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Target Audience: This knowledge-based educational activity is intended for rheumatologists, internists, nurses, pharmacists, and other health care practitioners who manage patients with rheumatoid arthritis and systemic lupus erythematosus.

Educational Needs: RA and SLE are topics of great clinical and research interest in rheumatology. Effective control of the inflammatory process in RA yields both better clinical outcomes and improved patient quality of life, as it addresses both pain control and prevention of joint damage. Long-term survival and optimum quality of life for patients with SLE depends on early diagnosis and initiation of effective therapy. To achieve maximum benefits of their early intervention and treat-to-target efforts, clinicians must be familiar with all of the agents in the pharmacologic armamentarium so that specific agents can be chosen according to individual patients’ clinical needs, and be prepared to incorporate newer agents into their practices as these medications become available.

Clinicians and their patients will benefit from this update regarding new findings and advances in the optimal use of currently available treatments for RA and SLE, the role of traditional DMARDs, and the potential availability of new biologic treatments that target novel disease pathways. This supplement provides an expert synthesis and discussion of topics presented at a recent international conference on rheumatology and recently published literature—both of which are discussed within the context of clinical applicability.

Learning Objectives: Upon completion of this activity, participants should be better able to:

- Discuss the current information about RA and SLE pathogenesis and emerging targets for future therapy.
- Demonstrate improved knowledge of the mechanisms of action, efficacy, and safety profiles of the biologic agents currently available for RA and SLE.
- Optimize the use of medications now available for RA and SLE.
- Evaluate the results of clinical studies on promising medications now under investigation in RA and SLE and appropriately incorporate new treatments. Improve office protocols, as needed, to better monitor patients more frequently to ensure tight control of RA symptoms.
- Safely and appropriately switch medications in patients with RA or SLE who do not respond optimally to initial therapy or whose symptom control decreases after initial good response to a medication regimen.
- Evaluate the clinical significance of recent studies that provide enhanced understanding of the pathogenesis of both RA and SLE.

Disclosure Declarations: Individuals in a position to control the content of this educational activity are required to disclose: 1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

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Introduction and Commentary

Roy M. Fleischmann, MD, and Arthur F. Kavanaugh, MD

The articles in this supplement to Rheumatology News review some of the recent presentations of interest to physicians who treat patients with rheumatic diseases. The author, Alan K. Matsumoto, MD, addresses these presentations in the context of other recent literature and observations from clinical practice. The topic areas include the role of triple nonbiologic treatment regimens in rheumatoid arthritis (RA), the risk for breast cancer associated with the use of tumor necrosis factor (TNF) inhibitor, dosage reduction and withdrawal of biologic therapy, special populations of patients with RA, and newer and emerging therapies for RA and systemic lupus erythematosus (SLE).

Triple Nonbiologic Therapy in RA

The first article discusses the effectiveness of triple therapy with disease-modifying antirheumatic drugs (DMARDs). The relative effectiveness of triple DMARD therapy compared with a TNF inhibitor plus methotrexate (MTX) continues to be debated. In the BeST study, less than 10% of patients receiving step-up combination therapy (ie, patients who had not achieved the therapeutic target on MTX monotherapy and added DMARDs) achieved low disease activity measured by the Disease Activity Score in 44 joints (DAS44). This percentage was much lower than in the group treated with an initial combination of a biologic DMARD (in this study, infliximab) plus MTX.1

In the Swedish Farmacotherapy (SWEFOT) trial, triple therapy was not as effective as a biologic DMARD + MTX in the first year, but the therapies were comparably effective over 2 years among the patients who had not dropped out of the study (a number of patients opted out before the 2-year mark).2 Some rheumatologists in clinical practice maintain that triple therapy is marginally more effective than MTX alone and is not as effective as a biologic DMARD + MTX.

A factor that may contribute to these findings, as discussed in the article by Dr Matsumoto, is patient compliance: If a patient does not take a medication, it cannot possibly work as intended.

Biologics and Cancer Risk

Patients frequently ask about the risk for malignancy with the use of biologic DMARDs. No evidence of a substantially increased risk for solid organ cancers has emerged after 15 years of use of TNF inhibitors in the clinic and even longer in clinical trials. The report from Raaschou and colleagues3 discussed by Dr Matsumoto suggests that the risk for breast cancer in patients without a history of this disease is not increased with the use of TNF inhibitors. More importantly, this analysis suggests that the risk for cancer recurrence in patients with a previous history of breast cancer is also not increased with TNF-inhibitor use. Nevertheless, the decision whether to use an anti-TNF agent needs to be reached by the patient and the physician after careful consideration of the risk-benefit ratio.

Dosage Reduction and Withdrawal of Biologic Therapy

Whether to taper or discontinue the use of a biologic DMARD has become a topic of great interest in rheumatology. The achievement of relatively good clinical control of RA has been proffered by many patients and health insurance carriers as sufficient reason to reduce the dosage of or to discontinue the use of biologic DMARDs. These arguments relate mainly to the cost of the medications, but also to other factors such as concern about potential toxicity. Some would maintain that, for the physician, patient well-being should be of paramount concern and cost should not be a consideration in this decision. However, realistically, the payer system does have a direct and significant bearing on whether a patient can continue using any medication.

The studies published to date do not completely answer questions regarding the effectiveness of tapering or discontinuing medication. No study has been done in which the decision to taper or discontinue is based on stringent definitions of remission, such as the achievement of Simple Disease Activity Index (SDAI) <3.3—the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) definition of remission—or remission as defined by the absence of tender or swollen joints, along with no evidence of inflammation by ultrasound or magnetic resonance imaging.

In the AVERT (Assessing Very Early Rheumatoid Arthritis Treatment) trial, the definition of remission was the DAS in 28 joints based on C-reactive protein (DAS28[CRP]).4 This value for DAS28[CRP] has not been validated as an accurate definition of remission, and multiple analyses have shown that the equivalent value of DAS28 based on erythrocyte sedimentation rate (ESR) <2.6 is a DAS28[CRP] of not higher than 2.4.5 Even at this level, patients still have several tender and swollen joints and/or an elevated ESR or CRP—not a remission in its strictest sense. If a patient still has active disease, even a single swollen joint, why would one consider discontinuing medication?

The trials quoted in Dr Matsumoto’s article show that very few patients achieve true remission. If true remission is achieved, will it be maintained if a patient’s medication is tapered or discontinued? The studies show that a few will, but only a few.

For this reason, in the clinic, it is usually the patient and not the clinician who initiates the discussion and makes the decision about tapering therapy. In such cases, it is crucial...
to carefully follow disease activity and restart medication when a flare occurs.

Comorbidities and RA
Effective therapy of RA has substantially reduced the mortality due to cardiovascular disease in patients with RA. The question remains whether a patient who has achieved good clinical control and who tapers or discontinues use of the effective DMARD will maintain the lower risk of cardiovascular disease (which is not due to traditional risk factors), or whether their risk will again increase.

In another interesting study reviewed in this supplement, Richter et al. analyzed data on a group of older patients with RA and comorbidities who were treated with higher doses of prednisone rather than with MTX or another DMARD. The patients did not do as well despite the prednisone. Although intuitively it may make sense to limit DMARDs in patients with RA and comorbidities, the choice of monotherapy with a biologic DMARD plus a higher-dose corticosteroid seems to result in less efficacy and corticosteroid-related adverse effects, including an increased incidence of serious infections.

Perioperative Biologic Use
Most physicians (and patients) are concerned about the immunosuppressive effects of biologic therapies, particularly around the time of surgery. A report from Kadota and colleagues suggests that holding medication for 2 to 3 half-lives "reduces" the infection risk to a level comparable to that in patients who do not take biologic DMARDs. However, this study did not use a control group of patients continuing biologic DMARDs to determine whether the risk for infection or serious infectious events (SIEs) was increased. Therefore, the possible association between increased infection risk and perioperative biologic DMARD use is still debatable and requires further study.

Biologic Use and Pregnancy
The accumulated data on patients with RA seem to suggest that the use of certain DMARDs, including hydroxychloroquine and also TNF inhibitors, may be safe during pregnancy. A recent report by Panchal et al. discussed by Dr Matsumoto, provides a good review of the literature. Studies in patients with inflammatory bowel disease also suggest that TNF inhibitors might be safe during pregnancy. Continuing DMARDs during pregnancy is certainly a decision that must be made by patients, in consultation with their treating physicians, and is affected by factors such as disease activity.

New and Emerging Agents in RA and SLE
A number of agents affecting different targets in RA and SLE—some that act intracellularly and others with extracellular mechanisms—are in development. Many of these agents have been shown to be effective, although not more so than the approved agents, and they do not appear to be safer than approved products. However, because not all patients with RA and SLE respond to currently available nonbiologic and/or biologic DMARDs, newer agents do have a role. New choices in route of administration—some of these newer agents are administered orally—also may be an important consideration for some patients.

Belimumab is the first new agent approved for SLE in the United States in the past 50 years. Experience with belimumab in the clinic has shown that responses appear to be similar to what was observed in the clinical trials. Although the beneficial effects may not be dramatic for all patients and the disease may continue to be active, it seems that about half of patients with SLE improve to at least some degree, particularly with respect to disease manifestations such as arthritis, rash, and fatigue.

There is still a need for new effective and safer medications for SLE. Conducting trials of new agents for SLE is challenging; the disease can present with a variety of manifestations, and treatment of these different manifestations may well require different medications. Therefore, recruiting a truly homogeneous population to study is difficult. Another difficulty in performing these trials is the outcomes used. Practicing rheumatologists do not routinely use the Systemic Lupus Erythematosus Activity Index (SLEDAI) or the British Isles Lupus Assessment Group (BILAG) index. Moreover, these end points may not be sufficient measures of response. A third—and very significant—problem is background medication; the studies done to date have added new medications to standard of care, so observing a response due to the new medications may be difficult.

References
The use of methotrexate as the treatment of first choice in patients with newly diagnosed rheumatoid arthritis (RA) is generally accepted, although several large randomized trials have demonstrated that monotherapy with methotrexate results in low disease activity in less than a third of patients.1-4 When a trial of methotrexate fails to adequately control the disease, clinicians must choose whether to add other conventional disease-modifying antirheumatic drugs (DMARDs) to the methotrexate regimen or to institute biologic therapy.

In its latest guidelines for the treatment of RA, EULAR (the European League Against Rheumatism) recommended that patients who are newly diagnosed should receive either methotrexate monotherapy or methotrexate in combination with other DMARDs, with the goal of achieving remission or low disease activity, and with (1) treatment adjusted at 3 months if there has been no improvement or (2) at 6 months if, despite improvement, the treatment goal has not been reached.5 For patients with a poor prognosis who fail to achieve the treatment target with this initial strategy, the use of biologic agents or switching to DMARD combination therapy—such as the so-called triple nonbiologic DMARD therapy with methotrexate, hydroxychloroquine, and sulfasalazine—were recommended alternatives.

The widespread impression among rheumatologists has been that triple DMARD treatment is less well tolerated than biologic therapy, but the data from controlled trials demonstrating the statistical noninferiority of the triple DMARD regimen1-4 present a dilemma.

Recently, the results of a study were presented that provide some insight into this question from the standpoint of adherence and persistence with treatment rather than efficacy per se. Bonafede and colleagues6 evaluated data collected between January 2009 and July 2012 from Medicare and commercial databases in the United States on 3,724 patients who initiated therapy with etanercept plus methotrexate and 818 who began a triple nonbiologic DMARD regimen. The objective of the study was to estimate 1-year adherence and persistence with each of these regimens. Adherence was defined as >80% of days covered for each drug. Nonpersistence was defined as a 45-day gap in the use of nonbiologic agents or starting or changing a biologic agent.

The investigators reported that adherence was significantly higher among the patients who were on the biologic regimen: 27.9% of those taking etanercept plus methotrexate were adherent, whereas adherence was 18.2% in the triple DMARD group, a difference of 53% (P<0.0001). Adherence to individual agents also was compared (Table).

In addition, patients using the biologic regimen were more likely to be persistent than patients in the triple DMARD group (23.7% vs 19.1%, respectively; P=0.005). Finally, the researchers reported that 25.7% of patients initially on triple DMARD therapy switched to the biologic regimen; 19.5% of patients who began etanercept plus methotrexate switched to another biologic agent.

Conclusion
Bonafede et al6 did not include reasons for lack of adherence or persistence as study parameters, so it is not known how many patients in either group failed to adhere to their medication regimen or stopped taking their initial medication because of lack of efficacy, medication intolerance, or some other reason. Nevertheless, this study does provide support for the widespread clinical impression that, overall, triple DMARD therapy seems to be less well tolerated.

TABLE. Summary of Adherence Rates

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Adherence to Combination*</th>
<th>Adherence to Single Agents Within Combination†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept + MTX</td>
<td>27.9%</td>
<td>Etanercept, 49.7% MTX, 45.5%</td>
</tr>
<tr>
<td>Triple DMARD</td>
<td>18.2%</td>
<td>Sulfasalazine, 32.8% Hydroxychloroquine, 52.6% MTX, 55.7%</td>
</tr>
</tbody>
</table>

*Difference between groups, P<0.0001.
†When the second agent was added in the triple-therapy group, adherence dropped to between 23.3% and 36.2%.
MTX=methotrexate; triple DMARD= methotrexate + hydroxychloroquine + sulfasalazine.

Source: Bonafede et al.6

Continued on page 14
Breast Cancer Risk and Anti-TNF Therapy

Most patients with rheumatoid arthritis (RA) are female and are typically in an age cohort in which breast cancer is most common, so breast cancer is a topic of concern among both patients with RA and the clinicians who treat them. With respect to biologic treatment for RA, two questions arise: Can a patient with a history of breast cancer safely be treated with tumor necrosis factor (TNF) inhibitors? And is de novo breast cancer a risk for women with RA treated with biologic agents?

To date, the accumulated evidence—notably, several meta-analyses incorporating surveillance data on tens of thousands of patients1-4—demonstrates that the use of TNF inhibitors is not associated with an increased risk for the de novo development of solid tumors, including breast cancer. However, the issue of whether treatment with a TNF inhibitor predisposes patients with a history of breast cancer to tumor recurrence has not been so clearly established.

To examine this question, Raaschou and colleagues5 identified 240 patients with RA and a previous history of breast cancer in the Swedish nationwide database, 120 of whom had been treated with anti-TNF therapy between 1999 and 2000, and 120 matched cohorts who had never been treated with biologics. The investigators followed the patients using register linkages and chart review through 2011 for the first recurrence of breast cancer.

Among the patients who used TNF inhibitors, the median time from their breast cancer diagnosis until the start of treatment (and, therefore, of follow-up) was 9.4 years. The median follow-up in the patients not on biologic therapy was 4.6 years; the median follow-up in the anti-TNF therapy group was 4.9 years. The authors noted that “modest differences” were present in the characteristics of the cancers or treatment between the two groups at the time breast cancer was diagnosed.

During the follow-up period, 9 patients in the nonbiologic group (15/1,000 patient-years) and 9 in the anti-TNF treatment group (16/1,000 patient-years) developed a recurrence of breast cancer, for a hazard ratio of 0.8 (95% CI, 0.3-2.1). When the investigators adjusted for the differences in breast cancer characteristics, the hazard ratio was 1.1 (95% CI, 0.4-2.8). Among the patients who began anti-TNF therapy within 5 years after breast cancer, the hazard ratio for recurrence was 1.4 (95% CI, 0.2-8.6); for those who started TNF inhibitors more than 5 years after breast cancer, the hazard ratio was 0.8 (95% CI, 0.3-2.4).

Thus, no statistical difference was seen in breast cancer recurrence among women with RA regardless of TNF inhibitor use. However, the investigators pointed out that their results may or may not be generalizable to populations whose breast cancer carries a poor prognosis or is very recent.

Ischemic Stroke in RA

Cardiovascular events are seen with increased frequency in patients with RA and are associated with substantial morbidity and mortality. According to a meta-analysis of 24 observational studies that included more than 110,000 patients, the risk for cardiovascular disease is 50% higher in patients with RA than among individuals in the general population.6 This study also demonstrated that the mortality risk for ischemic heart disease was 59% higher among patients with RA, and the risk for cerebrovascular accident was 52% higher. Although it is known that, in general, patients with a long history of RA have an increased risk for ischemic stroke, few large studies have been published that characterize the ischemic stroke risk factors in patients with RA compared with patients without this disease.

Mantel and colleagues7 recently presented the results of their study that examined three of the potential differences in these populations: clinical presentation, case fatality, and the impact of traditional ischemic stroke risk factors.

Using the Swedish nationwide patient registry, the investigators identified 39,065 patients with RA and 171,965 patients without RA from the general population as comparators, matched for sex, age, and area of residence. The populations were followed over 4 years (2005 to 2009), and individuals who had ischemic stroke during this time were identified. The investigators used the national patient registry to determine the presence of preexisting comorbid conditions; using the cause-of-death registry, they tracked fatalities from the time ischemic stroke occurred through the end of the follow-up period, December 31, 2011.

Ischemic stroke occurred in 640 patients (1.6%) with RA and 2,040 patients (1.2%) in the comparator cohort. No statistically significant differences were seen between the two groups in the severity of stroke (determined on the basis of level of consciousness on hospital admission), the proportion of patients who received thrombolysis therapy, the length of hospitalization after ischemic stroke, the proportion of cases in which follow-up care was required, and overall survival during the first month after the event (Table 1).

<table>
<thead>
<tr>
<th>No statistically significant differences were seen between RA and comparator cohorts who had ischemic stroke in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Level of consciousness at admission</td>
</tr>
<tr>
<td>• Proportion of cases treated with thrombolysis</td>
</tr>
<tr>
<td>• Length of hospitalization</td>
</tr>
<tr>
<td>• Need for follow-up care after stroke</td>
</tr>
</tbody>
</table>

Source: Mantel et al.7

Alan K. Matsumoto, MD

Update on Safety and Tolerability of Biologic Therapy for Rheumatoid Arthritis in Special Populations

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As Table 2 summarizes, differences were noted between the groups in first-year fatalities and fatalities during the entire follow-up period (mean, 2.8 years). During the first year after stroke occurred, 25% of patients with RA died compared with 19% of patients in the non-RA comparator cohort. During the entire follow-up period, 46% of patients with RA died compared with 33% of patients in the comparator cohort, a difference that is similar to mortality seen in the patients with and without RA who did not have an ischemic stroke.

Finally, the investigators analyzed the recognized major risk factors for ischemic stroke and found that atrial fibrillation had a similar effect on stroke risk in both RA and non-RA patients, but hypertension, diabetes mellitus, and heart failure had significantly less effect on the RA cohort (Table 3). Thus, Mantel and colleagues confirmed previous data showing an increased risk for ischemic stroke in patients with RA, but also demonstrated that mortality associated with ischemic stroke is higher in patients with RA. Perhaps most interesting was the finding that traditional risk factors for ischemic stroke actually had more influence in the non-RA population than in those with RA, supporting the widespread impression that RA-associated inflammation plays a role in cardiovascular disease in this population.

### Biologic Monotherapy for RA in Older Patients With Comorbidities

Studies of biologic agents in patients with RA have consistently and clearly shown that the addition of methotrexate (MTX) yields better efficacy. Overall, serious adverse effects from MTX—such as pulmonary toxicity, hepatotoxicity, and bone marrow suppression—are unusual and, if they occur, often are reversible on cessation of MTX use; less serious, gastrointestinal adverse effects are much more commonly seen. Clinicians whose patients with RA do not tolerate MTX often choose biologic monotherapy, although this practice has not been well studied.

Recently, Richter and colleagues described treatment continuation rates for biologic monotherapy compared with biologics plus MTX in an elderly population of patients with RA. The investigators collected data from the German RABBIT (Rheumatoid Arthritis oBservation of Biologic Therapy) registry on a total of 1,937 older patients with RA enrolled over a 5-year period (2007 to 2012). Table 4 summarizes the numerical distribution of medications in the study population, along with the mean ages and mean DAS28 scores in each group. Patients took abatacept, adalimumab, etanercept, or tocilizumab, either as monotherapy or in combination with MTX.

When the data were analyzed, the investigators found more patients on monotherapy rather than combination therapy—regardless of the biologic used—had more co-morbidities, had poorer physical function, and were significantly more often treated with prednisone at doses exceeding 10 mg/day (P<0.01). Patients in the monotherapy group also were significantly older than those in the combination therapy population; chronic kidney and liver diseases were found 2 to 5 times more often among those on monotherapy, a significant difference compared with the RA patients who received combination biologics plus methotrexate (P<0.01).

The trends shown in this study suggest that, although older age and the presence of comorbidities may influence the decision to use biologics without methotrexate, the combination of biologics and methotrexate may result in improved outcomes in this population.

### TABLE 2. Fatalities After Ischemic Stroke

<table>
<thead>
<tr>
<th>Factors Considered</th>
<th>RA Cohort</th>
<th>Non-RA Comparator Cohort</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death during first year after stroke</td>
<td>25%</td>
<td>19%</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>Death during entire follow-up period</td>
<td>46% (IR 18.4/100 PY)</td>
<td>33% (IR 11.5/100 PY)</td>
<td>1.5 (1.3-1.7)</td>
</tr>
</tbody>
</table>

IR=incidence rate; PY=person-years of population cases.

Source: Mantel et al.7

### TABLE 3. Major Risk Factors for Developing Ischemic Stroke: RA vs Non-RA Cohorts

<table>
<thead>
<tr>
<th>Factors Considered</th>
<th>RA Cohort Hazard Ratio (95% CI)</th>
<th>Non-RA Comparator Cohort Hazard Ratio (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>2.2 (1.7-2.6)</td>
<td>2.2 (2.0-2.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.9 (2.5-3.4)</td>
<td>5.7 (5.2-6.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7 (1.4-2.1)</td>
<td>2.6 (2.3-2.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.1 (1.7-2.6)</td>
<td>2.8 (2.5-3.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*P value reflects the difference in strength of association.

RA=rheumatoid arthritis.

Source: Mantel et al.7 Adapted with permission.
Perioperative Risk in Patients Using Biologic Therapy

The consensus among surgeons is that their patients with RA who are using biologic medications risk delayed wound healing and infection-related complications during the perioperative period. However, the evidence supporting the practice of discontinuing biologic therapy in the perioperative period is conflicting, and no clear conclusion can be drawn from the accumulated studies published to date.

Kadota and colleagues recently reported the results of their study of delayed wound healing and surgical site infection in patients with RA who were undergoing orthopedic surgeries. The investigators retrospectively reviewed the records from 1,039 orthopedic procedures performed at two Japanese medical centers between January 2004 and December 2012. The patients in the study who were taking biologic agents (n=198) used the TNF inhibitors adalimumab, etanercept, or infliximab, or the interleukin-6 receptor antagonist tocilizumab. The rest of the patients with RA were not using biologic agents (n=841). Among the patients on biologics, depending on the specific agent used, therapy was stopped between two and three half-lives before surgery and was not restarted until two to three half-lives after the operation.

The investigators reported that, among the total study population of 1,039 patients, delayed wound healing occurred in 17 patients (1.64%) and surgical site infections occurred in 19 patients (1.83%)—9 patients with superficial infection and 10 with deep infection. Of the 198 patients who had been treated with biologic therapy, delayed wound healing was seen in 4 patients; one case of superficial infection was reported. The other 13 cases of delayed wound healing and 8 cases of superficial infection occurred in the patients who had not taken biologics. Moreover, all 10 cases of deep infection were seen in the nonbiologics group.

In summary, the preoperative use of biologic agents in patients with RA is not an independent risk factor for delayed wound healing or surgical site infections. The number of surgical site infections was not found to be increased in the patients who had been treated with biologics compared with those who had not used biologics. This study further supports use of a regimen that withholds biologics for some time before and after surgery and demonstrates that when such a practice is followed, patients treated with biologics for RA are not at increased risk for delayed wound healing or surgical site infections.

Pregnancy and Biologic Therapy

The use of biologic agents before or during pregnancy is a practical issue about which clinicians must counsel patients and couples. Two presentations at a recent international symposium on rheumatology provide insight regarding pregnancy and biologic use in both women and men.

Panchal and colleagues reviewed the literature from 2006 through 2008 derived from a search using the keywords pregnancy and lactation, as well as RA, psoriatic arthritis, inflammatory arthritis, and juvenile idiopathic arthritis. They also reviewed articles derived from a search for papers focusing on agents commonly used to treat rheumatologic diseases published between 1996 and 2008. (Review articles and those published in languages other than English were not included in the analysis.)

The investigators identified publications with reports on some 4,530 drug exposures to corticosteroids (176 cases); the TNF inhibitor biologics, adalimumab, etanercept, and infliximab, (278 cases), and other disease-modifying anti-rheumatic drugs—specifically, azathioprine (210 cases), hydrochloroquine (189 cases), leflunomide (80 cases), sulfasalazine (57 cases), methotrexate (15 cases), and mycophenolate mofetil (1 case).

The data from the reviewed literature support the findings from numerous other studies indicating that corticosteroids, hydrochloroquine, azathioprine, and sulfasalazine are safe during pregnancy. Regarding biologic use, the authors noted that the risk for spontaneous miscarriages and congenital...
malformations does not appear to be increased among the pregnancies during which women used TNF inhibitors “predominantly in or immediately prior” to the first trimester. However, they also caution that data were limited on anti-TNF exposures, and that examination of larger numbers of exposures from registry data will be needed before the safety of these biologics throughout pregnancy can be established.

In a second study, these same authors examined data from 21 studies of men with rheumatic diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, and leukemia, and men who were being treated with immunosuppressant medication after organ transplantation. The method of identifying relevant literature was similar to that used for the previous study. The drug exposures included nonsteroidal anti-inflammatory drugs (705 cases), corticosteroids (517 cases), azathioprine (343 cases), cyclosporine (287 cases), methotrexate (100 cases), sulfasalazine (120 cases), infliximab (66 cases), etanercept (44 cases), hydroxychloroquine (13 cases), rituximab (11 cases), adalimumab (6 cases), and leflunomide (2 cases).

The authors identified 2,214 drug exposures among 1,963 men whose partners were trying to conceive; 2,112 pregnancies resulted in 1,778 live births. Congenital malformations were reported in 33 of the live births, but no specific drug was associated with these malformations.

Among the limitations of this study were the relatively small number of subjects and the possible (although not established) effects of the underlying diseases on male fertility. Furthermore, although 78 miscarriages were identified, not all of the studies reviewed specified the number of elective pregnancy terminations in their data. Finally, the evidence is not sufficiently robust to definitively establish the safe use of antirheumatic, immunosuppressive, and biologic drugs in men who are trying to conceive. Nevertheless, this review did not show an increased risk for adverse pregnancy outcomes in the partners of men who were being treated with these drugs. This finding is reassuring to clinicians when counseling men and couples, especially when an unintended pregnancy has occurred.

References

New Developments in Rheumatology: Highlights From an International Conference 9
Dosage Reduction and Withdrawal of Biologic Therapy in Rheumatoid Arthritis

Alan K. Matsumoto, MD

Clinicians may consider tapering or stopping biologic therapy for a number of reasons; among them are cost considerations and patient preferences, but the principle reason—and the one that makes dosage reduction or treatment withdrawal even possible—is the efficacy of available medications. Since the introduction of biologic agents, the concepts of low disease activity and remission have become reasonable goals for many patients and, thus, a new paradigm in RA management has emerged.

A number of controlled trials have been conducted in an attempt to determine how and when biologic agents should be withdrawn, and in whom. Among these are studies that have examined withdrawal of infliximab (in the RRR study\(^1\)), etanercept (in the PRESERVE trial\(^2\)), certolizumab pegol (in the CERTAIN trial\(^3\)), and adalimumab (in the HONOR\(^4,5\) and OPTIMA\(^6\) studies).

These studies examining the consequences of dosage reductions and withdrawal in RA are necessarily complex because they must account for numerous variables, including the duration of disease (early RA vs long-standing disease), previous treatments and outcomes, current therapeutic regimen, current disease state (current level of disease activity or remission), and duration of current disease state (stability of disease activity or remission). Thus, their results must be considered in light of the variables addressed in each.

At a recent international symposium on rheumatology, Emery et al\(^7\) and Peterfy and colleagues\(^8\) presented findings from studies based on AVERT (Assessing Very Early Rheumatoid Arthritis Treatment), the phase IIIb randomized, active-controlled efficacy and safety study evaluating subcutaneous abatacept in patients with early RA. The objective of the study by Emery and colleagues\(^7\) was to determine whether a 12-month course of therapy with abatacept and/or methotrexate (MTX) monotherapy (alone or in combination) would result in remission of disease in patients with early RA within 12 months. In this study, early RA was defined as (1) active synovitis in ≥2 joints for ≥8 weeks, (2) a Disease Activity Score in 28 joints based on C-reactive protein levels (DAS28[CRP]) >3.2, and (3) onset of symptoms within ≤2 years. The 351 MTX-naïve patients all had positive tests for anti-cyclic citrullinated-2 antibodies (anti-CCP2+). Patients were randomized to receive 12 months of weekly injections of abatacept 125 mg plus MTX (n=119 patients), abatacept monotherapy (n=116 patients), or MTX monotherapy (n=116 patients).

At month 12, all patients who achieved a DAS28[CRP] <3.2 entered a withdrawal period of 12 months, during which no treatment was given. At 12 months, a total of 223 patients had achieved DAS28[CRP] <2.6: 60.9% of patients in the combination therapy group, 42.5% of patients in the abatacept monotherapy group, and 45.2% of patients in the MTX monotherapy group. During the withdrawal period, an increase in disease activity caused 177 of the 223 patients (79%) to discontinue this phase of the study. The percentages of patients who had DAS28[CRP] <2.6 at both 12 and 18 months were 14.8% of the combination therapy group, 12.4% of the abatacept monotherapy group, and 7.8% of the MTX monotherapy group. Although the rate of remission maintenance after withdrawing therapy was low, the investigators noted that, compared with patients in the MTX monotherapy group, “a small but significantly higher number of patients” treated with combination therapy were able to maintain drug-free remission at 18 months.

In the study by Peterfy and colleagues,\(^8\) the AVERT data were analyzed with respect to therapeutic responses measured on magnetic resonance imaging (MRI). This analysis focused on joint damage progression, as assessed by gadolinium-enhanced MRI of the dominant hand-wrist at baseline, and at 6, 12, 18, and 24 months. The investigators assessed changes from baseline in synovitis, osteitis, and bone erosion MRI scores.

During the 12-month treatment period, the combination therapy group had improved synovitis, osteitis, and erosion scores that were numerically (but not statistically) higher than the scores in the abatacept-alone or methotrexate-alone groups. Among the patients receiving monotherapy, those treated with abatacept had better synovitis and osteitis scores than the patients receiving MTX alone. No evidence of disease progression was seen among patients who achieved a DAS28[CRP] <2.6 at 12 months and maintained that level of response to 18 months.

References


Continued on page 14
Newer and Emerging Treatments in RA

Alan K. Matsumoto, MD

The introduction of tumor necrosis factor (TNF) inhibitors in the treatment of rheumatoid arthritis (RA) has made it possible to substantially slow or arrest disease progression in many patients. Five of these agents have been approved in the United States: infliximab, adalimumab, certolizumab pegol, etanercept, and golimumab.

More recently, biologic agents that target other inflammatory pathways have been introduced: abatacept (T-cell costimulation blocker), anakinra (interleukin-1 receptor antagonist), rituximab (depletes CD20-positive B cells), tocilizumab (interleukin-6 receptor inhibitor), and tocilizumab (Janus kinase [JAK] inhibitor). Tofacitinib, recently approved for the treatment of RA, is a pan-JAK inhibitor—indicating that it inhibits, principally, JAK3, but also JAK1, JAK2, and TYK. Several others are being investigated at this time. Baricitinib, an agent currently in phase III trials, is more selective for JAK1 and JAK2. The compound filgotinib also works through JAK3 but is more selective for JAK1. Finally, decernotinib (VX509) and ASP015K—like tofacitinib—act chiefly by inhibiting JAK3.

The efficacy and safety of all of the approved agents has been clearly demonstrated, but some agents are contraindicated in various clinical circumstances, not all patients respond adequately (or maintain response) to these agents, and some patients develop adverse effects with some agents, requiring cessation of therapy.

For these reasons, many clinicians and patients welcome the possibility of newer treatments now being studied in clinical trials that may expand the roster of treatment options and allow even better individualization of therapy than is now possible. Most of these agents are novel molecules that target intracellular kinases, inflammatory pathways not currently addressed by most of the available agents.

Newer Investigational Agents

Genovese and coworkers reported the results of a phase III international study of sarilumab, an interleukin-6 receptor inhibitor. For this 52-week study, 1,197 patients with active, moderate-to-severe RA and an inadequate response to methotrexate (MTX) were randomly assigned (1:1:1) to receive either 150 or 200 mg of sarilumab plus MTX every 2 weeks or placebo.

The three primary end points were the proportion of patients who achieved a 20% improvement in American College of Rheumatology criteria (ACR20) at week 24, the change from baseline in HAQ-DI (Health Assessment Questionnaire Disability Index) at week 16, and the change from baseline in the van der Heijde modified total Sharp score (mTSS) at week 52. Patients in both sarilumab groups had statistically significant and clinically meaningful improvements compared with the placebo group in all three end points.

Regarding safety, in the sarilumab treatment groups, 62 serious adverse events were seen in the 150-mg dose group and 68 were reported in the 200-mg group; 40 serious adverse events were seen in the placebo group. The most frequently reported events were infections (11 and 17 in the two sarilumab groups, and 10 in the placebo group).

A number of other agents currently are in earlier stages of investigation. Filgotinib (GLPG0634) currently is undergoing phase II dose-finding studies, identified by the acronyms DARWIN1 and DARWIN2. Recently, Vanhouxe and colleagues presented findings from a 4-week phase IIa, double-blind, placebo-controlled, proof-of-concept study of filgotinib in a group of patients with moderate-to-severe RA whose response to MTX was not adequate. In this study, 36 patients continued their background regimen of MTX; 12 patients also received 200 mg filgotinib once daily, 12 received 100 mg filgotinib twice daily (for a total daily dose of 200 mg), and 12 patients received placebo. The primary end point, ACR20, was seen in 83% of the patients who received filgotinib and in 33% of those in the placebo group (P<0.01). (The investigators noted that no clinically relevant differences were seen in the two active treatment groups, attributed to the small sample size.) Significant differences also were seen in improvements between the active treatment and placebo groups in DAS28 and C-reactive protein levels (P<0.0001 for both measures). No severe adverse events were seen in this trial.

Takeuchi and colleagues reported the results of a phase Ib dose-response study of ASP015K in a population of Japanese patients with RA. The compound is an oral agent that selectively inhibits JAK3. In this 12-week, double-blind monotherapy study, 281 patients who had incomplete responses to a 4-week course of MTX were given ASP015K in doses ranging from 25 to 150 mg/day. After 12 weeks of treatment, the best responses were seen in patients using 100 or 150 mg/day; 54% and 64% of patients, respectively, achieved ACR20, the primary end point. Furthermore, 30% of patients who received these higher doses achieved ACR50, and ACR70 was seen in 16% of patients who received 100 mg/day of the drug and 12% of those who received 150 mg/day. Adverse effects were similar to those seen with the other JAK3 inhibitors currently being investigated (including tofacitinib, baricitinib, filgotinib, and decernotinib).

The results of a phase II study of itolizumab, an anti-CD6 monoclonal antibody, were reported by Chopra and colleagues. These investigators noted that the preliminary evidence from their study demonstrates efficacy and safety of this agent in patients with RA who have an inadequate response to MTX. In this 24-week study, 70 patients were randomized to four groups: three groups received one of three doses of itolizumab plus MTX; the fourth group received MTX...
New Findings in Systemic Lupus Erythematosus Therapy

Alan K. Matsumoto, MD

Until March 2011, the only systemic medications approved by the US Food and Drug Administration (FDA) for the treatment of systemic lupus erythematosus (SLE) were corticosteroids, hydroxychloroquine, and acetylsalicylic acid. In addition, several medications currently are being used to treat SLE but do not have FDA approval for this indication.

The antimalarial drug mycophenolate mofetil (MMF), which blocks proliferation of activated B and T cells, has been used in selected patients with SLE, for both lupus nephritis and nonrenal lupus. For example, in a review of key studies of this drug in SLE—Dall’Era1 noted that in the Aspreva Lupus Management Study (ALMS), MMF was shown to be comparable to intravenous pulse cyclophosphamide for induction treatment of lupus nephritis and more effective than azathioprine in reducing treatment failures during maintenance treatment. There was also some evidence from ALMS that nonrenal signs and symptoms of SLE improved in patients treated with MMF.

Several biologic agents also have been used with increasing frequency, according to investigators who provided an update from the International Registry for Biologics in SLE (IRBIS). van Vollenhoven and colleagues2 reported that of 455 patients with SLE treated with biologics, 382 (84%) received rituximab (a CD-20-directed cytolytic antibody currently approved for rheumatoid arthritis and other, non-rheumatologic indications); 45 (10%) received belimumab (approved by the FDA for SLE—discussed below); 23 (5%) were treated with efalizumab (currently in phase III clinical trials for SLE—discussed below); and the rest received a tumor necrosis factor inhibitor (abatacept, etanercept, or adalimumab, <1% each; none of these agents is approved for SLE).

In 2011, the FDA approved the use of belimumab, a human monoclonal antibody that inhibits B-cell activating factor (BAFF). At a recent international symposium on rheumatology, several studies were presented that may help guide clinicians regarding patient selection and optimum use of this novel medication.

Schwarting and colleagues3 reviewed results from the German multicenter, retrospective chart review called OBSERVE. The purpose of the study was to evaluate outcomes associated with belimumab in patients with SLE treated in clinical practice settings. Data on patients with SLE were collected from chart abstractions by 21 German rheumatologists. The clinicians were asked to assess changes in the manifestations of SLE for a 6-month period, beginning at the start of patients’ belimumab treatment, and to provide information about overall clinical response, reasons for discontinuation of therapy (if therapy was stopped), and any corticosteroid use during the study period. A total of 102 charts were abstracted.

The clinicians reported improvements of 50% or greater in arthritis (56% of patients showed improvement), high anti-ds-DNA (21% of patients improved), fatigue (25% of patients), low complement (23%), and rash (51% of patients improved). Among the 102 patients, mean corticosteroid dosage was reduced from 13.6 to 7.8 mg/day. Six patients discontinued belimumab: Three stopped because of disease progression or insufficient treatment response, two patients had a suspected drug reaction, and one patient requested cessation of therapy (the reason was not provided).

Collins and coworkers4 reported an analysis of 18-month data from the US OBSERVE study of belimumab. In this study, 92 rheumatologists were invited to participate in a chart review of randomly selected patients with SLE who had received at least eight belimumab infusions and to evaluate clinical response based on the physician’s impression of overall change in SLE every 6 months from the time of the start of belimumab therapy, up to 2 years of therapy. A total of 501 charts were examined after an initial 6 months of therapy; charts on 334 patients were reviewed for the period from baseline to month 18. The investigators found that more than 40% of patients improved by 50% or more, and the mean prednisone dose decreased from 19.5 to 3.8 mg daily.

In a third study of belimumab, Askanase5 invited clinicians who had participated in phase III clinical trials to complete a one-page questionnaire on patients who had used belimumab for at least 3 months. The questionnaire for each patient included demographic information, characteristics of SLE, and details about belimumab use. The mean age of the patients in this study was 41.9±12.6 years, and most of the patients (92.0%) were female. The racial/ethnic distribution was 67.1% white, 24.7% black, 5.7% Asian, and 5.3% Hispanic. The average duration of disease was 12.2±8.2 years. Prednisone was the most commonly used concomitant medication (73% of patients, with 41.7% using ≥10 mg/day); the other concomitant medications reported were antimalarials (71.7%), mycophenolate mofetil (34.2%), azathioprine (20.3%), and methotrexate (MTX) (11.8%). A small percentage of patients (3.7%) were taking no other medications for SLE. At baseline, the clinicians named arthritis (in 69.5% of patients), rash (in 44.4%), and inability to taper corticosteroid use (in 27.3%) as the main factors for initiating belimumab treatment. Other reported manifestations of the disease in this group of patients were serositis (16.0%), hematologic abnormalities (13.9%), and renal involvement (10.7%); in 65.2% of patients, two or
more SLE manifestations were active. According to the evaluating clinicians, 69 patients (46.0%) had clinical responses after 3 months of belimumab therapy, with “marked improvement” in arthritis, rash, or both. At 12 months, data were available for 112 patients, of whom 54 (48.1%) had improvements in arthritis, rash, and/or renal complications. The author noted that these findings reflect those reported in the phase III trials.

Interestingly, all three of these studies showed similar response rates: About 45% to 50% of patients experienced a response rate of 50% or better. In the studies by Schwarting and coworkers and Collins et al., most patients were able to achieve decreases in prednisone dosage at 6 months, and virtually all of the patients showed improved serologic profiles. Although these studies are based on subjective clinical impressions and relatively small numbers of patients, the information derived is useful as real-world experience with belimumab in clinical practice settings.

**Emerging Therapies in SLE**

Another medication in the anti-BAFF antibody class, blisibimod, is being studied in recently launched phase III clinical trials. Like belimumab, blisibimod neutralizes soluble BAFF, but the newer agent also neutralizes membrane-bound BAFF.

Farther along in phase III clinical studies is epratuzumab, a monoclonal antibody that targets CD22 on B cells. The results of EMBLEM, a 12-week phase IIb dose-ranging study of epratuzumab, demonstrated the tolerability of, and established an optimum dosing regimen for, epratuzumab in patients with moderate-to-severe SLE. In this study, the investigators used a new composite primary end point called BICLA, a Combined Lupus Assessment based on the British Isles Lupus Assessment Group (BILAG) criteria: BILAG improvement without worsening, no worsening in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or Physician Global Assessment (PGA) scores, and no treatment failure. BICLA also is the primary end point in the ongoing phase III studies.

Recently, Furie and colleagues reported the results of their study, undertaken to correlate BILAG response with clinical and laboratory parameters in an open-label extension (OLE) phase of EMBLEM. Any patient from EMBLEM eligible for enrollment who completed the 12-week study or who completed at least 8 weeks but discontinued in the study because of lack of efficacy. In the OLE, 203 patients received a 1,200-mg dose of epratuzumab at weeks 0 and 2 of each 12-week cycle. At weeks 48 and 96, changes in clinical and laboratory parameters were compared to baseline at the beginning of the EMBLEM double-blind study in BILAG responders (improvement in BILAG scores over baseline, no new BILAG A scores, and no new B scores ≥2) and nonresponders (lack of improvement, worsening, or withdrawal from the study prior to assessment). The investigators reported that 80 patients (39%) achieved a BILAG response at week 48 and 72 (35%) had a BILAG response at week 96. At both time points, significantly greater reductions were seen in SLEDAI, PGA, and patient global assessment scores in BILAG responders compared with nonresponders ($P<0.0001$). The responders also had improvements in more BILAG organ domains than did the nonresponders. Greater reduction also was seen in corticosteroid use among the responders, although the difference was not statistically significant. In addition, among responders compared with nonresponders, greater decreases were seen in absolute B cell (CD19+) and T cell (CD3+) counts, and smaller increases were seen in protein/creatinine ratios.

Gordon and colleagues recently presented the results of a double-blind placebo-controlled trial of atacicept, a fusion protein that inhibits two B-cell stimulating factors, B1yS and APRIL, in SLE. In a previous placebo-controlled trial of atacicept in APRIL-SLE, the drug—administered at 150 mg—reduced BILAG scores in both A and B domains. In this study, the investigators evaluated atacicept efficacy using both BILAG scores and the modified SELENA SLEDAI flare index. Patients with active SLE (defined as a score of ≥1 on BILAG A and/or B) were tapered from their corticosteroid medication over a period of 12 weeks. Those who reached BILAG C or D at weeks 10 and 12 were randomized to receive standard of care plus atacicept 75 mg, atacicept 150 mg, or placebo twice a week for 4 weeks, then once a week for 48 weeks. BILAG and SELENA SLEDAI flare scores and corticosteroid use were evaluated at monthly intervals.

Two fatal pulmonary infections occurred in the group of patients receiving the higher dose of atacicept, so the 150-mg arm of the study was stopped early. Significant reductions were seen in both musculoskeletal and mucocutaneous disease flares; decreases also were seen in the number of patients in the active treatment groups who had one or more increases in corticosteroid dosage, and in the number of patients who had increases of 20 mg/day or more.

Finally, the proteasome inhibitor bortezomib, currently approved for the treatment of patients with multiple myeloma, is being studied in patients with SLE. In a report presented at a recent international symposium on rheumatologic diseases, Alexander and colleagues described the use of bortezomib as induction therapy in patients with refractory SLE in a small prospective study. The patients received one to four cycles of the drug, administered intravenously. The investigators found significantly decreased disease activity with induction therapy, which remained stable for the subsequent 3 months with maintenance treatment. Serum antibody concentrations decreased significantly; protective antibodies decreased by about 30%, whereas anti-dsDNA antibodies decreased by about 60%. They also reported “strong” decreases in HLA-DR+ short-lived and HLA-DR+ long-lived peripheral blood plasma cells ($P=0.24$ and $P=0.038$, respectively), although the plasma cell numbers did increase between treatment cycles. There were no significant changes in circulating B cells.

Using standard doses of bortezomib, along with maintenance standard of care therapy, improvement was impressive over the 3-month treatment period. Moreover, the immunologic markers of lupus disease activity declined significantly,
and decreases were also seen in short-lived and long-lived plasma cells and immunoglobulin levels. Although this study involved a small number of patients, the results are interesting for the potential implications for those with SLE who are extremely refractory to treatment and who have failed multiple other therapies.

References

Dosage Reduction and Withdrawal of Biologic Therapy in RA

Continued from page 10


Role of Triple Nonbiologic Therapy in RA

Continued from page 5

References

Newer and Emerging Treatments in RA

Continued from page 11

alone. At week 12, 58.3% of the patients in the three itolizumab groups had moderate or good responses according to DAS28-EULAR criteria, compared with 20% of those in the MTX monotherapy group. Most of the commonly reported adverse events were described as mild or moderate; fever and cough were the most commonly reported events.

References
New Developments in Rheumatology
Highlights from an International Conference
Part I: Focus on Rheumatoid Arthritis and Systemic Lupus Erythematosus

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CME QUESTIONS: For each question or incomplete statement, choose the answer or completion that is correct.

1. In the AVERT (Assessing Very Early Rheumatoid Arthritis Treatment) trial, the definition of remission was the DAS in 28 joints based on C-reactive protein (DAS28(CRP)) <2.4. This value: a. Correlates with tender and swollen joint counts of 0
   b. Has not been validated as an accurate definition of remission
   c. Has been shown to be equivalent to DAS28 based on erythrocyte sedimentation rate (DAS28(ESR)) <2.4
   d. Is a validated, accurate definition of remission

2. Several large randomized trials have demonstrated that monotherapy with methotrexate results in low disease activity in:
   a. About 40% of patients
   b. About 50% of patients
   c. Less than 15% of patients
   d. Less than 33% of patients

3. Which one of the following statements applies to the study of triple DMARD therapy presented by Bonafede et al, discussed in this supplement?
   a. More patients in the nonbiologic DMARD group than in the biologic/methotrexate group stopped taking their initial medication because of medication intolerance.
   b. Overall, triple DMARD therapy seems to be as well tolerated as the combination regimen with a biologic plus methotrexate.
   c. Significantly more patients in the nonbiologic DMARD group failed to adhere to their medication regimen than those in the biologic therapy/methotrexate group.
   d. Triple DMARD therapy was significantly less effective than the biologic/methotrexate treatment.

4. In a recent study, Raaschou and colleagues studied 240 patients with rheumatoid arthritis (RA) and a previous history of breast cancer, half of whom had been treated with tumor necrosis factor (TNF) inhibitors. This study demonstrated that women with RA and a previous (and not recent) history of breast cancer:
   a. Had a statistically higher incidence of cancer recurrence with anti-TNF use
   b. Had a statistically higher incidence of de novo solid tumors at non-breast sites with anti-TNF use
   c. Had no statistical increase in solid tumors at de novo solid tumors at non-breast sites with anti-TNF use
   d. Had no statistical increase in breast cancer recurrence with anti-TNF use

5. In the study of ischemic stroke risk in patients with rheumatoid arthritis by Mantel and colleagues, discussed in this supplement, the investigators found that:
   a. Patients with early RA have a lower risk for ischemic stroke than do patients with disease of longer duration
   b. Traditional risk factors for ischemic stroke had more influence in the non-RA population than in patients with RA
   c. Use of biologic agents increases the already increased risk for ischemic stroke mortality in RA
   d. Younger patients with RA and multiple traditional risk factors have a lower mortality than older patients without RA

6. The study by Kadota and colleagues discussed in this supplement involved patients with rheumatoid arthritis who were undergoing orthopedic surgeries. These investigators found that the preoperative use of biologic agents in patients with RA:
   a. Can continue safely until one drug half-life prior to surgery
   b. Is an independent risk factor for delayed wound healing and surgical site infections
   c. Is not an independent risk factor for delayed wound healing or surgical site infections
   d. Should be discontinued at least 1 month prior to surgery

7. Designation of an agent as a "pan-JAK inhibitor" indicates that it inhibits Janus kinase 1, 2, and 3, and also:
   a. CD-20-positive B cells
   b. Interleukin-6 (IL-6)
   c. T cell costimulation
   d. Tyrosine kinase (TYK)

8. In their study of treatment continuation rates for biologic monotherapy compared with a biologics-plus-methotrexate (MTX) in an elderly population of patients with RA, Richter and colleagues found that ________ had more comorbidities, had poorer physical function, and were significantly more often treated with prednisone at doses exceeding 10 mg/day.
   a. More patients on biologic monotherapy rather than biologics + MTX
   b. More patients on monotherapy with certain biologics
   c. More patients on biologics + MTX
   d. More patients on methotrexate monotherapy

9. In 2011, the FDA approved the use of the first biologic for systemic lupus erythematosus, belimumab, a human monoclonal antibody that inhibits B-cell activating factor (BAFF). Currently nearing completion of phase III trials in SLE is epratuzumab, __________.
   a. A biologic that inhibits tumor necrosis factor
   b. A monoclonal antibody that targets CD22 on B cells
   c. Another medication in the anti-BAFF antibody class
   d. A T cell costimulation inhibitor

10. In a study of an investigational biologic therapy for systemic lupus erythematosus, Wallace and colleagues used a new composite primary end point called ________.
    a. BASDAI-SELENA (Bath Ankylosing Spondylitis Disease Activity Index and Safety of Estrogens in Lupus Erythematosus National Assessment)
    b. BASDAI-SLEDAI (Bath Ankylosing Spondylitis Disease Activity Index and Systemic Lupus Erythematosus Disease Activity Index)
    c. BICLA (Combined Lupus Assessment based on British Isles Lupus Assessment Group criteria)
    d. BI-SLEDAI (British Isles Assessment Group criteria and Systemic Lupus Erythematosus Disease Activity Index)

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New Developments in Rheumatology: HIGHLIGHTS FROM AN INTERNATIONAL CONFERENCE

PART I: Focus on Rheumatoid Arthritis and Systemic Lupus Erythematosus • Activity Evaluation Form

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants.

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Please indicate your profession/background (check only one): MD/DO MSN/BSN/RN PA APN/NP PharmD/RPh Resident/Fellow Researcher Administrator Student Other; specify _________________________________________

LEARNING OBJECTIVES: Having completed this activity, you are better able to

Discuss the current information about rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) pathogenesis and emerging targets for future therapy. 5 4 3 2 1

Demonstrate improved knowledge of the mechanisms of action, efficacy, and safety profiles of the biologic agents currently available for RA and SLE. 5 4 3 2 1

Optimize the use of medications now available for RA and SLE. 5 4 3 2 1

Evaluate the results of clinical studies on promising medications now under investigation in RA and SLE and appropriately incorporate new treatments. 5 4 3 2 1

Improve office protocols, as needed, to better monitor patients more frequently to ensure tight control of RA symptoms. 5 4 3 2 1

Safely and appropriately switch medications in patients with RA or SLE who do not respond optimally to initial therapy or whose symptom control decreases after initial good response to a medication regimen. 5 4 3 2 1

Evaluate the clinical significance of recent studies that provide enhanced understanding of the pathogenesis of both RA and SLE. 5 4 3 2 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Based on the content of the activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (Check one)


☐ Do nothing differently as the content was not convincing. ☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

☐ Yes. Please provide your email address __________________________________________

☐ No. I don’t plan to make a change.

If you are not able to effectively implement what you learned at this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)?

OVERALL EVALUATION

The information presented increased my awareness/understanding of the subject. 5 4 3 2 1

The information presented addressed my educational needs. 5 4 3 2 1

The information presented will influence how I practice/do my job. 5 4 3 2 1

The information presented will help me improve patient care/my job performance. 5 4 3 2 1

The program was educationally sound and scientifically balanced. 5 4 3 2 1

The educational materials were useful. 5 4 3 2 1

The active learning and assessment strategies (questions, cases) were appropriate and effective. 5 4 3 2 1

Overall, the program met my expectations. 5 4 3 2 1

I would recommend this program to my colleagues. 5 4 3 2 1

Alan K. Matsumoto, MD

Author demonstrated current knowledge of the topic. 5 4 3 2 1

Author was organized in the written materials. 5 4 3 2 1

Roy M. Fleischmann, MD, MACR

Author demonstrated current knowledge of the topic. 5 4 3 2 1

Author was organized in the written materials. 5 4 3 2 1

Arthur F. Kavanaugh, MD

Author demonstrated current knowledge of the topic. 5 4 3 2 1

Author was organized in the written materials. 5 4 3 2 1

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.

Rutgers, the State University of New Jersey, thanks you for your participation in the CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.

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