improvement in disease activity. Once RA is stable, and after a switch to a drug compatible with pregnancy, women can attempt to conceive.<sup>69</sup>

Regardless of disease activity, treatment with TNF inhibitors should be discontinued as soon as pregnancy is recognized, owing to a lack of data on the long-term effects of exposure during pregnancy. Other agents, including chloroquine, hydroxychloroquine, sulfasalazine, azathioprine and cyclosporin, are better alternatives during pregnancy. Many patients choose to discontinue use of all DMARDs and rely on corticosteroids, NSAIDs and analgesics to manage RA symptoms during pregnancy.<sup>69</sup>

In many patients, disease activity flares quickly during the postpartum period. Up to 90% of women will experience a postpartum flare of RA symptoms within the first three months of delivery, particularly after their first pregnancy.<sup>71</sup> Thus, many experts recommend restarting RA medications in the first few weeks after delivery.<sup>69</sup>

Despite clear recommendations against the use of certain medications before and during pregnancy, women are frequently given potentially teratogenic medications without contraceptive counseling.<sup>72</sup> One recent study of contraceptive counseling practices in a rheumatology clinic included 90 women who were taking approximately 40 different medications, including 4 pregnancy category X drugs and 6 pregnancy category D drugs. Among the 90 patients, 6 conceived while taking potentially teratogenic medications. Only 4 of these 6 patients were counseled on contraception before conceiving.<sup>72</sup>

**FIGURE 2**  
TREATMENT ALGORITHM FOR PATIENTS WITH RA PLANNING A PREGNANCY<sup>69</sup>

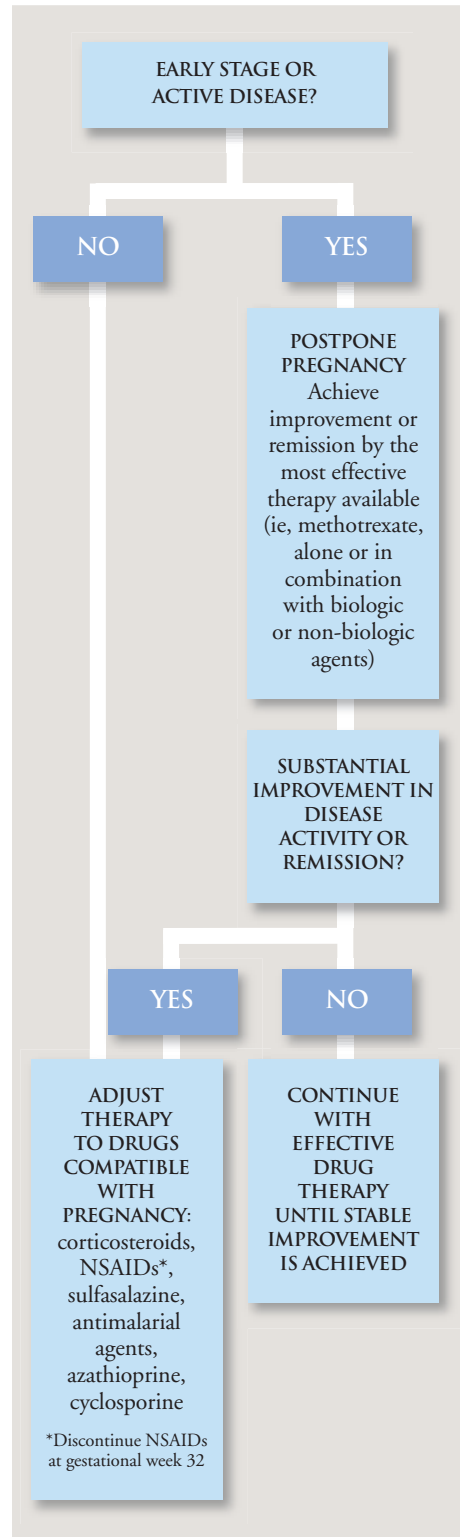




TABLE 2

ANTIRHEUMATIC DRUGS AND BIOLOGIC AGENTS DURING PREGNANCY<sup>69</sup>

DRUG	PREGNANCY CATEGORY	RECOMMENDATION
<b>INCOMPATIBLE WITH PREGNANCY</b>		
METHOTREXATE	X	DISCONTINUE 3 MONTHS BEFORE PREGNANCY
LEFLUNOMIDE	X	DISCONTINUE WHEN PLANNING PREGNANCY AND WASHOUT BEFORE PREGNANCY
ABATACEPT	C	DISCONTINUE 10 WEEKS BEFORE PREGNANCY
RITUXIMAB	C	DISCONTINUE 12 MONTHS BEFORE PREGNANCY
INFLIXIMAB	B	DISCONTINUE AT MISSED PERIOD OR AFTER A POSITIVE PREGNANCY TEST
ETANERCEPT	B	DISCONTINUE AT MISSED PERIOD OR AFTER A POSITIVE PREGNANCY TEST
ADALIMUMAB	B	DISCONTINUE AT MISSED PERIOD OR AFTER A POSITIVE PREGNANCY TEST
CERTOLIZUMAB PEGOL	B	DISCONTINUE AT MISSED PERIOD OR AFTER A POSITIVE PREGNANCY TEST
GOLIMUMAB	B	DISCONTINUE AT MISSED PERIOD OR AFTER A POSITIVE PREGNANCY TEST
ANAKINRA	B	CONTINUE ONLY IF CLEARLY NEEDED
<b>COMPATIBLE WITH PREGNANCY</b>		
SULFASALAZINE	B/C	SULFASALAZINE, AT A DOSE OF 2 G PER DAY, MAY BE GIVEN THROUGHOUT PREGNANCY, BUT REQUIRES FOLIC ACID SUPPLEMENTATION
ANTIMALARIAL THERAPY	C	ANTIMALARIALS CAN BE REGARDED AS SAFE FOR THE FETUS, THOUGH HYDROXYCHLOROQUINE IS PREFERRED OVER CHLOROQUINE.

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# ACTIVITY LEARNING ASSESSMENT REQUEST FOR CREDIT & EVALUATION FORM

## ACTIVITY INSTRUCTIONS & CRITERIA FOR SUCCESS

Continuing Nursing Education contact hours are offered to all activity participants. To successfully complete this activity and obtain a Certificate of Contact Hours awarded, the learner is required to read the entire newsletter, complete the post-test, and complete the activity evaluation form. Learners are required to correctly answer 70% of the post-test questions. Statements of Credit will be forwarded via regular mail within 4 to 6 weeks. All forms must be received by December 15, 2011, to be eligible for CE credits.

1. Please fax both sides of this evaluation to ICHE at (215) 592-9085, *OR*
2. Please complete the evaluation online by going to [www.iche.edu](http://www.iche.edu) and clicking on **Enduring Materials**.

NAME \_\_\_\_\_

DEGREE/CERTIFICATION \_\_\_\_\_

## ACTIVITY POST-TEST QUESTIONS

*Please circle the letter that matches the correct response to each question below.*

1. Which DMARD is most commonly selected by U.S.-based rheumatologists as a first-line agent for the treatment of RA?
  - a. Hydroxychloroquine
  - b. Abatacept
  - c. Methotrexate
  - d. Etanercept
2. Which of the following biologic agents have been shown to be safe and efficacious when combined to treat RA?
  - a. Infliximab and rituximab
  - b. Adalimumab and golimumab
  - c. Certolizumab pegol and abatacept
  - d. None of the above
3. According to the FDA, how many TNF inhibitors must an RA patient fail before being prescribed either rituximab or abatacept?
  - a. 1
  - b. 2
  - c. 3
  - d. 4 or more
4. Approximately what percentage of pregnant women with RA will require drug therapy during their pregnancy?
  - a. 25%
  - b. 50%
  - c. 75%
  - d. 90%
5. According to recommendations from the Centers for Disease Control and Prevention, RA patients receiving methotrexate should receive which of the following vaccinations?
  - a. Pneumococcus
  - b. Influenza
  - c. Hepatitis B
  - d. All of the above
6. Of the following agents, which would be the best choice to prescribe to a pregnant patient with RA?
  - a. Sulfasalazine
  - b. Methotrexate
  - c. Golimumab
  - d. Leflunomide
7. Which of the following have been identified as common reasons why patients with RA do not adhere to prescribed medication plans?
  - a. They do not understand the prescribed treatment regimen
  - b. They cannot afford the cost of the prescribed treatment regimen
  - c. They disagree with the regimen prescribed for them by their provider
  - d. All of the above
8. Which formulation of the H1N1 vaccine is recommended for patients with RA?
  - a. The live, attenuated vaccine, which is administered via nasal spray
  - b. The inactivated vaccine, which contains fragments of killed influenza virus and is given by injection
  - c. Either of the vaccines are appropriate for patients with RA
  - d. Neither of the vaccines are appropriate for patients with RA
9. An ophthalmologic examination is recommended for RA patients using which of the following agents?
  - a. Methotrexate
  - b. Certolizumab pegol
  - c. Hydroxychloroquine
  - d. Rituximab
10. According to CDC recommendations, which of the following prioritized patient groups should receive the 2009 H1N1 vaccine?
  - a. Pregnant women
  - b. People who live with or care for children younger than 6 months of age
  - c. Healthcare and emergency medical services personnel
  - d. All of the above

The learning objectives designed for this activity (listed below), can help me strive toward:	Nothing at this time	Reinforcement of current practices	Moderate Improvement	Significant Improvement
1. Discuss the mechanism of action of biologic agents commonly used to treat rheumatoid arthritis (RA)	1	2	3	4
2. Determine the safety of commonly used disease-modifying antirheumatic drugs (DMARDs) for the treatment of RA in women of childbearing age	1	2	3	4
3. Develop strategies to help overcome common barriers that limit patient adherence to treatment regimens	1	2	3	4
4. Identify current patient groups who should receive a recommendation to receive influenza vaccination, including vaccination for H1N1	1	2	3	4

Please indicate the extent of your agreement with the following statements:	Strongly Disagree		Not Sure		Strongly Agree	
1. The information presented in this newsletter was pertinent to my professional needs	1	2	3	4	5	6
2. The content of this newsletter provides valuable information that will assist me in improving patient outcomes	1	2	3	4	5	6
3. Based on my experience, I would recommend future newsletters to my colleagues	1	2	3	4	5	6
4. Were you able to locate information about faculty disclosure at the beginning of the newsletter?	YES				NO	
5. Did you perceive any bias or commercial influence in the newsletter? If so, your help in identifying it is appreciated: _____	YES				NO	

6. How many women of childbearing age do you currently see each month as RA patients?

- a. Less than 5
- b. 5–15
- c. 15–25
- d. More than 25

7. How carefully do you consider potential teratogenic risk when discussing therapeutic options with your female patients of childbearing age?

- a. Not carefully
- b. Somewhat carefully
- c. Carefully
- d. Very carefully

8. The following is the primary barrier to implementing change at my facility:

- a. Lack of knowledge regarding evidence-based strategies
- b. Misperceptions of or negative attitudes about research and evidence-based care
- c. Demanding patient workloads
- d. Fears about practicing differently from peers

For purposes of certification, please complete the following information. Please note that the Institute will not forward or sell your name to any lists. PLEASE PRINT CLEARLY.

Number of credits claimed \_\_\_\_\_ (Maximum credits=1.2 ANCC-COA contact hours/1.5 California Board of Nursing contact hours)

First Name \_\_\_\_\_ Middle Initial \_\_\_\_\_ Last Name \_\_\_\_\_

Confirm certification types here  RN  NP  CNS  CRNA  CNM  LPN  Other \_\_\_\_\_

Your certificate will be mailed to the address you list below.

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I certify that I have participated in the above-named continuing-education activity.

Signature \_\_\_\_\_ Date \_\_\_\_\_

We are interested in adding to our base of faculty and educational development. To help us better plan for education in this area, and to invite you to participate in future educational development, we may contact you for your expertise. If you opt NOT to be contacted, please check here:



## MY MOST *Memorable* PATIENT...

BY NICOLE FURFARO

I HAVE BEEN WORKING WITH ARTHRITIS PATIENTS FOR MORE THAN 15 YEARS, AND THROUGHOUT THIS TIME, I HAVE BEEN FORTUNATE TO MEET A NUMBER OF INDIVIDUALS WHO HAVE TOUCHED ME DEEPLY WITH THEIR STORIES OF SUCCESS AND FAILURE, WHO HAVE OFFERED SUPPORT TO OTHERS WHILE STRUGGLING WITH THEIR OWN DISEASE, AND WHO CONTINUE WORKING TOWARD THEIR LIFE GOALS AFTER BEING THROWN A MEDICAL CURVEBALL.

My patient, Judi, is one of those inspiring individuals who embody everything that keeps us going in our careers. When French author Alphonse Karr wrote, *“Some people are always grumbling because roses have thorns; I am thankful that thorns have roses,”* he may very well have been writing about Judi.

Judi was initially diagnosed with rheumatoid arthritis (RA) in 1996 when her life was going full throttle. She was a busy executive raising a daughter, and developing a chronic medical condition wasn't even a possibility in her mind. So, when she developed morning stiffness and joint pain on a daily basis, she ignored it and did her best to continue living in the manner in which she was accustomed. Eventually though, as fatigue and pain made working increasingly difficult, she could no longer ignore her symptoms and she made many significant lifestyle changes, including a complete overhaul of her diet. To this day, Judi says that she feels that changing her eating habits improved her symptoms by about 75%.

Eventually, Judi did see a rheumatologist, who diagnosed her as having RA. She was initially started on methotrexate, but she was unable to tolerate the medication even in low doses. Fortunately, she had a much better response to infliximab, and by the time I met her 6 years later, she was able to do everything she had done before being diagnosed with RA.

Instead of giving in to depression and fatigue as so many of our patients do, Judi has managed to take the adversities and turn them into personal motivators.

Judi recently traveled from Seattle to Washington, D.C., where she joined 17 other RA advocates from around the country for the Arthritis Foundation Healthcare Reform Fly-in. She spent days meeting with congressional and senatorial representatives speaking to them about the importance of affordable healthcare. She specifically emphasized the importance of preventive care and the need to provide reimbursement coverage for the early use of biologics in chronic diseases such as RA to prevent long-term disability and joint replacement.

Judi works diligently with our local chapter of the Arthritis Foundation and chaired last year's local gala event and auction fundraiser. She again served as the chair for this year's "Bone Bash" gala that took place just before Halloween.

Judi is among those fortunate individuals who were diagnosed early with RA and started aggressive treatment with biologics to control their disease while it was still manageable. It is often those patients who feel the need to "give back" to ensure that future patients have the same access to high-quality, affordable care that they did. Patient advocates are a wonderful resource that all rheumatology nurses should take advantage of in demonstrating to our new patients that a diagnosis of RA does not have to end their way of life. This is a disease that can, especially as better and more plentiful therapeutic options reach the marketplace, be successfully managed for many years.



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