New Developments in Rheumatology
HIGHLIGHTS FROM AN INTERNATIONAL CONFERENCE
PART II: Focus on Psoriatic Arthritis and Ankylosing Spondylitis

- Introduction and Commentary
- Optimizing the Management of Psoriatic Arthritis
- Advances in Outcome Measures and Therapy for Psoriatic Arthritis
- Improving the Clinical Assessment of Patients With Ankylosing Spondylitis
- New Developments in Therapy for Ankylosing Spondylitis

FACULTY:
Alvin F. Wells, MD, PhD, FACP, FCR
Visiting Foreign Professor
Karolinska Institute
Stockholm, Sweden
Director, Rheumatology and Immunotherapy Center
Oak Creek, Wisconsin
Adjunct Assistant Professor
Duke University Medical Center
Durham, North Carolina

With Commentary From:
Allan Gibofsky, MD, JD, FACP, FCLM
Professor of Medicine and Public Health
Weill Medical College of Cornell University
Attending Rheumatologist
Hospital for Special Surgery
New York, New York

Review Faculty:
Roy M. Fleischmann, MD, MACR
Clinical Professor of Medicine
University of Texas Southwestern Medical Center
Co-Director, Division of Rheumatology
Texas Health Presbyterian Medical Center
Co-Director, Metroplex Clinical Research Center
Dallas, Texas

Arthur Kavanaugh, MD
Professor of Medicine
University of California, San Diego School of Medicine
San Diego, California

Original Release Date: December 2014
Expiration Date: November 30, 2016
Estimated Time to Complete Activity: 2.5 hours

Supported by educational grants from
AbbVie, Inc., Celgene Corporation, Eli Lilly and Company, and UCB, Inc.
New Developments in Rheumatology
HIGHLIGHTS FROM AN INTERNATIONAL CONFERENCE

PART II: Focus on Psoriatic Arthritis and Ankylosing Spondylitis

4 Introduction and Commentary
By Allan Gibofsky, MD, JD, FACP, FCLM

5 Optimizing the Management of Psoriatic Arthritis

7 Advances in Outcome Measures and Therapy for Psoriatic Arthritis

9 Improving the Clinical Assessment of Patients With Ankylosing Spondylitis
By Alvin F. Wells, MD, PhD, FACP, FACR

11 New Developments in Therapy for Ankylosing Spondylitis

12 Post-Test

13 Evaluation From

ACCREDITATION

Physicians
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Rutgers, The State University of New Jersey, and Global Academy for Medical Education, LLC. Rutgers, The State University of New Jersey, is accredited by the ACCME to provide continuing medical education for physicians.

Rutgers, The State University of New Jersey, designates this enduring material for a maximum of 2.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing
Rutgers, The State University of New Jersey, Center for Continuing and Outreach Education (CCOE) is an approved provider of continuing nursing education by the New Jersey State Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. Provider Number P173-12/12-15.

This activity is awarded 2.5 contact hours (60-minute CH).

Pharmacists
Rutgers, The State University of New Jersey, is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This course ACPE # 0374-9999-14-005-H01-P qualifies for 2.5 contact hours (2.5 CEUs) of continuing pharmacy education credit.

TARGET AUDIENCE
This educational activity is intended for rheumatologists and other health care practitioners who treat patients with psoriatic arthritis and ankylosing spondylitis.

EDUCATIONAL NEEDS
Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were well-represented topics at a recent international conference on rheumatology. Presenters discussed new findings with respect to the use of traditional therapies and widely used biologic agents, as well as other, newer biologic agents that target a variety of pathogenetic inflammatory pathways in these spondyloarthropathies.

Clinicians who manage patients with PsA and AS must consider a number of possible changes in their current approach to diagnosis and managing clinical outcomes. Both health care providers and patients will benefit from the expert review and synthesis of diagnosis- and treatment-related research findings that were recently presented.
LEARNING OBJECTIVES
By reading and studying this supplement, participants should be prepared to:
• Discuss cutting-edge research findings regarding the diagnosis and treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS).
• Optimize the use of both traditional therapies and currently available biologic agents for selected patients with PsA and AS.
• Evaluate the results of clinical studies on promising medications now under investigation in PsA and AS.
• Safely and appropriately incorporate new medications into the treatment regimens of patients with PsA and AS, as these agents become available.
• Make ongoing modifications to therapy, as required, in patients with PsA to maximize outcomes and patient satisfaction.
• Implement better screening and diagnostic procedures to diagnose AS early, and before permanent bone damage has occurred.

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.

FACULTY
Allan Gibofsky, MD, JD, FACP, FCLM, Consultant: AbbVie, Inc., Amgen, Inc, Antares Pharma, Celgene Corporation, Genentech, Horizon Pharma, Iroko Pharmaceuticals, LLC, Medac Pharma Inc, Pfizer Inc, and UCB, Inc. Speaker’s Bureau: AbbVie, Amgen, Antares, Celgene, Genentech, Iroko, Pfizer, and UCB. Member Scientific Advisory Board: AbbVie, Amgen, Antares, Celgene, Genentech, Horizon, Iroko, Pfizer, and UCB. Stock Shareholder: AbbVie, Amgen, GlaxoSmithKline, Johnson & Johnson, Pfizer, and Regeneron.

Alvin F. Wells, MD, PhD, Grant/Research Support: AbbVie, Inc, Celgene Corporation. Speakers Bureau: Amgen, AbbVie, Bristol-Myers Squibb, Celgene, Pfizer Inc, and UCB, Inc.

In order to help ensure content objectivity, independence, and fair balance, and to ensure that the content is aligned with the interest of the public, CCOE has resolved all potential and real conflicts of interest through content review by a non-conflicted, qualified reviewer. This activity was peer-reviewed for relevance, accuracy of content, and balance of presentation by:

Vivien M. Hsu, MD, Associate Professor of Medicine; Medical Director, Clinical Research Center; Director, Scleroderma Program, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ. Dr Hsu has no relevant financial relationships to disclose.

Field Testers: Reena Patel, MD; Shreya Patel, MD; Steve Drakikwicz, MD; Claudia E. Carron, MSN, RN, NE-BC; have no relevant financial relationships to disclose. Mary Bridgeman, PharmD, BCPS, has disclosed the following relevant financial relationships: Grant Research: Carefusion Foundation 2014 Circle of Excellence Grant; Consultant: Merck Consumer Care; Speaker’s Bureau: Amerisource Bergen Corporation.

Nurse Planner: Margaret Evans, MSN, RN, has no relevant financial relationships to disclose.

CCOE Staff: Tristan Nelsen, MNM, CMP, and Elizabeth Ward, MSJ, have no relevant financial relationships to disclose.

Global Academy for Medical Education Staff:
Sylvia H. Reitman, MBA, DipEd; Shirley V. Jones, MBA; and Joanne Still, BA, have no relevant financial relationships to disclose.

OFF-LABEL/INVESTIGATIONAL USE DISCLOSURE
This activity discusses the investigational use of the following approved agents: rituximab, tocilizumab, tofacitinib, and ustekinumab. Also discussed are the following investigational products, not yet approved: ixekizumab and secukinumab.
Introduction and Commentary

Allan Gibofsky, MD, JD, FACP, FCLM

This supplement to Rheumatology News focuses on psoriatic arthritis (PsA) and ankylosing spondylitis (AS), with articles authored by Alvin F. Wells, MD, PhD, FACP, FACR, Director of the Rheumatology and Immunotherapy Center in Oak Creek, Wisconsin, and a member of The Rheumatology Education Group, LLC.

Over the past decade, interest in PsA and AS has increased substantially, with renewed emphasis on understanding the basic mechanisms involved in the immunopathogenesis of these diseases and, as a result, altering the immune response to inflammation to achieve potential therapeutic benefits.

Taken as a group, the seronegative spondyloarthropathies pose several serious challenges. Although their central feature is inflammation with destruction of bone, they are clinically distinct from other inflammatory conditions such as rheumatoid arthritis (RA), as well as from each other. They exist both as primary, idiopathic clinical entities and secondary features of nonarticular diseases (eg, inflammatory bowel disease, reactive arthritis, and psoriasis). They are treated with many of the same agents used to treat RA, as well as several others that are unique to these clinical entities.

As might be expected, the findings of numerous studies have been reported to help clinicians understand how to optimize management of PsA. The relationship between antidiagnostic antibodies and serum concentrations of tumor necrosis factor (TNF)–inhibiting biologic agents was a particular focus of several studies on PsA presented at a recent international rheumatology symposium. Decisions made by clinicians in determining and then prescribing optimal dosages of TNF inhibitors have important implications, not only for optimizing their efficacy but for cost-effectiveness as well. Another closely related issue is the concomitant use of nonbiologic therapies and how—if at all—their use impacts the effectiveness of the biologic agent used. Furthermore, no discussion about optimizing therapy for PsA would be complete without considering the effect of lifestyle modifications. Dr Wells discusses a study that demonstrated the combination of diet changes and exercise in patients with PsA was more effective than either intervention alone, reminiscent of gangster Al Capone’s famous quip: “You can get much further with a kind word and a gun than you can with a kind word alone.”

Dr Wells also reviews data from studies on new and emerging therapies for PsA. Recently, we have seen the introduction of two new agents for this disease—ustekinumab and apremilast—that make use of two mechanisms of action and different immunologic targets. Studies on tofacitinib (a small molecule that inhibits the Janus kinase-STAT pathway and is currently approved for use in patients with moderate to severe RA) and inhibitors of the cytokine interleukin-17 are under investigation for use in PsA. Although preliminary data on these newer agents are encouraging, more patients need to be studied before any definitive efficacy can be demonstrated.

In the absence of reliable biomarkers, the diagnosis of AS is entirely clinical. Reliable, objective diagnostic methods are needed, and clues from our knowledge of the epidemiology and pathogenesis of AS will be critical for defining and optimally utilizing new therapeutics. The difference in gender distributions between AS and RA has always been of particular interest, and Dr Wells reviews several studies that further explore this difference and its relationship with inflammatory activity, as well as appropriate disease activity tools.

Also of great interest has been the evolution in terminology from AS to axial spondyloarthropy, as well as the implications of this change for disease classification and therapy. This newer nomenclature, widely utilized in Europe, has yet to gain complete acceptance in the United States. The concept that a clinical phenotype may exist without radiographically defined changes (so-called nonradiographic axial spondyloarthropathy) has caused some controversy. This dilemma—and what it means for therapeutic optimization—is reviewed as well.

Finally, Dr Wells reviews data on newer therapies for AS and how a new biomarker might assist in the precise assessment of disease activity.

The data presented in both parts of this supplement not only greatly advance our knowledge about new developments in rheumatology in the international arena, but also open up new areas of investigation as well. Although few questions can be definitively answered at this time, such discussions raise new questions and can lead to new areas for investigation. This is as it should be in a field as intellectually rich and rewarding as rheumatology. Stay tuned: Based on reports from current avenues of research, the best is yet to come.
As the published literature and presentations at rheumatology conferences worldwide attest, the treatment of patients with psoriatic arthritis (PsA) has been a topic of intensified interest for the past several years. In addition to more information on established therapies such as conventional disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF) inhibitors, data from studies on newer and emerging agents have been presented recently. Moreover, investigation into other areas of clinical interest—including new assessment methods and the potential efficacy of lifestyle modifications—has garnered attention. This article highlights some of these developments.

Antidrug Antibodies and Anti-TNF Concentration Effect in PsA

Experience with TNF inhibitors over the past 10 to 15 years has demonstrated that not all patients with PsA respond to treatment with these agents, and among those who do respond, some patients experience loss of efficacy over time. This has been attributed partly—at least, theoretically—to the development of antidrug antibodies (ADAbs). Thus, the development of ADAbs, along with serum levels of anti-TNF biologic agents, is a current area of investigation with potentially valuable practical applications in clinical practice.

Vogelzang and colleagues recently published the results of their prospective cohort study of the pharmacodynamics and pharmacokinetics of adalimumab in patients with PsA. The study involved 103 consecutive patients diagnosed with PsA and treated with 40 mg adalimumab every other week. At baseline, disease activity was measured using the Disease Activity in 28 joints (DAS28) assessment. At week 28, serum trough samples were measured for adalimumab and DAS28 was again assessed. The serum trough concentrations of adalimumab ranged from 0.0 to 18.8 mg/L (mean, 7.2 mg/L). Although “reasonable efficacy” of the medication was seen at concentrations as low as 1.0 mg/L, maximum clinical benefit seemed to be achieved at drug concentrations from 5 to 8 mg/L, which was found in 18% of the patients (35% had adalimumab concentrations >5 mg/L and 47% had concentrations <8 mg/L).

The researchers also reported that those patients with any detectable ADAbs had significantly lower serum concentrations of adalimumab than did patients without ADAbs at week 28 (1.3 vs 8.7 mg/L, respectively; P<0.001) and after 52 weeks of follow-up (0.9 vs 9.4 mg/L, respectively; P=0.0001). This same group of investigators previously demonstrated similar results in a group of patients with rheumatoid arthritis (RA). It is clear from both of these studies that ADAbs affect the concentration-effect curve of adalimumab—an important finding that at least partially explains why some patients respond to the medication whereas others do not, and why clinical benefit varies among responders. This finding suggests that important areas for future study include predicting which patients will develop antibodies and at what point during treatment ADAbs might occur.

The immediate practical application of this research is to know the optimum clinical benefits of adalimumab can be seen when the serum range is 5 to 8 mg/L. Lower doses may not be as effective, whereas doses higher than this range do not produce greater benefit. This knowledge may help clinicians determine if the dosage should be decreased in patients with concentrations above 8 mg/L, and if patients with serum concentrations below 5 mg/L should receive a higher dosage or switch to another medication to try to achieve a better clinical response. According to the package insert for adalimumab, the serum level of the drug is increased with the concomitant use of methotrexate. The biggest clinical challenge is that testing methods for ADAbs and drug levels are still experimental and no test is readily available commercially.

Anti-TNF Concentration Effect and DMARD Background Therapy

A relatively recent debate in optimizing anti-TNF therapy concerns evaluating the efficacy of combining an anti-TNF biologic agent with methotrexate and/or other DMARDs. Kriekelaar et al recently presented data from a study of the effects of different DMARDs on adalimumab serum concentration levels in patients with RA or PsA. In the study, 375 consecutive patients—103 with PsA and 272 with RA—treated with adalimumab had trough concentrations of the agent measured at baseline and at weeks 4, 16, and 28. Results were reported on four groups of patients: those on adalimumab monotherapy (n=67), those who received concomitant therapy with methotrexate (n=224), those who received concomitant therapy with DMARDs other than methotrexate (leflunomide, hydroxychloroquine, sulfasalazine, or a combination of these medications) (n=26), and those who received concomitant therapy with both methotrexate and other DMARDs (n=58).

Throughout the 28 weeks, adalimumab monotherapy yielded the lowest serum concentrations. In contrast to monotherapy, adalimumab levels were significantly higher in the patients who had concomitant therapy with any DMARD (Table). No statistically significant difference was seen between both groups who received MTX and the other DMARDs group.

Lifestyle Modifications Enhance Therapeutic Response

The association between rheumatologic diseases and increased body mass index (BMI) has long been recognized. Recently, Abou-Raya and colleagues presented the results of
their study to determine the effects of a 12-month program of exercise and dietary weight loss on obese patients with PsA.

The investigators randomized 55 patients with PsA who had BMI ≥30 kg/m² to one of four groups: diet only, exercise only, diet plus exercise, or a control group who made no changes in lifestyle. All patients in the study continued their previous regimens of standard therapy—nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs, or TNF inhibitors. Data were collected every 6 months. In addition to weight monitoring, assessments included a physician's global assessment (PGA), a 20% improvement in American College of Rheumatology criteria (ACR20), the Psoriasis Area Severity Index (PASI), the DAS28 based on C-reactive protein, the Health Assessment Questionnaire–Disability Index (HAQ-DI), Beck's Depression Inventory (BDI), and a numeric fatigue rating scale. The primary outcome measures were improvement in ACR20, markers of systemic inflammation, BMI, physical function, pain, fatigue, depression, and HAQ-DI.

The researchers found that diet alone and exercise alone yielded similar clinical responses, but combined diet and exercise—even without background medication—was associated with significant improvement. In patients on medication, the interventions provided significant improvement beyond the clinical benefits of the therapeutic agents.

At 12 months, the mean reduction in body weight was 15% and 2% in the intervention and control groups, respectively—a significant difference (P=0.001). In the patients who incorporated both diet and exercise, significant improvements were seen in ACR20, PASI, DAS28 (CRP), HAQ-DI, and the fatigue rating scale, and measurements of serum levels as important markers of systemic inflammation—interleukin (IL)-6, IL-17, TNF-alpha, and high-sensitivity CRP—also were significantly improved compared to controls. Exercise alone produced significant improvements in ACR20, PASI, HAQ-DI, BDI, and the fatigue rating scale compared to controls. Diet alone produced significant improvement in ACR20, PASI75, and systemic inflammatory markers compared to controls.

References
Disease activity measurement in psoriatic arthritis (PsA) has been problematic for clinicians. Biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)—which are essential for the diagnosis of rheumatoid arthritis (RA) and disease monitoring in patients with RA—are not useful in PsA. Although skin disease can be a surrogate marker for PsA, not all patients have or ever will develop cutaneous manifestations. As a result, health-reported outcomes, imaging studies (principally, magnetic resonance imaging [MRI] and ultrasound), and serum markers of systemic inflammation all are being studied as potential methods to guide diagnosis and therapy.

One area of intense research is the use of ultrasonography (US) to detect the presence of enthesitis and to monitor the involved sites for clinical response. MRI has been studied and also may be helpful to detect enthesitis, although at a far greater cost than US. MRI also has been shown to be helpful for documenting the presence of inflammation in areas that may be difficult to evaluate clinically, such as the sacroiliac joints and axial spine. In essence, the use of US and MRI for these purposes is an intriguing area of investigation, but more studies are needed to validate the applicability of these modalities to general clinical practice.

New and Emerging Therapies in PsA
Conventional disease-modifying antirheumatic drugs (DMARDs) and biologic agents are effective for many patients. These therapies include the tumor necrosis factor (TNF) inhibitors and, most recently, the interleukin (IL)-12/23 blocker ustekinumab, the phosphodiesterase-4 (PDE-4) inhibitor, apremilast, and several IL-17 inhibitors. In addition to these latest additions to the roster of approved treatments, research continues on pathophysiologic pathways other than those targeted by the medications now available or in clinical trials.

PDE-4 Inhibitor
The first agent of this type, apremilast, was approved by the US Food and Drug Administration (FDA) for the indication of PsA in March 2014. Apremilast, an oral medication, is a small molecule that antagonizes PDE-4, an enzyme involved in the generation of inflammatory cytokines.

The PALACE series of clinical trials studied the use of apremilast 30 mg twice daily and reported efficacy data from weeks 16 and 24.

A study recently presented by Kavanaugh and colleagues1 at an international conference on rheumatology showed that the American College of Rheumatology criteria (ACR20) response during longer term active treatment (52 weeks) ranged from 52.6% to 63% in the patients who continued therapy for 52 weeks.

In addition, the safety data from the PALACE series demonstrated no significant serious adverse event issues with apremilast at 16 and 24 weeks. The 52-week data recently presented showed no safety signals with respect to tuberculosis or other infections or malignancy (including skin cancer). No laboratory monitoring is indicated during the use of apremilast. The major adverse events seen with apremilast were gastrointestinal tolerability issues—including nausea and diarrhea—which occurred in about 4.6% of apremilast-treated patients. Some weight loss was seen in about 10% of these patients, and headache was an uncommonly reported adverse effect.

The PALACE studies are ongoing, with PALACE 4 currently under way; this study will provide 5-year use efficacy and safety data on DMARD-naive patients with PsA. The data presented so far are promising, and we await the long-term results.

IL-12/23 Inhibitor
Ustekinumab, approved initially for the treatment of cutaneous psoriasis, received FDA approval for the treatment of PsA in 2013. Ustekinumab targets two inflammatory proteins—IL-12 and IL-23—that are known to play a role in the pathogenesis of psoriasis, PsA, and other immune-mediated inflammatory diseases. Approval of ustekinumab for the treatment of PsA was based on the results of the two pivotal clinical trials known as PSUMMIT12 and PSUMMIT23 (Study of the Safety and Effectiveness of Ustekinumab in Patients With Psoriatic Arthritis). The multicenter, randomized, double-blind, placebo-controlled phase III clinical trials involved 927 patients with active PsA with at least five tender and five swollen joints and C-reactive protein (CRP) levels of ≥0.3 who had previously been treated with conventional therapy. (The PSUMMIT2 study also included 180 patients who had previously been treated with between one and five anti-TNF biologic agents.)

The primary end point in both studies was achievement of a 20% improvement in ACR20 at week 24. Investigators from PSUMMIT1 reported that after 24 weeks of treatment, 42.4% of the patients who received ustekinumab 45 mg had achieved an ACR20 response; 49.5% of those who received ustekinumab 90 mg achieved an ACR20 response. In contrast, 22.8% of the patients in the placebo group achieved ACR20 (P<0.0001 compared with both treatment groups). The primary end point results were similar in the PSUMMIT2 study: 43.7% of the patients in the 45-mg ustekinumab group and 43.8% of those in the 90-mg ustekinumab group achieved ACR20 compared with 20.2% of patients in the placebo group (P<0.001 compared with both treatment groups).

However, although this agent offers statistically significant benefit, its overall effectiveness relative to that achieved by TNF inhibitors is less.
Recently, Kavanaugh and colleagues\(^1\) published an updated report on PSUMMIT1 and PSUMMIT2 demonstrating that, at both dosages, ustekinumab treatment can result in sustained inhibition of radiographic evidence of joint damage progression. To monitor the progression of joint disease, hand or foot x-rays were evaluated using the PsA-modified van der Heijde-Sharp score. In the lower-dose ustekinumab group, the average score was 0.4±2.1 at week 24; in the 90-mg ustekinumab group, the average score was 0.4±2.4. In contrast, the placebo group score at week 24 was 1.0±3.9, significantly higher than in both treatment groups\((P<0.02)\). This is similar to what is seen with TNF inhibitors.

**IL-17 Inhibitors**

Accumulating evidence suggests that the IL-17 pathway is an important pathophysiologic target in several immune-mediated inflammatory diseases. Two IL-17 inhibitors, ixekizumab and secukinumab, and the IL-17-R targeting agent, brodalumab, are being studied for the treatment of both plaque psoriasis and PsA.

In a phase II study of ixekizumab in patients with psoriasis, Leonardi and colleagues\(^4\) observed substantial reductions in joint pain—measured on a visual analog pain scale—among the patients who also had PsA. A subsequent phase III study of this agent in patients with active PsA, the SPIRIT-P1 study, currently is under way.

The efficacy and safety of secukinumab was evaluated in a 24-week, phase II proof-of-concept study in patients with PsA. McInnes and colleagues\(^5\) reported that, at week 24, 10 of 23 patients (43%) who received secukinumab had achieved the primary end point of an ACR20 response compared to 2 of 11 (18%) of patients on placebo\((P=0.14)\). This was not a statistically significant difference, the investigators noted, but the clinical benefits seen supported the launch of a phase III study known as FUTURE1, the results of which are expected to be reported in the near future.

As the data accumulate on the IL-17 inhibitors as a class, several questions must be addressed, including how effective they are compared to other available agents with respect to both joints and skin. It appears that the IL-17 class may be more effective for cutaneous than for joint disease, so it may be that IL-17 agents should be the choice after patients with PsA have failed treatment with NSAIDs and other biologics.

As the list of approved biologic agents grows, the IL-17 agents will have a pivotal role, but their placement in the therapeutic hierarchy will be determined by the approved indication(s), overall efficacy, and long-term safety.

**Janus Tyrosine Kinase Inhibitors**

Currently under investigation for the indication of PsA are the Janus tyrosine kinase–signal transducers and activators of transcription (JAK-STAT) molecules. One agent in this class, tofacitinib, has been approved by the FDA for use in RA. Three phase III clinical trials of tofacitinib in patients with PsA are ongoing. All three are safety and efficacy trials that involve patients with active PsA; the primary outcome measures for the two blinded trials are number of patients with an ACR20 response and improvement on the Health Assessment Questionnaire-Disability Index. One of these clinical trials, called OPAL BEYOND, is a randomized, double-blind, placebo-controlled study, scheduled for completion in August 2015. In OPAL BEYOND, an inadequate response to at least one TNF inhibitor is a requirement for enrollment. The second clinical trial, called OPAL BROADEN, is a study comparing the efficacy and safety of two doses of tofacitinib with that of adalimumab or placebo. The third clinical trial, called OPAL BALANCE, is a 36-month open-label extension study that will be ongoing until 2019. The primary outcome measures are number of patients with adverse events and serious adverse events and the number of patients with laboratory test values considered to be of possible clinical importance.

**Conclusion**

As is true for the population of patients with RA, many, but not all, patients with PsA respond well to therapy with anti-TNF agents. Newer biologic agents and novel small molecules may fill an unmet need for patients with PsA who do not respond adequately to TNF inhibitors or who are intolerant to these medications. Patient selection for these newer treatments will be based on individual clinical profiles, patient preference for oral versus injectable routes of administration, and the agents’ overall safety profiles.

**References**

Improving the Clinical Assessment of Patients With Ankylosing Spondylitis

Alvin F. Wells, MD, PhD, FACP, FACR

The early diagnosis of ankylosing spondylitis (AS) is based on clinical findings of inflammatory back pain, with or without associated findings on x-ray and/or magnetic resonance imaging (MRI). Typically, patients describe pain that wakes them from sleep, that is localized to the buttocks, and that improves with activity. Typically, the erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) levels are normal in these patients. Most, but not all, have a positive result on HLA-B27 testing. Newer data are emerging that a serum protein, 14-3-3-ŋ, produced by inflamed synovial cells and fibroblasts, may be elevated in patients with AS. Unfortunately, no biomarkers are currently available that help in the process of AS diagnosis and management of AS therapy. Thus, an important challenge in this era of existing and emerging biologic medications is how to better assess patients with active disease and determine who could benefit from changes in dosage and/or medication.

**Epidemiology and Demographics**

It has been widely accepted that AS affects men more frequently than women, in contrast to rheumatoid arthritis (RA), which has a higher prevalence in women. However, as studies from multiple countries have recently shown, AS affects more women than previously has been thought.

Recently, Jacobsson and colleagues in Sweden conducted a study with 197 patients, of which 38% were female. Because AS does not cause substantial inflammation in about 50% of men, laboratory markers of inflammation—such as ESR and CRP—usually are not helpful diagnostic tools in male patients; instead, clinicians consider AS in the differential for Caucasian males who present with back pain. This study, along with other studies, suggests AS also should be considered in female patients with back pain. Thus, female patients with back pain for more than 3 months that is responsive to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) should be evaluated for possible AS. As in male patients, a positive HLA-B27 test, absence of rheumatoid factor and anti-citrullinated peptide antibodies, and documented changes on x-ray and/or MRI increase the likelihood for a diagnosis of AS.

**Improved Use of Ankylosing Spondylitis Disease Activity Score**

Recently, Harvard and colleagues reported on the ASDAS Working Group’s efforts to improve the ankylosing spondylitis disease activity score (ASDAS), which was developed to allow researchers to classify patients’ disease activity as mild, moderate, or severe, with the ultimate goal of allowing better stratification of therapeutic targets. Harvard et al pointed out that the 2010 Assessments in Ankylosing Spondylitis Society (ASAS) and the European League Against Rheumatism (EULAR) management recommendations for AS had provided general principles of treatment for patients with axial spondyloarthritis (SpA) but did not allow for the identification of those patients with axial SpA who were receiving recommended care versus those who were not being treated according to the recommendations. Thus, quality criteria were needed to quantitatively define the items in the ASAS/EULAR recommendations.

To address this need, four members were appointed to work as a group and to draft quantitative definitions for each of the ASAS/EULAR recommendations. In several rounds of questionnaires, other members of the ASDAS Working Group were asked whether they agreed with the definitions; in later rounds, members were asked to consider alternate definitions for recommendations that had not been approved by at least 75% of the group in previous rounds.

Of the 11 items in the ASAS/EULAR recommendations presented, 6 were deemed by at least 75% of the members to be quantifiable so final definitions were approved: nonpharmacologic therapy, extra-articular manifestations and comorbidities, NSAIDs, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and tumor necrosis factor inhibitors.

Harvard et al maintain that using these AS-care quality criteria should improve the assessment of the clinical and economic benefits of using SpA management recommendations.

**Nonradiologic Ankylosing Spondylitis**

Another study was undertaken to better define AS disease in patients with nonradiographic ankylosing spondylitis (NR-AS)—that is, patients who do not have characteristic x-ray and MRI changes.

Poddubny and colleagues followed the patients in their...
study for 2 years and found that patients with AS and inflammatory back pain have comparable disease, whether or not radiographic changes are evident.

**Disease Markers in AS**

A new marker, 14-3-3-ƞ, recently has been shown to be present in RA, erosive PsA, and AS. This protein is from a family of proteins that act as “chaperones” for molecules involved in inflammation, cancer, and other diseases. With respect to rheumatic diseases, 14-3-3-ƞ levels have been shown to be increased in synovial fluid and sera in patients with RA compared to controls without the disease. Recently, increased levels of 14-3-3-ƞ have been found in patients with erosive PsA and AS.

In a recent study, Maksymowych and colleagues studied the 14-3-3-ƞ serum levels in 116 patients with AS and 106 controls. The serum levels were clearly increased in the patients with AS, but not in the healthy controls. In addition, 14-3-3-ƞ was associated with joint inflammation and was predictive of which patients will experience a worsening of their AS score over a period of 2 years. The investigators demonstrated that the serum marker is elevated and correlates with substantial inflammation and disease activity, based on the AS severity index. Thus, this marker may be useful to determine the presence of active synovial inflammation and may be useful in AS; furthermore, it seems that the higher the level, the more aggressive the disease course in some patients. This has been demonstrated in patients with RA, in whom the serum levels correlate with disease severity and radiologic damage.

One potential use of the 14-3-3-ƞ test would be to help better stratify patients with AS who may have a more aggressive disease course. Data from additional studies may demonstrate—and, thus, perhaps justify—the earlier and more aggressive use of biologic agents in these patients.

**References**


New Developments in Therapy for Ankylosing Spondylitis

Alvin F. Wells, MD, PhD, FACP, FACR

The introduction of the tumor necrosis factor (TNF) inhibitor class of biologic agents began a new era in effective treatment for patients with spondyloarthropathies. The TNF inhibitors also have established a new benchmark in expectations for response to newer agents developed subsequently. The newer agents currently being studied in ankylosing spondylitis (AS) include the interleukin (IL)-12/23 inhibitor, ustekinumab (already approved by the US Food and Drug Administration [FDA] for plaque psoriasis and psoriatic arthritis [PsA]); tocilizumab, an IL-6 inhibitor (now approved by the FDA for rheumatoid arthritis [RA] and juvenile idiopathic arthritis); tofacitinib, a pan-Janus kinase (JAK) inhibitor that principally targets JAK3 but also has activity against JAK1, JAK2, and tyrosine kinase (recently approved by the FDA for the treatment of RA); and secukinumab, an anti-IL-17A antibody.

Secukinumab
In a phase II, double-blind, proof-of-concept study of secukinumab versus placebo in patients with moderate to severe AS, Baeten and colleagues found that 59% of patients on secukinumab had an improvement of 20% on the Ankylosing SpondyloArthritis International Society (ASAS20) assessment. In contrast, ASAS20 was achieved in 24% of patients on placebo, for a 99.8% probability of secukinumab’s superiority over placebo. The results of a series of Phase III trials, known as the MEASURE studies, should be reported in the near future.

Ustekinumab
Poddubnyy and colleagues investigated the use of ustekinumab in patients with AS and demonstrated that ustekinumab therapy resulted in the reduction of tenderness and swollen joints, as assessed by ASAS40 and Bath Ankylosing Spondylitis Disease Activity Index responses. Because these investigators wanted to test response to treatment in patients with early disease, magnetic resonance imaging (MRI) was used to assess joint changes.

This study showed that ustekinumab use resulted in a significant impact on bone marrow inflammation (osteitis), not only in the spine but in other joints as well. Ustekinumab is approved by the FDA for RA, PsA, and other inflammatory diseases; however, it is not currently approved for patients with AS. Nevertheless, this small study demonstrated that 24 weeks of treatment with ustekinumab was effective in reducing MRI-detected inflammation of the axial skeleton. The investigators also noted a “clear correlation” between MRI and clinical responses.

References
PART II: Focus on Psoriatic Arthritis and Ankylosing Spondylitis

New Developments in Rheumatology
Highlights From an International Conference

Original Release Date: December 2014
Expiration Date: November 30, 2016 • Estimated Time to Complete Activity: 2.5 hours

To get instant CME/CE credits online, go to www.globalacademycmeevaluation.com/rheumnewstreg2 (Internet Explorer is the best browser to use). Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. For questions or concerns regarding content or continuing education, please contact Rutgers at 973-972-4267.

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

1. In a prospective cohort study of antidrug antibodies (ADAbs) in patients with psoriatic arthritis treated with adalimumab, Vogelzang and colleagues reported that, at weeks 28 and 52:
   a. Patients with any detectable ADAbs had significantly lower serum concentrations of adalimumab than did patients without ADAbs
   b. Patients with high levels of ADAbs experienced no clinical benefit from adalimumab
   c. Patients with low levels of ADAbs had adalimumab serum concentrations comparable to those seen in patients with no detectable ADAbs
   d. Patients with no detectable ADAbs had serum concentrations of adalimumab >8 mg/L and had significantly greater clinical benefit than patients with serum concentrations <8 mg/L

2. In a 28-week study of the effects of different disease-modifying antirheumatic drugs (DMARDs) on adalimumab serum concentrations in patients with psoriatic arthritis, Kriekckaert and coworkers found that:
   a. Adalimumab levels dropped in patients who also received multiple DMARDs
   b. Adalimumab levels were significantly higher in patients who also received methotrexate, compared to adalimumab plus hydroxychloroquine
   c. Adalimumab monotherapy yielded the lowest serum concentrations throughout the study
   d. Adalimumab yielded low serum concentrations when combined with any DMARD other than methotrexate

3. Abou-Raya and colleagues performed a controlled trial of nonpharmacologic interventions in obese patients with psoriatic arthritis and found that:
   a. Exercise provided significantly greater benefit than either weight loss or exercise plus weight loss
   b. Exercise and weight loss combined provided greater benefit than either modality alone
   c. Weight loss and exercise should become the first step for patients with psoriatic arthritis because these interventions are likely to improve the efficacy of pharmacologic therapy
   d. Weight loss is of significantly greater benefit than exercise

4. The mechanism of action of apremilast in psoriatic arthritis is inhibition of:
   a. Interleukin-17
   b. Interleukin-12 and IL-23 combined
   c. Phosphodiesterase-4
   d. Tumor necrosis factor

5. The results of a study by Poddubnyy and colleagues in patients with ankylosing spondylitis showed that in patients with AS and inflammatory back pain, disease activity and burden:
   a. Is comparable, whether or not radiographic changes are evident
   b. Is less severe in those with no evident radiographic changes
   c. Is less severe in those with a negative HLA-B27 test and no evident radiographic changes
   d. Is more severe if radiographic changes are evident and an HLA-B27 test is positive

6. Which one of the following agents, currently under investigation for the indication of PsA, is in the class of Janus tyrosine kinase–signal transducers and activators of transcription (JAK-STAT) molecules?
   a. Secukinumab
   b. Tocilizumab
   c. Tofacitinib
   d. Ustekinumab

7. The newer biologic agents brodalumab, ixekizumab, and secukinumab—now being studied for psoriatic arthritis—target which one of the following pathways?
   a. Interleukin-17
   b. Interleukin-12 and IL-23 combined
   c. Phosphodiesterase-4
   d. Tumor necrosis factor

8. In a recently reported study by Maksymowych and colleagues, the disease marker, 14-3-3-σ, was shown to be associated with joint inflammation and was predictive of which patients will experience:
   a. Development of antidrug antibodies to a given biologic agent
   b. Poor response to therapy with a biologic agent
   c. Severe side effects to agents that target the interleukin-17 inflammatory pathway
   d. Worsening of their ankylosing spondylitis disease activity over a period of 2 years

CLAIM CREDIT AT:
www.globalacademycmeevaluation.com/rheumnewstreg2

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.

© 2014 Global Academy for Medical Education, LLC. All Rights Reserved.
PART II: Focus on Psoriatic Arthritis and Ankylosing Spondylitis • 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.

CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: www.globalacademycmeevaluation.com/rheumnewstreg2 (Internet Explorer is the best browser to use).

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

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>5       4 3 2 1</td>
<td></td>
</tr>
</tbody>
</table>

Discuss cutting-edge research findings regarding the diagnosis and treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Optimize the use of both traditional therapies and currently available biologic agents for selected patients with PsA and AS.

Evaluate the results of clinical studies on promising medications now under investigation in PsA and AS.

Safely and appropriately incorporate new medications into the treatment regimens of patients with PsA and AS, as these agents become available.

Make ongoing modifications to therapy, as required, in patients with PsA to maximize outcomes and patient satisfaction.

Implement better screening and diagnostic procedures to diagnose AS early, and before permanent bone damage has occurred.

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)

- [ ] Implement a change in my practice/workplace.
- [ ] Seek additional information on this topic.
- [ ] 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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Description</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The information presented increased my awareness/understanding of the subject.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>2</td>
<td>The information presented addressed my educational needs.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>3</td>
<td>The information presented will influence how I practice/do my job.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>4</td>
<td>The information presented will help me improve patient care/my job performance.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>5</td>
<td>The program was educationally sound and scientifically balanced.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>6</td>
<td>The educational materials were useful.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>7</td>
<td>The active learning and assessment strategies (questions, cases) were appropriate and effective.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>8</td>
<td>Overall, the program met my expectations.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>9</td>
<td>I would recommend this program to my colleagues.</td>
<td>5</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

#### Author Demonstrations

- **Alvin F. Wells, MD, PhD, FACP, FACR**
  - Author demonstrated current knowledge of the topic.
  - Author was organized in the written materials.

- **Allan Gibofsky, MD, JD, FACP, FCLM**
  - Author demonstrated current knowledge of the topic.
  - Author was organized in the written materials.

- **Roy M. Fleischmann, MD, MACR**
  - Author demonstrated current knowledge of the topic.
  - Author was organized in the written materials.

- **Arthur Kavanaugh, MD**
  - Author demonstrated current knowledge of the topic.
  - Author was organized in the written materials.

#### 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.

© 2014 Global Academy for Medical Education, LLC. All Rights Reserved.
PART I: Focus on Rheumatoid Arthritis and Systemic Lupus Erythematosus

**Alan K. Matsumoto, MD**
Assistant Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland
Arthritis and Rheumatism Associates
Private Practice, Wheaton, MD

PART II: Focus on Psoriatic Arthritis and Ankylosing Spondylitis

**Alvin F. Wells, MD, PhD, FACP, FACR**
Visiting Foreign Professor, Karolinska Institute
Stockholm, Sweden
Director, Rheumatology and Immunotherapy Center
Oak Creek, Wisconsin
Adjunct Assistant Professor
Duke University Medical Center
Durham, North Carolina

Commentary from Allan Gibofsky, MD, JD, FACP, FCLM, Roy M. Fleischmann, MD, MACR, and Arthur Kavanaugh, MD