

RHEUMATOLOGY NURSE NEWSLETTER



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

Initial release date: July 1, 2011
CE available until: July 1, 2012

Educational Planning Committee

KORI A. DEWING, DNP, ARNP

Nurse Practitioner
Virginia Mason Medical Center
Seattle, Washington

JACQUELINE FRITZ, RN, MSN, CNS

Medical Advancement Center
Critical Care and Rheumatology Specialist
Cypress, California

NICOLE M. FURFARO, MSN, ARNP

Nurse Practitioner
Rheumatology and Internal Medicine
Seattle Rheumatology Associates
Seattle, Washington

JOYCE M. KORTAN, RN

Clinic Nurse Manager
Arthritis and Rheumatology Consultants, PA
Edina, Minnesota

VICKY RUFFING, RN

Nurse Manager
Johns Hopkins Arthritis Center
Johns Hopkins University
Baltimore, Maryland

Inside this Issue

- What do recent screening guidelines suggest to prevent the possibility of hydroxychloroquine retinopathy?
- Why does methotrexate behave differently in patients with rheumatoid arthritis (RA) compared to those with cancer?
- How do antidrug antibodies predict why some patients fail to respond or lose response to biologic disease-modifying antirheumatic drugs (DMARDs)?
- What new drug pathways are under investigation for the treatment of RA?

Learning Objectives

1. Evaluate the appropriate utilization of traditional DMARDs, such as methotrexate, sulfasalazine, and hydroxychloroquine, in current RA treatment regimens
2. Assess the impact of recently released “treat to target” guidelines on the overall care of patients with RA
3. Describe the potential role of late-stage agents under investigation for the treatment of RA

RHEUMATOLOGY NURSE IS ONLINE!

Visit www.iche.edu/content/rheumatology-nurse-newsletter

to access a PDF of this newsletter and take the post-test electronically!



Like us on facebook. Search for “Rheumatology Nurse Newsletter”



Rheumatology
Nurses Society

Provided as an educational service of

the
Institute
for Continuing Healthcare Education



Accreditation Statement

The Institute for Continuing Healthcare Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity offers 1.5 contact hours to participating nurses. This credit may be applied toward licensure requirements in those states that recognize American Nurses Credentialing Center's Commission on Accreditation (ANCC-COA) accredited providers.

Accreditation applies solely to educational activities and does not imply approval or endorsement of any commercial product by the ANCC-COA.

The Institute for Continuing Healthcare Education is approved by the California Board of Registered Nursing, Provider Number 13313. The Institute for Continuing Healthcare Education approves this activity for 1.8 contact hours.

Jacqueline Fritz, RN, MSN, CNS, is the nurse planner for this activity.

Disclosure

It is the policy of the Institute for Continuing Healthcare Education (the Institute) that the education presented within Institute-provided, CNE-certified activities be unbiased and based upon scientific evidence. To help participants make judgments about the presence of bias, the Institute provides information that planners, teachers, authors, developers, and activity managers have disclosed about financial relationships they have with commercial entities that produce or market products or services related to the content of this educational activity. Any relationships that an individual may have with commercial entities have been disclosed and reviewed, and any potential conflicts have been resolved.

Relationships are abbreviated as follows: E, Educational planning committee; G, Grant/research support recipient; A, Advisor/review panel member; C, Consultant; S, Stock shareholder; SB, Speaker bureau; PE, Promotional event talks; H, Honorary; O, Other.

Kori A. Dewing, DNP, ARNP, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Jacqueline Fritz, RN, MSN, CNS, has disclosed the following relevant financial relationships that have occurred within the past 12 months: Novartis, Genentech, Inc., Amgen, Pfizer/SB, Bard, Johnson & Johnson, Statlock/PE.

Nicole M. Furfaro, MSN, ARNP, has disclosed the following relevant financial relationships that have occurred within the past 12 months: Genentech, Inc., Bristol-Myers Squibb/SB.

Joyce M. Kortan, RN, has disclosed the following relevant financial relationships that have occurred within the past 12 months: UCB/A, SB; Centocor/A, H; Roche/A; American College of Rheumatology/H; Genentech, Inc., Novartis/H, SB; Amgen, Wyeth, Bristol-Myers Squibb/SB.

Vicky Ruffing, RN, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Content Freelancer

Anne Jacobson, MPH, CCMEP, Medical Writer, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Content Peer Reviewer

This newsletter was reviewed by Deanna Harris, RN, BSN. Ms. Harris has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content included in this educational activity.

Activity Development and Management Team

Cathy Pagano, CCMEP; Sandra Davidson; Christine M. O'Leary, PharmD, BCPS, CCMEP; Karen Thomas, CCMEP; Scott Kober, CCMEP; April Reynolds, MS, ELS; Courtney Cohen; Tina Chiu, MEd; and Melissa Schepacarter, CMP, are employees of the Institute and are collectively responsible for the planning, development, and management of this CNE activity. These individuals have disclosed that they have had no relevant financial relationship specific to the subject matter of this activity that have occurred within the past 12 months. Shunda R. Irons-Brown, PhD, MBA, CCMEP, also an employee of the Institute, has disclosed the following relationships: Merck & Co./S; Bristol-Myers Squibb, GlaxoSmithKline/O.

Off-Label/Investigational Use Disclosure

Off-label and/or investigational uses of the following agents are discussed within the literature of this enduring activity: tofacitinib, INCB028050, fostamatinib, belimumab, atacicept, ALD518, CAT6001, MEDI-571, MEDI5117.

What's New in the Treatment of Rheumatoid Arthritis?

With the steady flow of new clinical evidence, updated treatment algorithms, and emerging therapies, standards of care for patients with rheumatoid arthritis (RA) are constantly evolving. Advances have arisen not only in the form of new treatments, but also in the better use of therapies that have been on the shelves in rheumatology clinics for decades. Rheumatology nurses should be aware of new trends in RA treatment, including the optimal use of synthetic and biologic disease-modifying antirheumatic drugs (DMARDs).

A NEW LOOK AT OLD FRIENDS

Methotrexate

Even in the era of biological disease-modifying antirheumatic drugs, methotrexate (MTX) remains the preferred first-line therapy for patients with early RA. According to the European League Against Rheumatism (EULAR) 2010 guidelines for the management of RA, MTX should be the foundation of treatment for all patients without contraindications to the medication. Once a diagnosis of RA is confirmed, treatment should begin with single-agent MTX and expand to include combination therapy with add-on synthetic or biological DMARDs in patients with residual disease activity after 3 to 6 months.¹

SMOKING AND MTX RESPONSE

Smoking is a well-established risk factor for RA that also appears to interfere with responsiveness to standard RA treatment. In a study of patients with early RA, 36% of current smokers failed to have an adequate reduction in disease activity after 3 months of MTX, compared with 27% of patients who never smoked.² Current smokers were also less likely than never smokers to respond to tumor necrosis factor (TNF) inhibitors (43% vs. 29%). In one promising finding, smoking cessation was able to restore treatment responsiveness to MTX and TNF inhibitors. Former smokers — those who successfully quit smoking before starting RA treatment — responded equally well to treatment with MTX or TNF inhibitors as those who had never smoked.² This underscores the importance of screening RA patients for smoking habits and encouraging current smokers to quit.

MTX DOSING

Many patients with RA do not achieve the full benefits of MTX because of suboptimal dosing, inadequate titration, or both. In a meta-analysis of 38 clinical trials, higher starting doses of MTX (25 mg/week) were more effective than lower starting doses (5-15 mg/week) in controlling the signs and symptoms of RA. Faster dose escalation (5 mg/month) was also more effective than slower dose escalation (5 mg every 3 months). However, higher starting doses and faster dose escalation were also associated with more gastrointestinal (GI) side effects, so the risk/benefit of this approach must be carefully weighed. Thus, the goal of therapy should be to achieve high doses of MTX (25-30 mg/week) as quickly as possible, but in a schedule adapted to individual tolerability. Treatment with leucovorin or other forms of folic acid supplementation can increase the tolerability of high-dose MTX. In the meta-analysis, the mean tolerable dose of oral MTX was 17-20 mg/week.

SUBCUTANEOUS VS. ORAL MTX

Although current RA guidelines recommend starting most patients on oral MTX, there is renewed interest in the potential benefits of subcutaneous MTX. When administered at the same dose, subcutaneous MTX is associated with better clinical outcomes than oral MTX.^{3,4} Moreover, switching from oral MTX to same-dose subcutaneous MTX provides significant additional reduction in disease activity, particularly among patients with intolerance to oral MTX.⁵ Current evidence supports switching to subcutaneous MTX in patients with an insufficient response to the highest tolerable dose of oral MTX (up to 25-30 mg/week).³



Methotrexate: From Anti-Cancer Treatment to Cornerstone of RA Therapy

Since gaining approval for the treatment of RA in 1988, MTX has become the most widely used drug in rheumatology practices. Yet even after decades of use in RA, MTX continues to be stigmatized as a ‘cancer drug’ by patients and clinicians. However, with different dose intensities that result in different mechanisms of action and different safety profiles, the use of MTX in cancer vs. its use in RA leads to “two different drugs in practical terms.”¹¹

Oncologists began using MTX in 1948, first to treat childhood acute leukemia and later to treat other blood cancers and solid tumors. The average dose used to treat cancer is 1 g/m² (range, 500 mg/m² to 33.6 g/m²), or approximately 1.73 g per cycle for a 5-foot-5, 140-pound woman. At this dose, MTX acts as an anti-folate drug and inhibits dihydrofolate reductase (DHFR), an enzyme critical to folate metabolism. With depleted folate levels, cells cannot produce enough thymidine and purine to maintain DNA, RNA, and protein synthesis. Thus, high-dose MTX kills not only rapidly proliferating cancer cells, but also cells in the bone marrow, mucosa, and hair follicles. This anti-proliferative activity accounts for the side effects associated with high-dose MTX in cancer treatment, including myelosuppression, infection risk, nausea, vomiting due to gastrointestinal mucositis, and alopecia.¹¹

Treatment goals are different in rheumatology, where clinicians exploit the anti-inflammatory effects of low-dose MTX. In rheumatology, the typical dose range for MTX is 7.5-30 mg once weekly – several times lower than the doses used in oncology. At this dose, MTX is thought to inhibit pathways associated with adenosine metabolism, resulting in excess adenosine. Elevated adenosine concentrations then down-regulate inflammation by suppressing pro-inflammatory cytokines such as TNF and interleukin-6 (IL-6), IL-8, and IL-12, and stimulating anti-inflammatory cytokines such as IL-10. In these low-dose ranges, MTX has a mild side-effect profile that includes minor GI symptoms, transient elevations in liver enzymes, and a low risk of hematological toxicity.¹¹

MTX is one of many drugs used at different doses to achieve diverse therapeutic effects. High-dose aspirin (3-4 g/day) is used to manage pain and inflammation, whereas low-dose aspirin (75-325 mg/day) is used to prevent platelet aggregation in individuals at risk for cardiovascular disease. In the case of MTX, the drug behaves so differently at the rheumatologic and oncologic dose ranges that some experts are urging for low-dose and high-dose MTX to have separate pharmacologic names.¹¹ Understanding the history of MTX as an anti-cancer drug as well as its distinct activity in RA can help rheumatology nurses reassure patients with concerns about taking MTX.

Hydroxychloroquine

The antimalarial agents chloroquine and hydroxychloroquine (HCQ) have immunomodulatory and anti-inflammatory properties that are useful in the management of rheumatic diseases.⁶ Compared with other DMARDs, antimalarial drugs have a less prominent role in current RA treatment guidelines because they do not appear to provide sufficient protection from structural damage, particularly in patients with moderate or severe disease activity and in comparison with sulfasalazine (SSZ).¹ However, given its favorable safety profile, HCQ has a role in the management of patients with very mild disease who have contraindications to other first-line therapies.¹ As an FDA pregnancy class C medication, HCQ is one of the safest DMARDs in pregnancy.⁷

NEW RETINOPATHY SCREENING GUIDELINES

Retinal toxicity is the most feared side effect of antimalarial therapy, but this occurs very rarely with HCQ when appropriate dosing and routine eye exams are employed. In 2011, the American Academy of Ophthalmology (AAO) issued updated recommendations for the management of chloroquine and HCQ retinopathy. The 2011 AAO guidelines recommend baseline screening to rule out maculopathy, which is a contraindication to antimalarial use. Additional recommendations include the following⁸:

- Rather than weight-based dosing, most patients should be given 400 mg HCQ daily. To avoid overdosage, patients of short stature should receive lower doses (6.5 mg/kg) based on ideal body weight.
- Annual ophthalmic screening to detect early retinal changes should begin after 5 years. It should begin earlier if patients have unusual risk factors such as underlying retinal disease.
- Patients should be instructed to report any new visual symptoms, including reduced visual sensitivity, reading difficulty, or blind spots, as well as new retinal disease or changes in overall health status, such as major weight loss or kidney/liver disease.
- Prolonged or excessive exposure to HCQ should be avoided, given that the risk of toxicity increases to approximately 1% after 5-7 years and/or a cumulative dose of 1000 g.

OTHER SYNTHETIC DMARDs

Leflunomide and SSZ are also commonly used in the treatment of RA. Although each of these appears to be as effective as first-line MTX, the greater weight of evidence supporting MTX has pushed leflunomide and SSZ into the second tier of synthetic DMARD therapies.^{1,9}

As the popularity of MTX has grown over the last 2 decades, treatment with other synthetic DMARDs has fallen. For instance, the use of SSZ in patients with RA dropped from 60% in 1998 to 16% in 2008.¹⁰ Across the same time period, MTX use grew from 5% to 62%.¹⁰ In the 2010 EULAR guidelines, leflunomide, SSZ, and parenteral gold are included as alternative first-line agents in patients with contradictions or intolerance to MTX.¹

CURRENT RA TREATMENT TRENDS

New RA Classification Criteria

In 2010, the ACR and EULAR published new classification criteria for RA that facilitate diagnosis earlier in the disease process.¹² Prior to this update, the classification of RA was based on criteria established by the ACR in 1987, an era when the importance of early treatment was not well recognized.¹³ Indeed, the 1987 criteria were focused on patients with established RA of several years¹

duration and were intended to differentiate RA from other chronic rheumatic diseases, including osteoarthritis, psoriatic arthritis, and systemic lupus erythematosus.¹³ The 2010 ACR/EULAR criteria, however, are focused on identifying early RA, when treatment may have the greatest beneficial effect.¹²

According to the 2010 ACR/EULAR criteria, classification as “definite RA” requires all of the following¹²:

- Confirmed synovitis in 1 or more joints
- Absence of another diagnosis to explain the synovitis (eg, lupus or gout)
- Total score of ≥ 6 (out of 10) from the individual scores in 4 domains:
 - Number and site of involved joints (range, 0-5)
 - Serologic abnormality (range, 0-3)
 - Elevated acute-phase response (range, 0-1)
 - Symptom duration (range, 0-1)

In a recent study, Cader and colleagues applied the 2010 ACR/EULAR and 1987 ACR classification criteria to a sample of 265 patients with RA. The 2010 criteria identified 62% of patients who required treatment with DMARD therapy within 18 months. By comparison, the 1987 criteria identified only 38% of these patients. Although more aggressive criteria for the diagnosis of RA increase the potential for overdiagnosis — diagnosing and treating patients with RA whose symptoms would resolve without intervention — the overall risk is low. Only 8% and 2% of patients classified as having RA based on the 2010 and 1987 criteria, respectively, saw their symptoms resolve without ever requiring DMARD therapy.¹⁴

What are my chances of developing cancer due to this medication?

This is one of the most frequent questions I am asked during biologic education classes I hold with my patients. While they are hoping for a clearer black and white answer, the best that I can tell them is that evidence remains inconclusive linking biologics and most cancer subtypes. However, there is evidence indicating that patients with RA, irrespective of their treatment regimen, have a higher risk of developing certain types of lymphoma. Based upon data from Baecklund, high inflammatory activity may be the driving force for lymphoma development,¹ but at the present time we are unable to determine what amount of inflammatory activity increases lymphoma risk.

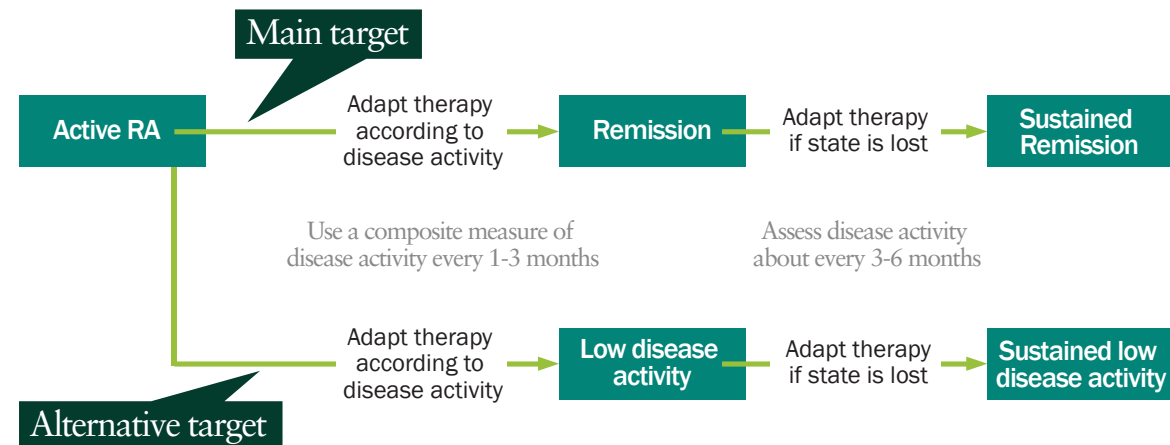
In August 2008, the FDA announced that it was requiring manufacturers of TNF inhibitors to update their boxed warnings to alert healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with these agents. The FDA also mandated that the warning section be updated to include a description of reported cases of leukemia in adults, adolescents, and children. These updates were based on the initial analysis of the association between TNF inhibitors and lymphoma in children and adolescents as well as a subsequent analysis of TNF inhibitors and postmarketing leukemia in all patients.²

Links between TNF inhibitors and other forms of cancer have also been studied in clinical trials. In 2007, Wolfe et al reviewed a large observational database to measure the risk of malignancies in patients treated with biologic therapy. They reported an association between biologic therapy and skin cancer, but no association with solid tumors or lymphoproliferative malignancies. These links were consistent irrespective of the biologic agent used.³ —**Joyce M. Kortan, RN**

REFERENCES

1. Baecklund E. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum.* 2006;54:692-701
2. FDA: Cancer Warnings Required for TNF Blockers. Available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm>. Accessed May 22, 2011.
3. Wolfe, F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum.* 2007;56:2886-2895.



FIGURE 1 TREAT TO TARGET ALGORITHM¹⁸

In current practice, diagnosis and treatment of RA are often delayed, with damaging results. In one recent study, 69% of patients with RA waited 12 weeks or longer after symptom onset to be assessed by a rheumatologist. Compared to patients who had received a timely referral (<12 weeks from symptom onset), delayed assessment by a rheumatologist increased the risk of not achieving DMARD-free remission by 87%. Delayed referral also increased the risk of joint destruction over 6 years by 30%. Certain patients were at especially high risk of delayed referral and, as a consequence, poorer outcomes. These included older patients, women, those with gradual symptom onset, and those whose symptoms involved small joints.¹⁵ Delays in referral to a rheumatologist can result in patients being seen past the ideal window of opportunity for treatment, which is now considered to be within a few months of symptom onset.¹⁶ The new RA classification criteria, which are meant to capture patients at the earliest stages of disease, may shorten the delay to timely care.

The benefits of an early treatment strategy are clear — identifying patients with the earliest stages of RA expedites treatment and gives patients the best chance for remission. The IMPROVED (Induction Therapy With Methotrexate and Prednisone in Rheumatoid or Very Early Arthritic Disease) study enrolled 261 patients with the earliest signs of RA. Upon entering the study, patients had RA symptoms for a median duration of 4 months and mean disease activity score (DAS) of 3.4. All patients began treatment with MTX 25 mg/week plus prednisone 60 mg/week, tapered over 7 weeks to 7.5 mg/day. After 4 months, 58.6% of RA patients achieved remission, defined as DAS <1.6. Patients with lower disease activity at baseline were able to achieve remission earlier. According to the IMPROVED study authors, the strategy of very early intervention dramatically improves remission rates in RA. In previously published reports, comparable remission rates for patients with more active disease are less than 30%.¹⁷

Treat-to-Target Strategy

With a new treat-to-target strategy, RA joins the ranks of other major chronic diseases with clearly defined treatment goals, including hypertension (blood pressure <140/80 mm Hg) and diabetes (glycosylated hemoglobin <7.0%). Patients with RA should now be treated with the primary goal of achieving clinical remission, defined as the absence of signs and symptoms of significant disease activity (Figure 1).¹⁸ In 2010, the international treat-to-target (T2T) task force described four overarching principles that should guide RA management¹⁸:

1. RA treatment must be based on shared decisions by patients and rheumatologists
2. The primary goal of RA treatment is to maximize long-term health-related quality of life through symptom control, prevention of structural damage, and normalization of physical and social functioning
3. Eliminating inflammation is the most important method for reaching these treatment goals
4. The treat-to-target strategy requires measuring disease activity and adjusting therapy accordingly to optimize outcomes

Recognizing that complete remission may not be possible for all patients, the T2T task force set “low disease activity” as an acceptable alternative goal for individuals with longstanding disease, considerable joint damage, and several prior treatment failures. Regardless of specific treatment target, drug therapy should be adjusted every 3 months until the desired goal is reached. This may include modifying the dose of existing therapy, switching medications, or adding another agent to the current regimen. Once the RA treatment goal is achieved – clinical remission for most patients, low disease activity for others – this

state should be maintained continuously with ongoing drug therapy. Only sustained remission can prevent further joint damage, whereas any increase in disease activity can restart the process of joint destruction.¹⁸

To guide treatment decisions, disease activity should be routinely measured and documented on a schedule that increases with more intense disease activity. For instance, patients with moderate-to-high disease activity may require monthly evaluation, whereas those with sustained low disease activity or remission may require evaluation as infrequently as every 3 to 6 months. The T2T task force recommended using validated composite measures that include joint assessments, such as the DAS, the DAS with the 28-joint count (DAS28), or the clinical (CDAI) or simplified (SDAI) disease activity index. The choice of composite measure and target value for each patient is up to the rheumatology practice and may be influenced by patient comorbidities, drug-related risks, and other factors. Structural and functional changes should also be considered when assessing response to therapy.¹⁸

The T2T task force emphasized the importance of patient education in achieving treatment goals. According to the T2T report, patients must be appropriately informed about the reasons for aiming at a specific therapeutic target, as well as the planned strategy for reaching treatment goals. Patients should also understand the need for adjusting therapy and ongoing disease

monitoring.¹⁸ Rheumatology nurses can take the lead on addressing these issues with their RA patients. The recently published patient version of the T2T guidelines may be a useful tool for patient education.¹⁹

Updated ACR/EULAR Remission Criteria

In 2011, the ACR and EULAR jointly issued new definitions for disease remission in RA that can be used in the research and clinical practice settings. The goal of the new criteria was to improve the ability to identify patients with minimal risk of significant disease progression. Prior definitions of remission, including the traditional DAS28 <2.6 and the more stringent DAS28 <2.0, failed to exclude patients with substantial residual clinical disease activity. Moreover, while the DAS instrument is useful in the research setting, it can be cumbersome to apply in the rheumatology clinic.²⁰

The new ACR/EULAR research and clinical definitions differ in their incorporation of C-reactive protein (CRP), a laboratory measure that may not be practical to collect in routine practice. All definitions use the 28-joint count for tenderness (TJC28) and swolleness (SJC28), as well as global assessments on a scale of 0 to 10.

Am I at risk of cardiovascular disease because of the drugs I'm taking?

In general, RA patients have a greater than twofold risk of myocardial infarction and are twice as likely to experience sudden cardiac death compared to the average population. While the precise molecular mechanism that accelerates risk of cardiovascular disease (CVD) remains unclear, inflammation appears to be the key link.¹

Several possible reasons have been offered as to the cause of increased risk of CVD in patients with RA²:

1. Chronic inflammatory conditions such as RA accelerate atherosclerosis, an inflammatory disease of the arterial wall
2. Chronic pain and anxiety lead to vascular remodeling and hypertension
3. Elevated CRP levels and cytokines increase lipid levels, alter glucose metabolism, and create a hypercoagulability state that can precipitate thrombosis, resulting in myocardial infarction

Now for the good news: In 2004, Krishnan et al demonstrated that patients with RA treated between 1980 and 1997 had no increase in rates of mortality compared to the general population. One of their explanations for this was the reduced time between diagnosis and implementation of treatment such as TNF inhibitors and MTX.³ Although caution must be used when implementing a TNF inhibitor in patients with a history of heart failure, observationally, the biologics and glucocorticoids seem to decrease the incidence of future CVD events in patients with RA.⁴

Many patients with RA commonly present with one or more risk factors of CVD (obesity, immobility, hypertension, or smoking). It's important to remind our patients that RA is an inflammatory disease of the whole body and not just their bones. Reducing saturated fats in their diet, quitting smoking, losing weight, and initiating exercise are key to their overall wellness. —**Jacqueline Fritz, RN, MSN, CNS**

REFERENCES

1. Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Cardiovascular disease in rheumatoid arthritis: A population-based study. *Arthritis Rheum.* 2005;52:722-732.
2. Kramer H, Giles J. Cardiovascular disease risk in rheumatoid arthritis: progress, debate, and opportunity. *Arthritis Care Res (Hoboken).* 2011;63:484-499.
3. Krishnan E, Lingala VB, Singh G. Declines in mortality from acute MI in successive incidence and birth cohorts of patients with RA. *Circulation.* 2004;110:1774-1779.
4. Jacobson LT, Turesson C, Gølle A, et al. Treatment with TNF blockers is associated with lower incidence of first cardiovascular events in patients with RA. *J Rheumatology.* 2005;32:1213-1218.



Understanding Antidrug Antibodies

Immunogenicity describes the potential for a drug to stimulate the immune system to develop antidrug antibodies. All biologic DMARDs have the potential to trigger the production of antidrug antibodies. Patients who develop antibodies to biologic therapies are more likely to develop infusion-related reactions, allergic reactions, and loss of treatment response. Therefore, monitoring for the production of antibodies against biological therapies may identify patients with an elevated risk of antibody-related adverse events, as well as those whose response to therapy may diminish.²² This strategy may be incorporated into routine clinical practice once assays for anti-drug antibodies become commercially available.

The first long-term study of antidrug antibodies in RA was recently published, allowing clinicians to understand how this phenomenon might influence treatment response.²³ In a 3-year study by Bartelds et al, the development of antibodies against adalimumab decreased the efficacy of treatment and resulted in low remission rates in patients with RA. Overall, 28% of patients developed antibodies to adalimumab, and most of these patients (67%) developed antibodies within the first 28 weeks of treatment. Only 4% of patients who developed anti-adalimumab antibodies achieved sustained remission, compared with 34% of patients who did not develop antibodies. Patients who developed antidrug antibodies were 3 times more likely than those without antibodies to stop taking adalimumab due to treatment failure. According to study investigators, these findings are potentially applicable to other biologic therapies, and may explain why some patients fail to respond or lose response to biologic DMARDs. Guidelines are currently under development to guide clinicians in the assessment and management of immunogenicity in patients undergoing treatment with biologic therapy.²⁴

RESEARCH CRITERIA

The ACR/EULAR committee defined 2 sets of criteria for remission that are appropriate in the research setting. According to the first definition, a patient with RA must satisfy all of the following to be considered to be in remission²⁰:

- TJC28 \leq 1
- SJC28 \leq 1
- CRP \leq 1 mg/dL
- Patient global assessment \leq 1

Alternatively, the criteria for remission are met with an SDAI \leq 3.3, meaning that the arithmetic sum of TJC28, SJC28, patient's global assessment, physician's global assessment, and CRP (mg/dL) is \leq 3.3.²⁰

CLINICAL PRACTICE CRITERIA

The threshold of SDAI \leq 3.3 can be used to define remission in daily practice as well as in the research setting. However, for rheumatology practices that want to avoid routine CRP measurements, CDAI \leq 2.8 can be used to define remission.²¹ The CDAI is calculated as the arithmetic sum of TJC28, SJC28, patient global assessment, and physician global assessment.^{20,21}



A PEEK AT THE FUTURE OF RA THERAPY

New Formulations of Existing Agents

With advances in drug technology, several existing classes of agents are being studied in new formulations.²⁵ An investigational form of subcutaneous abatacept, for example, provides greater convenience and a more flexible treatment schedule than intravenous therapy, with similar efficacy and low immunogenicity in patients with RA.²⁶ In a phase II study, a new formulation of subcutaneous tocilizumab showed a favorable safety and efficacy profile when given weekly or twice weekly in patients with RA.²⁷

IL-Targeted Therapy

The interleukins play leading roles in joint destruction in patients with RA. Tocilizumab, the first IL-6 receptor inhibitor approved for the treatment of RA, is associated with rapid improvements in the signs and symptoms of RA in patients with active disease.²⁸ Among investigational IL-6 inhibitors, ALD518 is a glycosylated monoclonal antibody that directly binds to free IL-6 rather than the IL-6 receptor.²⁹ CAT6001 and MEDI5117 are novel anti-IL-6 monoclonal antibodies with promising preclinical and early-phase findings in RA.^{30,31} IL-17 acts synergistically with TNF to induce joint inflammation and joint and cartilage destruction in RA, and is therefore emerging as another important therapeutic target.³² Investigational IL-17 inhibitors with preliminary evidence in RA include secukinumab (AIN457) and MEDI-571.^{33,34}

JAK Inhibitors

The Janus kinase (JAK) family of tyrosine kinases, including JAK1, JAK2, and JAK3, are leading mediators in the cytokine signaling pathways that promote inflammation. By disrupting this broad signaling network, JAK inhibitors can arrest the inflammatory activity of many cell types, including T cells, B cells, and osteoclasts. Two investigational, orally available JAK inhibitors are currently under evaluation for the treatment of RA.

Tofacitinib (CP-690,550), previously known as tasocitinib, suppresses inflammatory activity by inhibiting JAK1 and JAK3.

In a phase II/III study, treatment with tofacitinib maintained therapeutic efficacy alone and in combination with MTX for up to 24 months in patients with RA.^{35,36} Based on these promising results, the ongoing phase III ORAL clinical trials program is evaluating different options for oral JAK inhibitor therapy in the management of RA.

In the ORAL Solo study, tofacitinib monotherapy significantly improved physical functioning compared with placebo and showed a trend toward greater disease remission in patients with moderate-to-severe RA and an inadequate response to traditional or biologic DMARDs.³⁷ According to a recent preliminary analysis of the ORAL Scan study, tofacitinib added to MTX was superior to placebo in patients with moderate-to-severe RA who had an inadequate response to MTX alone. Compared with placebo, tofacitinib significantly improved the signs and symptoms of RA, slowed the progression of structural damage, and improved physical function at 6 months.³⁸

The ORAL Sync study is a 12-month study of tofacitinib added to background traditional DMARDs in patients with a prior inadequate response to traditional DMARDs. Compared with patients in the placebo group, those in the tofacitinib group were more likely to achieve an ACR20, were more likely to achieve disease remission, and had a greater reduction in disease-related disability. There were 4 deaths and 4 opportunistic infections reported in the tofacitinib arm. However, given that only one-fifth of the study cohort was initially randomized to placebo, and that patients in

Why are you performing certain labs? What information are you looking for?

Diagnosing RA relies on more than an articular history and joint examination. Values from several laboratory tests, including the following, can help to definitively determine whether or not an individual has RA:

Rheumatoid factor (RF): RF is an autoantibody (usually immunoglobulin M) that binds to the Fc portion of immunoglobulin G. It is present in 75%-85% of patients with established RA.¹ Conversely, in nearly 20% of patients, RF may be absent in the first few months of active disease. Because RF can be positive in the presence of other conditions (ie, Sjogren's syndrome, systemic lupus erythematosus, endocarditis, etc.), it is not by itself a definitive indicator of RA. Additionally, because RF does not correlate well with disease activity, serial measurements are rarely performed.

Anti-cyclic citrullinated (anti-CCP) antibody: Anti-CCP antibodies are very specific for RA (95%).² Anti-CCP correlates strongly with aggressive RA, radiographic damage, and the presence of RF. Conversely, low levels of anti-CCP may demonstrate a less aggressive disease process.

In addition to RF and anti-CCP antibodies, tests of acute-phase markers, such as erythrocyte sedimentation rate and C-reactive protein, are often performed along with lipid tests. These tests measure response to therapy. However, results may be affected by disease duration and other comorbidities.³

Finally, a complete metabolic panel and complete blood count are often used to monitor the effects of therapy, renal and hepatic function, infection, anemia, and thrombocytosis, among other considerations. —**Jacqueline Fritz, RN, MSN, CNS**

REFERENCES

1. Sattar N, McCarey DW, Capell H, et al. Explaining how "high grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation*. 2003;108:2957-2963.
2. Imboden J, Hellmann DB, Stone JH. *Current Rheumatology Diagnosis and Treatment*. The McGraw Hill Companies; New York: 2007.
3. Shmerling RH. Diagnostic tests for rheumatic disease: clinical utility revisited. *South Med J*. 2005;98:704-711.



the placebo group were switched to tofacitinib as early as 3 months into the trial, most of the adverse events were expected in the tofacitinib arm. Three of the 4 deaths were due to causes unrelated to treatment (acute heart failure, traumatic brain injury, and worsening RA).³⁹

Three additional phase III ORAL trials are currently underway³⁸:

- **ORAL Start:** 24-month study of first-line tofacitinib vs. MTX in patients with active RA
- **ORAL Step:** 6-month study of tofacitinib vs. placebo in RA patients taking MTX with a prior inadequate response to anti-TNF therapy
- **ORAL Standard:** 12-month study of tofacitinib/MTX vs. adalimumab/MTX in RA patients who had an inadequate response to anti-TNF therapy

A second JAK inhibitor, INCB028050, selectively targets JAK1 and JAK2 and is being tested in once-daily oral dosing. In a recent phase II study, INCB028050 produced clinically meaningful responses, including disease remission and reduction in swollen joint counts, in RA patients with inadequate responses to traditional DMARDs and/or biologic therapies.⁴⁰ INCB028050 is currently being evaluated in a phase II trial as add-on therapy in patients with active RA despite treatment with MTX.⁴¹

Syk Inhibitors

Spleen tyrosine kinase (Syk) is a mediator of inflammatory cell signaling that is involved in bone and cartilage destruction.⁴² Fostamatinib (R788) is an investigational Syk inhibitor that reduces major inflammatory cytokines, including TNF, IL-1, IL-6, and IL-18, leading to a reduction in bone degradation in preclinical models of RA.⁴² It is orally bioavailable and administered twice daily.

Fostamatinib has shown promising activity against RA in phase II clinical trials as add-on therapy for patients who have an inadequate response to treatment with DMARDs such as MTX.^{43,44} In a recent phase II study, there was no difference between fostamatinib and placebo in the primary endpoint of ACR20 response at 3 months in RA patients who did not respond to biologic therapies.⁴⁵ However, fostamatinib was superior to placebo for the secondary endpoints of reduced CRP level and synovitis score on MRI, suggesting a beneficial effect on underlying disease activity.⁴⁵ Building on these results, the ongoing Oral Syk Inhibition in Rheumatoid Arthritis (OSKIRA) clinical trials program will evaluate the safety and efficacy of fostamatinib in patients with RA (see next page).⁴⁶⁻⁵⁰

Why does this medication cost so much?

With price tags in the tens of thousands of dollars, the cost of biologic therapies is a common issue. For many of our patients living on a fixed income, cost compounds their decision-making process as they must not only understand the clinical benefits and risks of available medication, but the financial impact as well. This is overwhelming for many patients, especially those who don't fully understand their insurance policy's out-of-pocket fee structure.

When discussing the cost of biologics to my patients, I explain that biologics aim to target the causes of diseases rather than just the symptoms, targeting specific parts of the inflammatory process involved in RA while sparing others. Because of the complexities involved in the manufacturing of these products, costs naturally increase. The route of administration — typically injection or infusion — is another cost driver. So is the lack of generic alternatives — or, more accurately, biosimilar alternatives — that would bring more competition into the marketplace.

One recent article closely examined the cost issue with biologics, and the author highlighted two factors that he saw as the primary reasons for the high price tags¹:

- The most expensive drugs are those that have no competitors. When a truly novel drug hits the market, there is very little to guide manufacturers and insurers in their negotiations over price.
- The average cancer medicine, for example, costs approximately \$1.75 billion to develop (factoring in research and development costs, failed drugs, etc.). Most chemicals that a company experiments with never make it to market. Of those that do, only 20% are ultimately profitable. Drug companies cover these losses by squeezing as much profit out of their few successful agents as possible.

As rheumatology nurses, we can do our best to explain the high cost of medications to our patients, but we must also be prepared to assist them with weighing risk and benefits of specific agents, along with providing directions to patient assistance plans. There are pharmaceutical company programs and pharmacy discount programs that some of our patients will be eligible for that may help defer out-of-pocket expenses. —**Joyce M. Kortan, RN**

REFERENCE

1. Palmer B. The \$8,000 Pill: Why are some pharmaceuticals so expensive? Available at www.slate.com/id/2264116/. Accessed June 1, 2011.



TRIAL	DURATION	PHASE	DESCRIPTION
OSKIRA-146	12 months	Phase III	Fostamatinib vs. placebo as add-on therapy in patients who are not responding to MTX
OSKIRA-247	12 months	Phase III	Fostamatinib vs. placebo as add-on therapy in patients who are not responding to non-biologic DMARDs
OSKIRA-348	6 months	Phase III	Fostamatinib vs. placebo in patients who are taking MTX and are not responding to anti-TNF agents
OSKIRA-449	6 months	Phase II	Fostamatinib monotherapy vs. adalimumab monotherapy in patients with an inadequate response to DMARDs
OSKIRA-X50	12 months	Phase II	Extension trial of long-term fostamatinib safety

Anti-BLyS Antibody

Belimumab is a monoclonal antibody that targets the pathogenesis of autoimmune diseases by inhibiting the activity of B-lymphocyte stimulator (BLyS). In 2011, the FDA approved intravenous belimumab to treat patients with active lupus who are already receiving standard therapy. Belimumab has also shown activity in RA.⁵¹ Atacicept, another B-cell-targeted therapy that inhibits both BLyS and a proliferation-inducing ligand (APRIL), is also under evaluation for the treatment of RA.^{52,53}

SUMMARY

For patients with RA, the goals of treatment are to achieve early suppression of disease activity, prevent long-term joint damage, and maintain physical and social functioning and quality of life. The new treat-to-target approach encourages early treatment with DMARDs to achieve rapid and sustained clinical remission. New remission criteria allow clinicians to more accurately gauge whether disease activity has been suppressed enough to minimize the risk of future joint damage. Armed with new information about the optimal use of MTX and other synthetic and biologic DMARDs, rheumatology nurses are now in a better position to help patients with RA achieve their treatment goals.

How long is this drug going to work?

Patients often ask difficult questions like this one, which we cannot answer with any real confidence. But before you fire off a rapid response — such as “As long as it does!” — it's important to think about several issues, including the following:

- How should you even define response?
- If remission is not attainable, what level of disease activity is acceptable?
- What prognostic indicators may help to answer this type of question?

In the absence of reliable biomarkers or everyday clinical tools that would help predict a patient's response to treatment, we must rely on data from randomized clinical trials. Studies suggest that many patients derive some benefit from one of the three first-generation TNF inhibitors (etanercept, infliximab, and adalimumab); however, 40%-50% fail to achieve an ACR50 response, and more than 70% fail to achieve clinical remission (defined as DAS28 <2.6) after six months of therapy.¹

Many patients can expect to see some improvement after the initiation of therapy, but it's hard to predict whether this improvement will be enough to improve physical functioning and prevent erosive disease and disability. Clinical trials often differ in the number and type of previous medications allowed by enrolled patients, duration of therapy, concomitant medications, and other factors. Therefore, while generalizations can be made, predicting an individual's response to any specific therapy over time is impossible. Certainly, with the improvements in drug design, we can offer an optimistic outlook to our patients, but making concrete promises remains difficult.

Rather than answering your patient with a definitive response, it may be better to educate them on data from various randomized controlled trials and encourage them to report any physical changes or worsening of disease, side effects, or other indicators that their RA is not controlled so that you may quickly escalate or change therapy as needed. —**Nicole M. Furfaro, MSN, ARNP**

REFERENCE

1. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762-784.



References

- Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69:964-975.
- Saevarsdottir S, Wedren S, Seddighzadeh M, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: Observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum.* 2011;63:26-36.
- Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis.* 2009;68:1094-1099.
- Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum.* 2008;58:73-81.
- Hameed B, Jones H. Subcutaneous methotrexate is well tolerated and superior to oral methotrexate in the treatment of rheumatoid arthritis. *Int J Rheum Dis.* 2010;13:e83-e84.
- Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol.* 2011;23:278-281.
- Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med.* 2000;160:610-619.
- Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology.* 2011;118:415-422.
- Gaujoux-Viala C, Smolen JS, Landewé R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:1004-1009.
- Kievit W, Franssen J, de Waal Malefijt M, et al. Major improvements in outcomes of rheumatoid arthritis since the biologic era and beyond: an historical overview from 1989 until 2008 in a large inception cohort of RA patients. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 641.
- Malaviya AN, Sharma A, Agarwal D, et al. Low-dose and high-dose methotrexate are two different drugs in practical terms. *Int J Rheum Dis.* 2010;13:288-293.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69:1580-1588.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31:315-324.
- Cader MZ, Filer A, Hazlehurst J, et al. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. *Ann Rheum Dis.* 2011;70:949-955.
- van der Linden MPM, le Cessie S, Raza K, et al. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum.* 2010;62:3537-3546.
- Bykerk V, Emery P. Delay in receiving rheumatology care leads to long-term harm. *Arthritis Rheum.* 2010;62:3519-3521.
- De Boer KVC, Visser K, Ronday HK, et al. Induction therapy with methotrexate and prednisone in rheumatoid or very early arthritic disease: IMPROVED Study. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 1396.
- Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69:631-637.
- de Wit MPT, Smolen JS, Gossec L, et al. Treating rheumatoid arthritis to target: the patient version of the international recommendations. *Ann Rheum Dis.* 2011;70:891-895.

20. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis.* 2011;70:404-413.

21. Jacobsson LTH, Hetland ML. New remission criteria for RA: 'modern times' in rheumatology—not a silent film, rather a 3D movie. *Ann Rheum Dis.* 2011;70:401-403.

22. Wolbink GJ, Aarden LA, Dijkman BA. Dealing with immunogenicity of biologicals: assessment and clinical relevance. *Curr Opin Rheumatol.* May 2009;21:211-215.

23. Bartelds GM, Kriekkaert CLM, Nurmohamed MT, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA.* 2011;305:1460-1468.

24. European Medicines Agency. Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. November 26, 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099362.pdf. Accessed June 28, 2011.

25. Buch MH, Emery P. New therapies in the management of rheumatoid arthritis. *Curr Opin Rheumatol.* 2011;23:245-251.

26. Kaine JL, Gladstein GS, Strusberg I, et al. Subcutaneous (SC) abatacept is well-tolerated, demonstrates clinical efficacy and is associated with low immunogenicity following withdrawal and re-introduction: Phase III evaluation in rheumatoid arthritis (RA) patients responding to abatacept. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 1834.

27. Ohta S, Tsuru T, Terao K, et al. Optimal dose prediction by pharmacokinetic and biomarker response of subcutaneous tocilizumab treatment – A phase I/II study evaluating the safety, pharmacokinetics and clinical response in patients with rheumatoid arthritis. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 1115.

28. Burmester GR, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase III real-life study (TAMARA). *Ann Rheum Dis.* 2011;70:755-9.

29. Mease P, Strand V, Shalamberidge L, et al. Inhibition of IL-6 with ALD518 improves disease activity in rheumatoid arthritis in a randomized, double-blind, placebo-controlled, dose ranging phase 2 clinical trial. The European League Against Rheumatism 2010 Annual Congress; June 16-19, 2010; Rome, Italy. Abstract OP0136.

30. Finch DK, Rendall E, Salter S, et al. Utilising assay systems relevant to IL-6 mechanisms in rheumatoid arthritis to demonstrate efficacy of a novel human anti-IL-6 antibody, CAT6001. American College of Rheumatology 2009 Annual Scientific Meeting. Philadelphia, PA. October 17-21, 2009. Abstract 45.

31. Moisan J, Faggioni R, Liang M, et al. MEDI5117: A human high affinity anti-il-6 monoclonal antibody with enhanced serum half-life in development for the treatment of inflammation and rheumatological diseases. American College of Rheumatology 2009 Annual Scientific Meeting. Philadelphia, PA. October 17-21, 2009. Abstract 401.

32. Toh ML, Gonzales G, Koenders MI, et al. Role of interleukin 17 in arthritis chronicity through survival of synoviocytes via regulation of synovialin expression. *PLoS One.* 2010;5:e13416.

33. Baeten D, et al. The anti-IL17A monoclonal antibody secukinumab (AIN457) showed good safety and efficacy in the treatment of active ankylosing spondylitis. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract L7.

34. Langham C, Russel C, Barker W, et al. In vitro and in vivo properties of MEDI-571, a human anti IL-17A antibody in development for the treatment of patients with rheumatoid arthritis. American College of Rheumatology 2009 Annual Meeting. October 17-21, 2009; Philadelphia, PA. Abstract 8.

35. Connell CA, Riese R, Wood S, et al. Tascocitinib (CP-690,550) appears to be effective and tolerated when administered either as long-term monotherapy or on background methotrexate in patients with rheumatoid arthritis. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 2171.

36. Connell CA, Riese R, Wood S, et al. Tascocitinib (CP-690,550), an orally available selective janus kinase inhibitor, exhibits sustained safety and efficacy in the treatment of rheumatoid arthritis over 24 months. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 1129.

37. Strand V, Kanik KS, Connell C, et al. Oral Solo (A3921045): Effects of the oral JAK inhibitor tofacitinib (CP-690,550) monotherapy on patient reported outcomes in a phase 3 study of active rheumatoid arthritis. The European League Against Rheumatism 2011 Annual Congress; May 25-28, 2011; London, England. Abstract OP0063.

38. Press Release. Pfizer announces top-line results of third phase 3 clinical trial of tofacitinib (CP-690,550) in patients with active rheumatoid arthritis. April 15, 2011. Available at: <http://www.businesswire.com/news/home/20110415005451/en/Pfizer-Announces-Top-Line-Results-Phase-3-Clinical>. Accessed June 30, 2011.

39. Kremer J, Li ZG, Hall S, et al. Tofacitinib (CP-690,550), an oral JAK inhibitor, in combination with traditional DMARDs: Phase 3 study in patients with active rheumatoid arthritis with inadequate response to DMARDs. The European League Against Rheumatism 2011 Annual Congress; May 25-28, 2011; London, England. Abstract LB005.

40. Greenwald MW, Fidelus-Gort R, Levy R, et al. A randomized dose-ranging, placebo-controlled study of INCB028050, a selective JAK1 and JAK2 inhibitor in subjects with active rheumatoid arthritis. American College of Rheumatology 2010 Annual Scientific Meeting. Atlanta, GA. November 6-11, 2010. Abstract 2172.

41. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT00960440>.

42. Bajpai M. Fostamatinib, a Syk inhibitor prodrug for the treatment of inflammatory diseases. *IDrugs.* 2009;12:174-185.

43. Weinblatt ME, Kavanaugh A, Genovese MC, et al. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *New Engl J Med.* 2010;363:1303-1312.

44. Baluom M, Samara E, Grossbard EB, et al. Fostamatinib, a Syk-kinase inhibitor, does not affect methotrexate pharmacokinetics in patients with rheumatoid arthritis. *J Clin Pharmacol.* 2011. Epub ahead of print.

45. Genovese MC, Kavanaugh A, Weinblatt ME, et al. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: A three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. *Arthritis Rheum.* 2011;63:337-345.

46. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01197521>.

47. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01197534>.

48. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01197755>.

49. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01264770>.

50. Clinicaltrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01242514>.

51. McKay J, Chwalinska-Sadowska H, Boling E, et al. Belimumab (BmAb), a fully human monoclonal antibody to B-lymphocyte stimulator (BLyS), combined with standard of care therapy reduces the signs and symptoms of rheumatoid arthritis in a heterogeneous subject population. American College of Rheumatology 2005 annual meeting. November 12-17, 2005; San Diego, Calif. Abstract 1920.

52. Genovese MC, Kinnman N, de La Bourdonnaye G, et al. Atacicept in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor antagonist therapy: Results of a phase II trial. *Arthritis Rheum.* 2011. Epub ahead of print.

53. van Vollenhoven RF, Kinnman N, Vincent E, et al. Atacicept in patients with rheumatoid arthritis and inadequate response to methotrexate: Results of a phase II, randomized, placebo-controlled trial. *Arthritis Rheum.* 2011. Epub ahead of print.

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 80% of the learning assessment questions. Statements of Credit will be forwarded via email within 4 to 6 weeks. All forms must be received by July 1, 2012, to be eligible for credit.

- Please fax both sides of this evaluation to the Institute at (215) 592-9085, OR
- Please complete the evaluation online by going to www.iche.edu/content/rheumatology-nurse-newsletter.

NAME _____ DEGREE/CERTIFICATION _____

Activity Post-Test Questions

(Please circle the letter that matches the correct response to each question below)

- According to EULAR guidelines, how long after the initiation of MTX therapy should a synthetic or biologic DMARD be added in patients with residual disease activity?
 - Within 45 days
 - Within 3-6 months
 - Within 9-12 months
 - As soon as their DAS28 score is 2.6 or less
- JH is a new patient who reports to you with 3 involved joints, elevated acute-phase response, and symptom duration of 2 years. Based on the 2010 ACR/EULAR diagnostic criteria, would you conclude that she has RA?
 - Yes
 - No
 - Not enough information is provided to reach a definitive answer
- Based upon recent research, which of the following patients would be considered to be at highest risk of a delayed referral to a rheumatologist?
 - AC, a 35-year-old female with sudden onset of symptoms and pain confined primarily to large joints
 - BF, a 65-year-old female with gradual onset of symptoms and pain primarily focused on small joints
 - TD, a 70-year-old male with sudden onset of symptoms and pain primarily focused on large joints
 - DL, a 28-year-old male with gradual onset of symptoms and pain primarily focused on small joints
- Which of the following overarching principles were included in recommendations from the 2010 international T2T taskforce?
 - RA treatment should be determined primarily by the rheumatologist, with minimal patient input
 - The primary goal of RA treatment is to restore short-term quality of life through a patient's return to the workforce
 - The treat-to-target strategy requires measuring disease activity and adjusting therapy accordingly to optimize outcomes
 - Avoiding adverse medication effects is the most important mechanisms to achieve treatment goals
- HJ has been your patient for 18 months. After 6 months of combination adalimumab + MTX therapy, she reports to your office today with 1 tender joint, no swollen joints, a CRP of 0.8 mg/dL, and a patient global assessment score of 0.8. According to the 2011 ACR/EULAR definitions of disease remission in RA, would she be considered to be in remission?
 - Yes
 - No
 - Not enough information is provided to reach a definitive answer
- Which of the following cell types have their inflammatory activity reduced by JAK inhibitors?
 - Osteoclasts
 - B cells
 - T cells
 - All of the above
- Approximately how much more potent is the average dose of MTX given to cancer patients vs. the average dose given to RA patients?
 - 10 times more potent
 - 100 times more potent
 - 10,000 times more potent
 - 1 million times more potent
- According to data from a 2004 study, how much of a mortality increase was seen in RA patients treated between 1980 and 1997 compared to the general population?
 - No increase
 - Twofold increase
 - Fourfold increase
 - Eightfold increase
- Which of the following factors play a role in the high cost of biologic agents commonly used for the treatment of RA patients?
 - Costs of failed drugs in past development pipeline
 - Relative economic prosperity of the average RA patient
 - The recent economic recession
 - Proliferation of generic/biosimilar alternatives
- According to 2011 AAO guidelines, what dose of hydroxychloroquine should a 5-foot-9, 130-pound woman be given?
 - 200 mg twice daily
 - 612.5 mg daily
 - 400 mg daily
 - 845 mg daily

To what extent did your participation in this activity enhance your ability to make improvements in competence and performance related to the following learning objectives?	Not Applicable (not in scope of practice)	Nothing at this time	Reinforcement of current practices	Moderate Improvement	Significant Improvement
Evaluate the appropriate utilization of traditional DMARDs, such as methotrexate, sulfasalazine, and hydrochloroquine, in current RA treatment regimens	NA	1	2	3	4
Assess the impact of recently released “treat to target” guidelines on the overall care of patients with RA	NA	1	2	3	4
Describe the potential role of late-stage agents under investigation for the treatment of RA	NA	1	2	3	4

Please indicate the extent of your agreement with the following statements:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
The information presented within this activity was pertinent to my professional needs	1	2	3	4	5
The content of this activity contributes valuable information that could assist me in improving patient outcomes	1	2	3	4	5
The content of this activity was based on scientific evidence and presented in a fair-balanced format	1	2	3	4	5
The educational format was conducive to learning and appropriate	1	2	3	4	5
Did you perceive commercial bias or influence within this activity? <input type="checkbox"/> NO <input type="checkbox"/> YES, please explain in detail: _____					
Was disclosure information provided to you at the beginning of this activity? <input type="checkbox"/> NO <input type="checkbox"/> YES					

To which of the following actions will you plan to commit as a result of completing this educational activity? Check all that apply:

- I will assess the potential role of late-stage agents under investigation for the treatment of RA.
- I will evaluate the appropriate utilization of traditional DMARDs, such as methotrexate, sulfasalazine, and hydrochloroquine, in current RA treatment regimens.
- I will assess the impact of recently released “treat to target” guidelines on the overall care of patients with RA.
- I will regularly review current peer-reviewed literature on the maintenance and treatment of RA.
- OTHER, please explain in detail: _____

Please identify one or more barriers that you believe prevent you and/or your colleagues from incorporating changes to your performance:

- a. Lack of knowledge regarding evidence-based strategies
- b. Fears about practicing differently from peers
- c. Demanding patient workloads
- d. Other: _____

How many years have you been in practice as a rheumatology nurse?

- 0-5 years
- 6-10 years
- 11-15 years
- 10 or more years

What is your primary practice setting?

- Hospital
- University/academic medical center
- Clinic
- Private practice
- Group or staff model health maintenance organization
- Other: _____

Do you plan on sharing this newsletter with a colleague?

- Yes
- No

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 credit hours claimed _____ (Max 1.5 ANCC-COA contact hours/1.8 California Board of Nursing contact hours)

First Name _____ Middle Initial _____ Last Name _____

Degree (please check all that apply) RN NP CNS CRNA CNM LPN Other _____

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

Address _____

City _____ State _____ ZIP _____

Telephone _____ E-mail Address _____

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

Signature _____ Date _____

To help us better plan for education in this area, and to invite you to partake in future educational development, we may contact you for your expertise. If you opt NOT to be contacted, please check here:

Safe Travels in the Summertime

— Vicky Ruffing, RN



Vacation season is upon us, and as our patients make their way far and near, it’s important to prepare them to travel safely. Recent updates have been made to the package inserts for many of the biologics, and fungal infections are common themes within black box warnings. While most of our patients likely do not live in endemic areas, a vacation or family visit could put them at risk for contracting a fungal infection.

Traveling with Injectable Medications

At our clinic, we have a templated letter that we give patients explaining that they have been prescribed an injectable medication that must accompany them in their carry-on luggage – the letter includes unique areas for the name of the patient and the medication, but the language otherwise remains static. Because many foreign countries may not have access to all current biologic medications, it is always advisable to have patients carry an extra dose of an injectable if there is a risk of becoming stranded due to weather or other factors. Patients may also want to consider a customized first aid kit that includes copies of prescriptions, hand sanitizer, a thermometer, sunscreen, bandages, triple antibiotic ointment, and other items.

The Fungus Among Us

Coccidioidomycosis is a fungal infection most commonly seen in the desert regions of the southwestern United States, parts of Mexico, and South America. The Centers for Disease Control and Prevention (CDC) estimates that 10%-50% of individuals living in endemic regions have evidence of exposure to *Coccidioides* spores. Coccidioidomycosis, which starts in the lungs, arises as a result of breathing in fungal spores present in the soil. These spores can become airborne after a disturbance of the soil by natural or artificial means (earthquakes, heavy rainstorms, construction work). Symptoms include flu-like illness with fever and cough, headache, rash (especially on lower extremities), night sweats, and body aches. These symptoms typically appear approximately 1-3 weeks after exposure. In a small percentage of individuals, infection may spread from the lungs to other parts of the body, including the skin, brain, bones, and heart.¹

Blastomycosis is very rare fungal infection found in moist soil, particularly in the presence of rotting vegetation. The fungus *Blastomyces dermatitidis* is found in parts of the southern, southeastern, and midwestern United States. Forestry workers, hunters, campers, and other individuals who spend significant time in wooded areas are at particular risk. Symptoms of infection are similar to that of coccidioidomycosis. Disseminated blastomycosis may result in chronic pulmonary disease, genitourinary involvement, and meningitis.¹

Histoplasmosis is a more common fungal infection found in the Ohio and Mississippi river valleys. The fungus *Histoplasma capsulatum* is found in soil where there may be an accumulation of bat or bird droppings. Also referred to as “cavers disease” or “spelunkers lung,” as many as 80% of individuals living in endemic areas exhibit a positive histoplasmin skin test. Signs of infection include chest pain, cough, and fever. Disseminated histoplasmosis may lead to pneumonia, pericarditis, meningitis, adrenal insufficiency, splenomegaly, and hepatomegaly.¹

Treatment for all of the aforementioned infections involves anti-fungal medications such as amphotericin B, voriconazole, posaconazole, fluconazole, and ketaconazole.

In light of recent natural disasters – tornadoes in Alabama and Missouri, flooding along the Mississippi River – it is also important to remind our patients either living in or visiting these areas of the most common microbes that arise after these events. Contaminated water, food, and even the tight quarters of evacuation facilities are rife with infectious diseases and parasites such as *Shigella*, *Cryptosporidium*, *Giardia*, and *Leptospiriosis*. Patients who will be near these areas should seek medical attention at the first sign of possible exposure. Prescribers may want to consider a prescription antibiotic for diarrhea to be used by patients as needed.

REFERENCES

- Centers for Disease Control and Prevention. A-Z Index for Foodborne, Bacterial, and Mycotic Diseases. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/index.html.
- Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762-784.

Vaccines

Travel to exotic locales often necessitates extra vaccinations. The following vaccines are contraindicated for patients on biologic medications²:

- Bacille Calmette-Guérin (BCG)
- Influenza, live attenuated
- Measles-mumps-rubella
- Typhoid, Ty21a
- Varicella (adults)
- Yellow fever

The typhoid Vi vaccine is not a live vaccine and is considered to be safe.²

While we can’t expect (nor do we want) our patients to live a sedentary lifestyle that includes staying within an arms length of home, cautioning them about possible infectious agents in the areas they may be visiting is part of our responsibility as nurses and may allow for a safer, more enjoyable vacation.

The Institute for Continuing Healthcare Education plans and implements continuing medical education activities that are fair, balanced, evidence-based, evaluated for bias, and in the best interest of the public.

Commercial Support

Supported by educational grants from Genentech, Inc., Biogen Idec, Amgen, and UCB.

General Disclosure and Copyright Statement

The opinions expressed in this publication are those of the participating faculty and not those of the Institute for Continuing Healthcare Education (the Institute), Genentech, Inc., Biogen Idec, Amgen, UCB, or any manufacturers of products mentioned herein.

This information is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a healthcare professional regarding diagnostic and treatment options of a specific patient's medical condition. In no event will the Institute be responsible for any decision made or action taken based upon the information provided in this activity.

Participants are encouraged to consult the package insert for all products for updated information and changes regarding indications, dosages, and contraindications. This recommendation is particularly important for new or infrequently used products.

Copyright 2011. Institute for Continuing Healthcare Education (the Institute). All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means—electronic or mechanical—without first obtaining written permission from the Institute.

The Institute reserves the right to cancel or modify the activity content, faculty, and activities if necessary.

Looking for **more**
CNE-certified education?

OSTEOMATTERS.COM

An academic, curriculum-based portal for rheumatologists, rheumatology nurses, endocrinologists, obstetricians/gynecologists, pharmacists, and other healthcare professionals who have an interest in the treatment and management of osteoporosis.

EDUCATION IN THE ROUND: REFLECTIONS ON EULAR 2010

This webinar presents specific emphasis on diagnostic and management recommendations, patient registry data, DMARD safety and efficacy, and genetic and biological markers.