# A CME-Certified Supplement to Rheumatology News

## 4th Annual Perspectives in Rheumatic Diseases

**Conference Highlights**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Treatment of Psoriatic Arthritis: What Is the Optimal Treatment Algorithm?</td>
<td>4</td>
</tr>
<tr>
<td>Biologic Therapies in the Management of Rheumatoid Arthritis</td>
<td>6</td>
</tr>
<tr>
<td>Rheumatoid Arthritis: Treat to Target</td>
<td>8</td>
</tr>
<tr>
<td>Psoriasis Update: Efficacy and Emerging Safety Issues</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary Disease in Scleroderma</td>
<td>12</td>
</tr>
<tr>
<td>Post-Test and Evaluation</td>
<td>15</td>
</tr>
</tbody>
</table>

**Original Release Date:** March 2012  
**Most Recent Review Date:** March 2012  
**Expiration Date:** March 2013  
**Estimated Time to Complete Activity:** 1.5 hours  
**Medium or Combination of Media Used:** Written Supplement  
**Method of Physician Participation:** Journal Supplement

**Faculty**

- **Daniel E. Furst, MD, Chair**  
  Carl M. Pearson Professor of Medicine  
  Department of Medicine  
  Division of Rheumatology  
  David Geffen School of Medicine  
  at the University of California  
  Los Angeles (UCLA)

- **Marc D. Cohen, MD**  
  Emeritus Professor of Medicine, Mayo Clinic  
  Adjunct Professor of Medicine  
  Acting Chair of Rheumatology  
  National Jewish Health  
  Denver, Colorado

- **Craig L. Leonardi, MD**  
  Clinical Professor of Dermatology  
  Saint Louis University  
  Saint Louis University Medical School  
  Missouri

- **Christopher T. Ritchlin, MD, MPH**  
  Professor of Medicine  
  Allergy, Immunology and Rheumatology Division  
  Director, Clinical Immunology Research Center  
  University of Rochester School of Medicine and Dentistry  
  New York

- **Lewis J. Rubin, MD**  
  Emeritus Professor of Medicine  
  University of California  
  San Diego

**Jointly sponsored by:**

[Image: University of Louisville and Global Academy for Medical Education]

This activity is supported, in part, by an educational grant from:  
[Images: Abbott and Actelion]

This activity is supported, in part, by an educational donation provided by:  
[Image: AMGEN]
This activity was developed from scientific presentations at the 4th Annual Perspectives in Rheumatic Diseases®, a continuing medical education (CME) conference convened in San Francisco, California, October 14-15, 2011.

The authors would like to thank Global Academy for Medical Education and Charles Bankhead for assistance with the preparation of this supplement.

This supplement was produced by Global Academy for Medical Education, LLC, an Elsevier business. Neither the editors of Rheumatology News, nor the Editorial Advisory Board, nor the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter, the joint sponsors, or of the Publisher.

Copyright © 2012 by Elsevier Inc. and its Licensor. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the Publisher. Elsevier Inc. will not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to the products, drugs, or services mentioned herein.

Copyright © 2012 by Elsevier Inc. and its Licensor. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the Publisher. Elsevier Inc. will not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to the products, drugs, or services mentioned herein.

4TH ANNUAL PERSPECTIVES IN RHEUMATIC DISEASES

CONFERENCE HIGHLIGHTS

JOINT SPONSORSHIP
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACME) through the joint sponsorship of the University of Louisville School of Medicine Continuing Health Sciences Education (CHSE) and Global Academy for Medical Education, LLC. CHSE is accredited by the ACCME to provide continuing education for physicians.

DESIGNATION STATEMENT
Credit designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

TARGET AUDIENCE
This activity has been designed for rheumatologists. Other health care professionals who provide care and support to patients with rheumatologic disorders may also participate.

LEARNING OBJECTIVES
After reading and studying this supplement, participants should be able to:
• Clarify the concepts of aggressive treatment and treatment to target in rheumatoid arthritis (RA)
• Discuss key principles of recent recommendations for the management of RA
• Differentiate the long-term safety and efficacy of biologic agents in the treatment of RA, psoriasis, and psoriatic arthritis
• Describe recent trends in the treatment of psoriasis, including the role of biologic therapies
• Recognize distinctions between pulmonary arterial hypertension associated with systemic sclerosis and other forms and the implications of these distinctions for diagnosis and treatment.

STATEMENT OF PROFESSIONAL PRACTICE GAP(S)
The field of rheumatology encompasses a wide range of medical conditions that challenge the clinical decision-making of physicians. Recent developments in basic and clinical sciences have dramatically increased knowledge about the etiology and pathogenesis of rheumatic diseases, provided the basis for new therapies and therapeutic strategies, and furnished clinicians with increased capability to improve patients’ health and quality of life.

In the field of rheumatoid arthritis (RA), increased understanding of the disease process has fueled the development of biologic therapies that offer the potential to achieve low disease activity and remission in a substantial proportion of patients. Moreover, the concept of tight control of disease activity has expanded into the management of RA and now represents the therapeutic standard that experts in the field support.

A similar evolutionary process has occurred in the clinical management of psoriasis. Many of the lessons learned from RA have led to new clinical thinking and decision-making related to psoriasis, including treatment strategies. At the same time, understanding about the etiology and pathogenesis of psoriatic arthritis (PsA) has increased dramatically. More than 40% of the patients with psoriasis have concomitant PsA. Increased recognition of PsA as a distinct clinical entity has led to the need for new strategies to manage the condition.

Pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc) remains a challenge to diagnose and treat, even among specialists in the field. Improved recognition characteristics that distinguish SSc-PAH from other types of PAH have provided clinicians with opportunities to improve the care that they can offer to patients with this difficult disease.

The ongoing rapid accumulation of information about rheumatic diseases also challenges rheumatologists and other clinicians by dramatically increasing the volume of information that they must process to remain abreast of current clinical standards and trends. The information in this educational activity is designed to help meet the information needs of practicing rheumatologists and other health care professionals involved in the care of patients with rheumatic diseases.

DISCLOSURE
As a sponsor accredited by the ACCME, CHSE must ensure balance, independence, objectivity, and scientific integrity in all its sponsored educational activities. All faculty participating in this CME activity were asked to disclose the following:
1. Names of proprietary entities producing health care goods or services—with the exemption of nonprofit organizations and non–health-related companies—with which they or their spouse/partner have, or had, a relevant financial relationship within the past 12 months.
2. Describe their role.
3. No relevant financial relationships.

CHSE committee members have no relevant financial relationships with any commercial interests: W. Daniel Cogan, EdD; Joyce Dunagan, MA, MSLS; Terri Gipson, MSL; Christopher Jones, MD; Lucy Juett, MS, Lisa J. Pfizer, MD; Uldis Streips, PhD; Debbio Thomas; Kathy M. Vincent, MD; Lori Wagner, MD; and Stephen Wheeler, MD. CHSE staff: Jim Creg, Joyce Korfhage, and Kimberly Moore have no relevant financial relationships with any commercial interests.

Marc D. Cohen, MD has no relevant financial relationships with any commercial interests.

Daniel E. Forst, MD has been a consultant for Abbott, Actelion, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, CORRONNA, Genentech, Gilead, GlaxoSmithKline, National Institutes of Health, Novartis, Pfizer, Roche, and UCB.

Craig L. Leonard, MD has been a consultant for Abbott, Amgen, Centocor, and Pfizer. He has been an investigator and/or consultant for Abbott, Amgen, Celgene, Centocor, Eli Lilly, Genentech, Genzyme, Incyte, Novartis, Novo Nordisk, Pfizer, Schering-Plough, Vascular Biogenics, and Wyeth. He is on the speakers’ bureau for Abbott, Amgen, and Centocor.

Christopher T. Ritchlin, MPH, has been an investigator and/or consultant for Agen, Centocor, Pfizer, and UCB.

Lewis J. Rubin, MD has been a consultant for Actelion, Aires, Amgen, Bayer, GlaxoSmithKline, Pfizer, and United Therapeutics.

Sylvia Reitman, MBA, has no relevant financial relationships with any commercial interests.

Charles Bankhead has no relevant financial relationships with any commercial interests.

TO OBTAIN CME CREDIT
To get instant CME credit online, go to http://uofl.me/rheumsupplement12. 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. Please add chse@louisville.edu to your e-mail “safe” list. Type the above address into your address bar or right-click on the address bar and select “Copy the Address.” Then open Internet Explorer, then hold down the control key and press the “O” key on your keyboard. A dialogue box will open—this is where you will type the above address. After you have typed the address, click “OK” to go to the evaluation.

Once you have completed the evaluation, it will give you a password. Please be sure to write it down; you will then be able to access your certificate. Please note, certificates will not be mailed, so be sure to print a copy for your records. If you have any questions or difficulties, please contact the University of Louisville School of Medicine Continuing Health Sciences Education office at (502) 852-5329.
INTRODUCTION

The field of rheumatic disease has a clinical diversity that overlaps multiple specialties. Management of the conditions that fall within the spectrum of rheumatic disease involves elements of rheumatology, dermatology, immunology, pulmonology, cardiology, and surgery.

The diversity makes for a rich clinical experience that challenges clinicians to make maximal use of their knowledge, experience, and expertise. Ongoing advances in the field of rheumatic diseases ensure that the challenge will remain and very likely will increase, as knowledge continues to accumulate rapidly.

Many busy clinicians do not have adequate time in their schedules to consume and assimilate the vast amount of information that might improve patient care and outcomes.

This supplement is based on the recent continuing medical education conference, the 4th Annual Perspectives in Rheumatic Diseases, which was presented by Rheumatology News®, Family Practice News®, and Internal Medicine News®. It was chaired by Daniel E. Furst, MD, Carl M. Pearson Professor of Medicine, Department of Medicine, Division of Rheumatology, at the David Geffen School of Medicine, University of California, Los Angeles. The co-chairs were Kenneth B. Gordon, Professor of Dermatology, Northwestern University’s Feinberg School of Medicine, Chicago, Illinois, and Brian Mandell, MD, PhD, Professor and Chairman of Medicine, Department of Rheumatic and Immunologic Diseases, at The Cleveland Clinic, Cleveland, Ohio. This annual conference provides attendees with the opportunity to update their knowledge of rheumatic diseases within the context of presentations by recognized authorities in the field, including rheumatoid arthritis, psoriasis, psoriatic arthritis, and systemic sclerosis and associated pulmonary hypertension. The following articles are a review of selected sessions and focus on key points about patient management that are readily applicable to clinical practice.

In the articles that follow, Dr Christopher T. Ritchlin reviews new developments and trends in the management of psoriatic arthritis, a long-neglected rheumatic condition that has risen to prominence because of its frequent association with psoriasis and the availability of more effective therapy. Dr Marc D. Cohen provides an update on the current status of biologic therapy for rheumatoid arthritis, a rapidly evolving area of rheumatology.

Dr Craig L. Leonardi offers a thoughtful examination of current therapies and therapeutic strategies for psoriasis. Dr Lewis J. Rubin provides keen insight into the challenges and opportunities of systemic sclerosis and associated pulmonary hypertension.

In an overview of current strategies for treating to target in rheumatoid arthritis, the supplement editor will take the editor’s prerogative to address a clinical concept that has practice-changing potential.

The information that follows reflects current knowledge, standards, and practices in various types of rheumatic diseases. Readers will find the summaries informative and readily applicable to clinical practice.

Daniel E. Furst, MD, Chair and Editor
As a recognized disease entity, psoriatic arthritis (PsA) languished in relative obscurity until fairly recently. Only within the past decade or so has the condition emerged from the shadows of two better-known cohorts: psoriasis and rheumatoid arthritis (RA). Intensified basic research has improved the understanding of the biology of PsA and stimulated more clinical interest in the disease. In turn, the increased clinical interest has provided the impetus for development of new therapies, many of which have progressed to clinical trials. Over the next 6 months, clinical investigation of therapies for PsA will expand dramatically. In the near future, clinicians should have more therapeutic options, affording unprecedented opportunity to have a meaningful impact on the disease and improve patients’ function and quality of life.

**Distinguishing Features of PsA**

More effective management of PsA begins with better recognition of the disease’s characteristics. As compared with RA, PsA is much more varied, phenotypically and pathologically. Patients with PsA typically have axial and peripheral joint involvement with enthesitis, or inflammation of the insertion points for ligaments and tendons.

RA is a catabolic process that leads to osteopenia, focal erosions, and joint destruction. Patients with PsA have mixed clinical features that include bone erosion and joint destruction, as well as new bone formation. Phenotypic variation is another distinguishing trait of PsA, as the same patient might have extensive joint destruction in the fingers but new bone formation in the spine. The mixed features make PsA particularly challenging to diagnose.

Patients with PsA often have extra-articular sites of inflammation that further distinguish the disease from RA. Examples include uveitis, inflammatory bowel disease, and psoriasis.

Along with extra-articular involvement, unusual manifestations can further complicate the evaluation of a patient with PsA. For example, a patient might present with posterior involvement of the retina, synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with extensive involvement of the chest wall, or intense chest-wall involvement without SAPHO, such as pustulosis and hyperostosis.

Enthesitis represents a major source of pain that can be mistaken for fibromyalgia or inflammatory muscle disease. Enthesitis can arise at multiple sites, including the supraspinatus, lateral epicondyle, iliac crest, trochanter, patella, and plantar fascia.

Patients with PsA typically have multiple comorbid conditions, perhaps the most common being obesity. Hypertension, type 2 diabetes, hyperlipidemia, and steatosis are other common comorbidities of PsA. Metabolic syndrome occurs more often in patients with PsA than in patients who have RA. Additionally, patients with PsA have an increased risk of myocardial infarction compared with that in the general population.

**Treatment Issues and Evidence**

The varied, complex nature of PsA has complicated treatment decisions. A few years ago, an international group of rheumatologists and dermatologists met to consider issues in PsA therapeutics and develop treatment recommendations.1

The group separated PsA into five clinical domains: peripheral arthritis, skin and nail disease, axial disease, dactylitis, and enthesitis. For each domain, members of the group sought to reach a consensus about the quality of supporting evidence for seven types of therapy: nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, topical agents, physiotherapy, psoralen and phototherapy, conventional disease-modifying antirheumatic drugs (DMARDs), and biologics.2

Only the biologics—and, more specifically, inhibitors of tumor necrosis factor-alpha (TNF-α)—had demonstrated efficacy in all five domains. In fact, none of the other therapies demonstrated efficacy in more than one, with the exception of DMARDs, which were efficacious for peripheral arthritis, and skin disease in the case of methotrexate. For most DMARDs, the efficacy in domains outside the skin and peripheral arthritis have not been formally evaluated in a well-designed clinical trial.

The varied, complex nature of PsA has complicated treatment decisions.

The international group also developed definitions for three levels of severity (mild, moderate, and severe) for each of the five clinical domains. The objective was to produce a concise treatment grid that takes into account the varied manifestations and presentations of PsA.2

Not uncommonly, patients with PsA have involvement of multiple domains, which vary in severity. A physician has to consider each domain and its severity to develop a treatment regimen for a specific patient.

**Therapeutic Choices**

Physicians have minimal evidence-based clinical guidance for treatment of PsA. Few well-designed, randomized clinical trials have examined the efficacy of conventional agents.3,4 To date, no studies have shown that conventional therapeutic agents slow the radiographic progression of PsA. No conventional agent has demonstrated efficacy for axial disease, dactylitis, or enthesopathy.

**Methotrexate**

Methotrexate has become the most widely used drug for treating PsA. Unfortunately, the choice is based on virtually no clinical evidence. Investigators have compared methotrexate and placebo in two randomized trials of patients with PsA. To date, neither study has been published. In brief, the results were contradictory.

In one of the trials, patients were randomized to methotrexate or placebo for 6 months.5 The primary end point was the change from baseline in the Psoriatic Arthritis Response Criteria (PsARC). Secondary end points included American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) and the 28-item Disease Activity Score (DAS28).

The results showed no difference between groups in PsARC, ACR20, or DAS28 at 3 or 6 months. The groups also did not differ with respect to number of swollen/tender joints or levels of inflammatory markers.
The second trial was limited to patients with PsA and no prior exposure to methotrexate. Patients with polyarticular PsA were randomized 2:1 to methotrexate alone or in combination with the TNF inhibitor infliximab. The primary end point was the proportion of patients who achieved an ACR20 response at week 16.

Although there was a methotrexate-only arm, there was no “No-MXT” arm, making it impossible to prove methotrexate’s efficacy. The results showed significantly higher response rates (ACR20, ACR50, and ACR70) in the group that received combination therapy. Additionally, the combination group had a significantly higher rate of remission by DAS28 criteria (68.6% vs 29.2%, P=0.0001). Response by the Psoriasis Area and Severity Index (PASI) criteria also showed significant advantages in favor of methotrexate plus the TNF inhibitor. The magnitude of the differences between groups for all comparisons was impressive (Table).

Aside from the lack of clinical trial evidence, the potential liver toxicity of methotrexate raises legitimate concern. One small study of patients with psoriasis showed a significant relationship between cumulative dose of methotrexate and extent of liver fibrosis. The liver toxicity was especially striking in patients who were overweight or who had diabetes.

**TNF Inhibitors**

Four TNF inhibitors have US Food and Drug Administration approval and the backing of phase III clinical-trial data for treatment of PsA.

The trial discussed above typifies these results. In general, the agents have demonstrated similar efficacy in patients with PsA and peripheral arthritis, as determined by ACR response criteria. However, PASI response criteria have suggested that the three antibodies (infliximab, adalimumab, and golimumab) have superior efficacy for skin disease than that of the receptor inhibitor (etanercept). That difference has caused controversy that remains unresolved.

Some clinicians have questioned whether patients with PsA are more likely to continue therapy compared to patients with RA or ankylosing spondylitis. One study that examined the issue showed that patients with PsA demonstrate persistence that is at least as good as that of patients with ankylosing spondylitis and substantially better than that of patients with RA. TNF inhibitors have been touted as effective therapy for several conditions, but the drugs are costly. Because of that, many patients have high expectations for efficacy. Clinicians should provide patients with information that offers a realistic view of the risks and benefits of TNF inhibitors.

Physicians can avail themselves of several options for patients whose disease does not respond to anti-TNF therapy. Flare at a specific site might warrant consideration of NSAIDs or a review of the adequacy of existing NSAID therapy. Adding a conventional DMARD to a TNF inhibitor restores disease control for some patients. Switching to a different TNF inhibitor has gained support in recent years as another option for patients who have inadequate responses to first-line treatment with a TNF inhibitor (Figure).

Data from a Nordic registry of patients with PsA provided evidence suggesting that treatment with a TNF inhibitor is more effective than methotrexate therapy for a number of outcomes. Comparisons for multiple outcomes showed a consistent advantage in favor of anti-TNF therapy, including inflammation, fatigue, pain, response to therapy, and global health status (all P<0.001).

Switching to a different class of biologic therapy might be an option. Ustekinumab and abatacept offer two possibilities.

**Ustekinumab**

An inhibitor of interleukin 12 and 23, ustekinumab demonstrated activity in PsA in a phase II randomized, placebo-controlled crossover trial involving 146 patients. Patients treated with ustekinumab had a significantly higher ACR20 response rate, which was the primary end point (42% vs 14%, P=0.0002). The ACR50 and ACR70 responses also were higher in the ustekinumab group (19% vs 7% and 11% vs 0%, respectively). Response as defined by PASI75 also showed a significant advantage for treatment with ustekinumab (52% vs 5%, P=0.0001).

**Rituximab**

The anti-CD20 antibody was evaluated in a 21-patient, open-label trial of patients with PsA who continued background therapy. The results showed modest improvement in joint and skin scores during 48 weeks of follow-up in patients with no prior exposure to anti-TNF therapy, and patients with no prior exposure to TNF inhibitors had better results than did those who had received anti-TNF therapy. The results suggest that rituximab is not an optimal therapeutic option for patients with PsA.

**Abatacept**

This T-cell inhibitor demonstrated good activity in patients who had no prior exposure to anti-TNF therapy in a randomized, placebo-controlled trial. Patients received one of three doses of abatacept or placebo, and the primary end point was ACR20 response. The two higher doses were significantly better than placebo in the overall response. The data from this trial are conclusive evidence that abatacept is an effective therapy for patients with PsA.

**Table. IFX + MTX vs MTX in MTX-Naïve PsA Patients: RESPOND Trial Response at Week 16**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IFX + MTX (%)</th>
<th>MTX (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>86.3</td>
<td>66.7</td>
<td>0.021</td>
</tr>
<tr>
<td>ACR50</td>
<td>72.5</td>
<td>39.6</td>
<td>0.009</td>
</tr>
<tr>
<td>ACR70</td>
<td>49.0</td>
<td>18.8</td>
<td>0.0015</td>
</tr>
<tr>
<td>DAS28 Remission</td>
<td>68.6</td>
<td>29.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>PASI50</td>
<td>100</td>
<td>80.0</td>
<td>0.0059</td>
</tr>
<tr>
<td>PASI75</td>
<td>97.1</td>
<td>54.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>PASI90</td>
<td>70.6</td>
<td>28.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Intent-to-treat analysis.*

ACR20, 50, 70=20%, 50%, or 70% improvement (respectively) in joint disease according to American College of Rheumatology criteria; DAS28=28-item disease activity score; IFX=infliximab; MTX=methotrexate; PASI=Psoriasis Area and Severity Index; RESPOND=Remicade Study in Psoriatic Arthritis Patients of Methotrexate-Naïve Disease.

Biologic Therapies in the Management of Rheumatoid Arthritis

Marc D. Cohen, MD
Emeritus Professor of Medicine, Mayo Clinic
Adjunct Professor of Medicine, Acting Chair of Rheumatology, National Jewish Health
Denver, Colorado

Beginning with inhibitors of tumor necrosis factor-alpha (TNF-α), biologic therapy has had a major impact on the treatment of rheumatoid arthritis (RA). By targeting specific molecules and pathways in the inflammatory cascade, biologic therapy has increased the options for treating RA and physicians’ ability to plan more individualized treatment strategies. The biologic cadre has expanded to include interleukin (IL)-1 receptor blockers, T-cell blockers, B-cell–depleting agents, and IL-6 receptor antagonists. The list of therapeutic classes will continue to grow as the understanding about the biologic basis of RA improves.

Therapeutic Standard
Despite the success of biologic therapy for RA, methotrexate remains the standard with which new therapies are compared.

Prior to the emergence of TNF-α inhibitors, few good clinical trials had thoroughly examined methotrexate’s safety and efficacy in RA. Because of its position as the most potent conventional disease-modifying anti-rheumatic drug (DMARD), methotrexate became the default comparator for many clinical trials of biologic therapy for RA.

SWEFOT Trial
European investigators conducted a randomized clinical trial involving patients with early RA, defined as symptom duration <1 year. Known by the acronym SWEFOT, the trial began with a 3-month methotrexate run-in for all patients. At the end of the run-in phase, patients who had a score of ≤3.2 on the 28-joint Disease Activity Score (DAS28) were considered responders and did not enter the randomized phase of the study but instead continued methotrexate.

The remaining patients were randomized to the conventional DMARD combination of methotrexate, sulfasalazine, and hydroxychloroquine or to methotrexate plus the TNF-α inhibitor infliximab. About 30% of the patients had good responses with methotrexate alone. After 12 months of randomized therapy, almost 40% of the patients in the infliximab arm met European League Against Rheumatism criteria for good response compared with 25% of the patients randomized to the conventional DMARD arm (P=0.0160).

The SWEFOT results probably influenced rheumatologists’ clinical decision making with regard to methotrexate. Many rheumatologists now initiate methotrexate as early as possible, titrate the dose to a maximum in about a month, and then follow patients to see whether they respond to methotrexate alone.

Follow-up in SWEFOT continued for 24 months. The statistical advantage that the infliximab arm demonstrated at 12 months had disappeared with an additional 12 months of follow-up. However, analysis of radiographic progression revealed a distinction between the anti-TNF and DMARD arms. The addition of the TNF-α inhibitor for patients with inadequate response to methotrexate resulted in less radiographic progression than that seen in patients who received conventional DMARDs in addition to methotrexate.2

Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis (COMET) Trial
Methotrexate also had a central role in the first RA clinical trial that evaluated remission as an end point. Known as COMET, the trial included 542 patients with early, moderate to severe RA and no prior exposure to methotrexate. The patients were randomized to methotrexate alone or in combination with the TNF-α inhibitor etanercept. After 52 weeks of follow-up, 28% of the patients in the methotrexate arm had achieved clinical remission (DAS28 <2.6) and 41% of the patients had achieved remission or low disease activity (DAS28 <3.2). In the etanercept arm, the 52-week rates were 50% and 64%, respectively (P<0.001).

Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial
The success of methotrexate monotherapy as initial treatment for RA has led to the question of whether more aggressive first-line treatment with a methotrexate-containing regimen might lead to greater benefits. That issue was addressed in a randomized clinical trial involving 755 patients with early RA (<3 years’ duration).4

Known as TEAR, the trial examined immediate combination therapy with methotrexate (plus etanercept or conventional DMARDs) versus initial methotrexate monotherapy for 24 weeks and then add-on therapy with etanercept or the conventional DMARDs for patients with DAS28 >3.2.

The primary end point was the average DAS28 value for weeks 48 to 102. The results showed a significant advantage at 48 weeks for immediate-combination groups (P<0.0007 to P<0.0001). By year 2, however, the treatment groups were indistinguishable.

As with the SWEFOT study, the radiographic data showed that patients who received the TNF inhibitor had less radiographic progression than did patients who were randomized to conventional DMARDs.5 The radiographic benefit was evident in patients who began treatment with the TNF-α inhibitor and in those in the step-up arm who received etanercept.

The Next Step
Add-on therapy improves responses in patients who obtain inadequate responses with methotrexate alone, regardless of whether the add-on therapy is a biologic agent or a conventional DMARD.6

The benefits of anti-TNF add-on therapy were examined in an analysis of three randomized, placebo-controlled clinical trials involving three different TNF-α inhibitors.7 All three trials showed that patients who received the biologic therapy had much higher American College of Rheumatology (ACR) response rates than did patients who continued methotrexate with placebo.

The benefits of adding a biologic agent to methotrexate have been demonstrated with other drug classes. For example, patients in a large, randomized clinical trial of abatacept were randomized to methotrexate plus the biologic or methotrexate plus placebo.8 After
1 year, the ACR20/50/70 response rates were two to three times greater in the group that received the biologic agent. Patients who received abatacept in addition to methotrexate also had less radiographic progression.

Similar improvement has occurred with the addition of rituximab or tocilizumab to methotrexate.

**Options After TNF-α Inhibitors**

Obviously, not every patient has an optimal response to anti-TNF therapy. The best approach for such patients has yet to be determined. However, several options exist.

Switching to a different TNF-α inhibitor has attracted the most interest, although only one randomized, placebo-controlled study has evaluated the strategy. The trial involved 461 patients who had discontinued treatment with a TNF-α inhibitor. In 58% of the cases, patients had discontinued because of lack of efficacy.

The patients were randomized to placebo or to one of two doses of golimumab and followed for 14 weeks. The primary end point was the proportion of patients who achieved an ACR20 response. When the trial ended, 18% of the placebo group met the primary end point compared with 35% and 38% of the two golimumab groups ($P<0.001$). Similar differences emerged from an analysis of ACR50 response.

A meta-analysis of 31 studies involving a total of 5,306 patients with RA examined the efficacy of second- and third-line anti-TNF therapy after inadequate response to the initial TNF-α inhibitor. Depending on the reason for discontinuation, ACR20 response rates ranged from 43% to 66%. Similar variation existed for ACR50 and ACR70 response rates. Once again, patients who discontinued the first TNF-α inhibitor because of intolerance had the highest response rates.

Switching to a different class of biologic agent is another possibility for patients who respond inadequately to a TNF-α inhibitor. A placebo-controlled trial of abatacept after anti-TNF therapy showed an ACR20 response rate of 59%, ACR50 of 24%, and ACR70 of 12%.

Similar results came from a trial evaluating rituximab after inadequate response to a TNF-α inhibitor. The respective ACR20/50/70 response rates at 24 weeks were 51%, 27%, and 12%, all of which were significantly better than that with placebo ($P<0.0001$). The trial also examined radiographic progression and showed that patients treated with the biologic agent had substantially less progression, whether defined by Sharp-Genant Score, joint-space narrowing, or erosion score.

**Safety**

Concerns about the safety of TNF-α inhibitors and other biologic agents have followed clinical development of the drugs since before biologics reached the market. The two principal areas of concern are infection and malignancy.

The risk of infection clearly is increased in patients treated with biologic agents. An analysis of data from 8,659 patients with RA treated with conventional DMARDs or TNF-α inhibitors showed a significantly increased risk of infection across the entire class of TNF-α inhibitors. The overall incidence rate ratio versus DMARDs was 4.6 and ranged from 3.9 with adalimumab to 5.6 with infliximab.

The infection risk extends to other biologic agents, as well. A meta-analysis of patients treated with rituximab, abatacept, or anakinra produced odds ratios of 1.35 to 2.75 versus placebo-treated patients with RA. However, the confidence intervals included 1.0, making the differences not statistically significant.

The malignancy risk has been clarified in recent years, and, for the most part, use of biologic agents has not been associated with an increased risk of cancer. A recent meta-analysis of 53 clinical trials involving 23,696 patients showed an odds ratio of 1.38 for cancer in patients treated with TNF-α inhibitors. However, the confidence intervals included 1.0. Investigators estimated that 305 patients would have to be treated for 12 months to cause one excess malignancy.

The one possible exception to the lack of cancer risk is skin cancer. Data from a large registry of patients with RA examined skin cancer risk in 11,757 patients treated for 6 months with anti-TNF agents and 3,515 patients treated with conventional DMARDs.

An analysis limited to patients with no history of nonmelanoma skin cancer yielded an overall skin cancer hazard ratio of 1.7 for the anti-TNF cohort versus the DMARD-treated patients. The risk was elevated for each of the TNF-α inhibitors, but none of the differences achieved statistical significance.

The cardiovascular safety of biologic agents also has been examined. An analysis of data from 10,870 patients in an RA registry showed that patients treated with a TNF-α inhibitor had a 70% lower risk of cardiovascular disease and events, and treatment with methotrexate was associated with a 40% lower risk.

**Summary**

The advent of biologic therapy has had a major effect on the treatment of RA. Aside from increasing the number of therapeutic options and strategies, biologics substantially enhance responses when added to methotrexate. Use of biologic agents confers an increased risk of infection, but concern about an increased cancer risk has yet to be supported by analyses of large numbers of patients treated with biologic therapies. Clinical development of biologic agents for RA is ongoing, and new agents might soon be added to the expanding list of effective treatments for RA.

**References**


2. van Vollenhoven RF, Albertsson K, Forslind K, et al. In early RA with insufficient response to MTX, the addition of anti-TNF results in less radiological progression over 24 months than the addition of conventional DMARDs: Results from the SWEFOT Trial. Presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Scientific Meeting; October 16-21, 2009; Philadelphia, PA. Abstract LB6.


Rheumatoid Arthritis: Treat to Target

Daniel E. Furst, MD, Chair
Carl M. Pearson Professor of Medicine, Department of Medicine, Division of Rheumatology
David Geffen School of Medicine at the University of California, Los Angeles (UCLA)

The concept of treat to target has a long history in medicine but is relatively new to clinical management of rheumatoid arthritis (RA). Historically, rheumatologists have approached RA therapy with goals such as symptom relief, prevention of disability, and slowing or preventing joint damage. More recently, the field of clinical rheumatology began to incorporate instruments to take into account multiple disease parameters to produce a single value to represent overall disease status, such as American College of Rheumatology (ACR) criteria, the Disease Activity Score (DAS), and the Clinical Disease Activity Index (CDAI).

Initially developed for clinical trials, RA disease activity scales have migrated into clinical rheumatology practice, as the instruments’ validity, reproducibility, and clinical utility were borne out in the investigational environment. Multiple studies, including some conducted in the clinical-practice setting, have shown that treating to target can improve disease control and quality of life for patients with RA.

Definition
Treat to target refers to a therapeutic strategy of intensive intervention with prespecified targeted outcomes measures for decision making within the context of a defined therapeutic algorithm. The definition works well in clinical trials, but the precepts are not so clear-cut in clinical practice. The points to remember are intensive intervention and prespecified outcomes measures.

Clinical Application
The Diabetes Control and Complications Trial (DCCT) provided one of the first clear demonstrations that treating to target can improve clinical outcomes. The DCCT showed that treating to a specific blood glucose level led to a significant reduction in the risk of retinopathy and nephropathy.

Intuitively, however, the concept made sense for managing RA. Like diabetes, RA is a chronic disorder. In both conditions, complications arise insidiously over many years, and patients with diabetes or RA often develop severe disability as a consequence of the disease. Most importantly, patients with diabetes or RA have an increased risk of premature mortality.

Evidence that treating to target could reduce symptoms, disability, and joint damage in RA emerged from the Tight Control in Rheumatoid Arthritis (TICORA) trial. Patients with early RA and active disease were randomized to intensive or routine care and followed for 18 months. Patients assigned to intensive care were evaluated monthly, and the treatment was intensified as needed to maintain a DAS <2.4.

Patients randomized to routine care were followed at 3-month intervals. Clinical management was at the discretion of the treating physician, and no formal measure of disease activity was used to monitor disease activity. When the trial ended, 65% of patients in the intensive-treatment arm had achieved disease remission (DAS <1.6) compared with 16% of patients allocated to routine care (P <0.0001). DAS-driven intensive therapy also was associated with significantly less radiographic progression (P = 0.02).

Since TICORA, the superiority of intensive treatment versus routine care has been demonstrated in multiple studies and with multiple types of drugs, including newer biologic therapies evaluated in RA. For example, a study of the B-cell–targeted monoclonal antibody rituximab showed that a treat-to-target protocol resulted in significantly greater reductions from baseline DAS than did administration of rituximab at physician discretion.

Table 1. Measures for Treat-to-Target Response

<table>
<thead>
<tr>
<th>Various Ways to Measure Clinical Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual measures (TJC, SJC)</td>
<td></td>
</tr>
<tr>
<td>ACR20, 50, 70</td>
<td></td>
</tr>
<tr>
<td>DAS</td>
<td></td>
</tr>
<tr>
<td>RAPID 3</td>
<td></td>
</tr>
<tr>
<td>CDAI</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td></td>
</tr>
</tbody>
</table>

Quality of Life/ADL: HAQ-DI and SF-36

Imaging

Fatigue, sleep

ADL=activities of daily living; ACR=American College of Rheumatology; CDAI=Clinical Disease Activity Index; DAS=Disease Activity Score; HAQ-DI=Health Assessment Questionnaire Disability Index; RAPID=Routine Assessment of Patient Index Data; SF-36=Short Form 36; TJC=tender joint count; SJC=swollen joint count.


Defining the Target
The DAS is one of several validated measures of clinical response (Table 1). Some measures are more practical than others for use in clinical rheumatology practice.

Joint Counts
Every rheumatologist learns how to recognize and tabulate the number of tender and swollen joints in a patient with RA (Figure). Joint counts remain a core component of the ACR criteria. About 20 years ago, rheumatologists were surveyed about the components of the ACR criteria and asked to rank them in order of perceived value in clinical assessments. Disability emerged at the top, but rheumatologists rated patient global assessment and the number of swollen and tender joints as the second most valuable and essentially of equal importance. The principal downside to the use of joint counts as a treatment target is the time required to perform accurate assessments.

Figure. Example of Mannequin Used to Assess Joint Count Measure Response

Clinical Disease Activity Index

Simpler than the ACR criteria or the DAS, the CDAI combines joint counts, patient global assessment, and physician global assessment. The sum of the three measures reflects disease activity: remission, ≤2.8; low disease activity, >2.8 to ≤10, moderate disease activity, >10 to ≤22, and severe disease, >22.

The CDAI has demonstrated about 90% correlation with the DAS and also correlates with the Health Assessment Questionnaire (HAQ), a measure of function. The absence of a laboratory parameter (as required by the DAS) means that the score can be calculated almost immediately, making it more attractive for use in clinical practice.

Routine Assessment of Patient Index Data (RAPID 3)

Perhaps simplest of all outcome assessments, the RAPID 3 consists of patient assessment of physical functioning, patient global assessment, and patient assessment of pain. Each outcome is based on a scale of 0 to 10, and the overall disease status is the sum of scores.

From the physician perspective, the RAPID 3 requires minimal time investment, as a patient can complete the questionnaire while in the waiting area or examining room. The RAPID 3 has only moderate correlation with the DAS (~65%) and CDAI (~75%).

Health Assessment Questionnaire

Like the RAPID 3, the HAQ requires no major time commitment by physicians. The HAQ focuses solely on physical functioning, particularly routine activities. Patients rate their current function with respect to eight areas or domains. Each domain has a possible score of 0 to 3, and the overall HAQ score is derived from the sum of the maximum individual domain scores.

The HAQ provides a reasonable estimate of disease status and has been shown to differentiate between therapies.

When to Perform an Assessment

Discernment of disease status and response to therapy involves regular and repeated use of various measures. A general recommendation is 3 to 6 months after initiating treatment or making a change in therapy. Choosing the right interval is not a precise science. However, studies have shown that a substantial proportion of patients with RA require more than 3 months to achieve a meaningful clinical response.

One recent study examined response to conventional disease-modifying antirheumatic drugs after 3 and 6 months. At 3 months, 33% of the patients had achieved a remission or low disease activity. By 6 months, the proportion had increased to 55%.

Given the variability in the time required to achieve a response, a reasonable approach might be to perform an initial assessment after 3 months of treatment. If RA status has not improved (by whatever means it is assessed), proceeding to the second step in a treatment algorithm would be appropriate.

On the other hand, if a patient has improved somewhat but does not meet the criteria for a clinical response, giving the therapy for an additional 3 months would not be unreasonable.

Summary

Remission has become the new standard for response to treatment in RA. The standard has emerged from research showing that treating to a specific target substantially increases the likelihood that a patient will achieve a meaningful clinical response, as opposed to a routine approach to treatment. Multiple measures of clinical response have been developed, and physicians should choose the tool or tools that best fit a specific clinical practice environment.

References

For years, dermatologists have followed a rigid stepwise algorithm for the treatment of psoriasis. According to the traditional paradigm, therapeutic failure had to occur with an existing therapy before the patient could progress to the next step. Patients would begin with non-prescription topical therapies, then step up to prescription topical agents, and then to phototherapy. Finally, for the most recalcitrant forms of psoriasis, patients would step up to the realm of systemic therapy, including cyclosporine, methotrexate, acitretin, and systemic corticosteroids.

According to patients, the traditional approach led to unsatisfying results. A survey of 17,000 patients with psoriasis showed that almost 80% were frustrated with therapy and a third thought that physicians did not treat psoriasis aggressively. Conducted before the introduction of biologic therapy, the results clearly showed that the field needed new, more effective treatment options.

The introduction of inhibitors of tumor necrosis factor-alpha (TNF-α) and other biologic agents has had a major impact on the treatment of psoriasis. Physicians and their patients have more treatment options, more therapeutic strategies, and more ability to achieve meaningful improvement in a disease that often exacts a heavy toll on a person’s quality of life.

The traditional treatment paradigm that emphasized stepwise changes in therapy has given way to individualization of therapy according to a patient’s specific disease status, needs, and circumstances.

A Brief History of Biologic Therapy in Psoriasis

The history of biologic therapy in psoriasis predates TNF inhibitors. The first biologic agents targeted molecules involved in T-cell activation. In general, the drugs were either ineffective or too toxic. The only surviving member of the T-cell inhibitor class is alefacept, which interferes with the interaction between lymphocyte function-associated antigen-3 and CD2, a step in the process of T-cell activation.

Targeting cytokines associated with inflammation represented another attractive approach to treating psoriasis. The inflammatory cascade involves numerous pro- and anti-inflammatory cytokines, and altering the activity of a cytokine to treat psoriasis seemed intuitive (Figure).

Over the past decade, drug manufacturers have developed numerous agents that targeted various cytokine pathways associated with inflammation. The only survivors from the development activity are TNF-α inhibitors and interleukin (IL)-12/IL-23 inhibitors.

Current State of Biologic Therapy

The standard metric for assessing the activity of a psoriasis therapy is 75% improvement in the Psoriasis Area and Severity Index (PASI75). The PASI75 response rate is the standard used by the US Food and Drug Administration to evaluate the clinical efficacy of a psoriasis drug. In reality, 75% clearance of psoriasis constitutes dramatic improvement. Patients who do not achieve a PASI75 response might nonetheless have substantial disease clearance that represents major improvement from baseline.

TNF-α Inhibitors

Etanercept was the first member of this class of biologic agents and was initially developed for the treatment of rheumatoid arthritis. When administered at a dosage of 50 mg weekly or a regimen of 100 mg for 12 weeks and 50 mg thereafter, etanercept leads to a PASI75 rate of about 45%. The PASI75 response rate increases to about 60% in patients who receive 100 mg weekly for the duration of treatment.

However, etanercept 50 mg weekly is the approved dose, and most insurers do not cover 100 mg weekly after 12 weeks. As a consequence, etanercept has intermediate efficacy as compared with other members of the TNF-α inhibitor class.

Treatment with infliximab can lead to PASI75 response rates in excess of 80% at 10 weeks, following initial infusions at weeks 0, 6, and 12. When the infusion schedule changes to every 8 weeks after week 12, the PASI75 response rate stabilizes in many cases, although some patients definitely lose response, sometimes in dramatic fashion. When dropouts are taken into account, the PASI75 response rate at 1 year might decline into the 60% range.

Similar to infliximab, adalimumab has demonstrated greater potency than that achieved with etanercept. The PASI75 response rate tends to peak at about 70% (including nonresponders and patients with missing data) and reaches the peak after about 16 weeks of treatment.

Inhibitors of IL-12/IL-23

Inhibition of IL-12 removes a key mediator of proinflammatory T-helper (T17) 1 cells. IL-23 blockade affects survival and proliferation...
of T17,17 and T1222 cells, which regulate the production and activity of additional proinflammatory cytokines.4 Two large randomized clinical trials of ustekinumab confirmed its efficacy in psoriasis.5,6 Both trials demonstrated PASI75 response rates >70% at 28 weeks with either of two doses of ustekinumab (an IL-12/IL-23 inhibitor). Responses are durable, persisting in a substantial proportion of patients well after the drug has been stopped.

As compared with ustekinumab, briakinumab has a checkered clinical history. Early clinical trials showed that treatment with the drug led to PASI75 response rates of about 80% within 12 weeks, similar to those with ustekinumab but achieved more quickly. Unfortunately, concern about a possible increased risk of major adverse cardiac events (MACE) dampened enthusiasm for the drug. Clinical development of briakinumab in psoriasis has been discontinued. The results of a recent randomized clinical trial showed a PASI75 response rate of 82% at 24 weeks as compared with 40% for patients treated with methotrexate.7 The 52-week results showed PASI75 rates of 66% for briakinumab and 24% for methotrexate.

Safety Issues
The evolution of biologic therapy has raised some safety concerns, which have been examined most extensively in TNF-α inhibitors. Most safety concerns with the drug class have involved infections and malignancy.

A recent meta-analysis of 20 double-blind, placebo-controlled clinical trials involving 6,810 patients provided some reassurance.8 The analysis included patients with psoriatic diseases treated with any of five TNF-α inhibitors. The results showed a small increase in the risk of infection but no increased risk of serious infections and no evidence of an increased risk of malignancy. However, the duration of treatment and follow-up in the trials was too brief to permit any definitive conclusions about an association with malignancy.

An analysis of the National Data Bank for Rheumatic Diseases provided some insight and reassurance about the risk of malignancy with TNF-α inhibitors.9 The analysis included more than 13,000 patients with rheumatoid arthritis treated with TNF-α inhibitors for a cumulative total of 49,000 patient-years. The results showed a small increased risk of nonmelanoma skin cancer and a trend toward an increased risk of melanoma among patients treated with biologic agents. No other analyses revealed a statistically significant risk of malignancy among patients treated with biologic agents.

The risk of myocardial infarction (MI) was examined in 131,000 patients with psoriasis identified in a general practice database in England.10 The analysis yielded two key findings. The adjusted risk of MI increased with the severity of psoriasis. Second, the youngest patients had the highest risk, which appeared to decline over time. In contrast to another analysis involving patients in a Swedish registry showed a 35% reduction in the adjusted hazard ratio for mortality in patients treated with TNF-α inhibitors.11 Most of the mortality benefit could be explained by a 54% reduction in the risk of cardiovascular events.

More reassurance about TNF-α inhibitors and vascular risk came from a study involving 24,000 patients with psoriatic diseases.12 Patients who received a TNF-α inhibitor for at least 2 consecutive months had a 48% lower risk of MI than did patients treated with other systemic therapies.

With regard to the safety of IL-12/IL-23 inhibitors, some issues remain unresolved. No concerns related to infection or malignancy have emerged with regard to ustekinumab. The issue of cardiac risk is less clear.

Analysis of data from two placebo-controlled trials of ustekinumab showed an apparent imbalance of cardiac events early in the course of treatment.5,6 Patients who received the higher dose of ustekinumab had a 47% increase in the hazard for MACE during the first 12 to 20 weeks of follow-up (not statistically significant [NS]). Combining the data on patients treated with either dose of ustekinumab resulted in a 23% increase in the hazard (NS). Moreover, MACE risk declined in ustekinumab-treated patients during long-term follow-up.

The situation with briakinumab is more complicated. Reanalysis of data from a randomized placebo-controlled trial showed that five MACE events occurred during the first 12 weeks of treatment versus none in the placebo group. Six patients treated with briakinumab developed nonmelanoma skin cancer as compared with none in the placebo group. Five serious infections occurred in the briakinumab group compared with one in the placebo group.

A recent meta-analysis produced additional data consistent with an imbalance in cardiovascular risk among patients with psoriatic disease treated with an IL-12/IL-23 inhibitor.13 The analysis comprised 22 randomized clinical trials involving a total of 10,183 patients. About 3,100 patients had received an IL-12/IL-23 inhibitor, 3,800 patients had a TNF-α inhibitor, and 3,100 patients had a placebo.

The results showed 10 MACE events in the IL-12/IL-23 group versus none in the corresponding placebo group (NS). The difference did not achieve statistical significance but suggested a possible trend toward an increased risk of MACE with IL-12/IL-23 inhibition. One MACE event occurred in patients treated with TNF-α inhibitors and one in placebo-treated patients (NS).

The association between IL-12/IL-23 inhibitors and MACE has yet to be explained but appears to be a class effect. Until the association can be explained, physicians should carefully consider treatment options for psoriasis, particularly for patients who have coexisting cardiovascular risk factors. TNF-α inhibitors might represent a better option for those high-risk patients. When choosing ustekinumab, physicians should consider starting all patients on a low dose and adding low-dose aspirin if a patient is not already on an aspirin regimen.

Summary
Recent developments in the treatment of psoriasis have revised the stepped approach to treatment that has prevailed for years. Topical therapies remain the initial treatment for most patients. When patients have inadequate improvement with topical therapy, the next therapeutic step should be based on an individualized assessment of a patient’s health status and circumstances. Psoriasis does not evolve in a stepwise manner, and the approach to treatment should offer the flexibility to adapt to the disease process.

References

continued on page 14
Pulmonary arterial hypertension (PAH) occurs frequently in patients with scleroderma (or systemic sclerosis, SSc) and represents a life-threatening complication. Most patients without heart, lung, or kidney involvement can expect to live for years with scleroderma. However, untreated PAH in scleroderma progresses rapidly and is associated with a 1-year survival rate of 50%.1

Early recognition of PAH in scleroderma is essential to improve the survival odds. In many instances, physicians can suspect the diagnosis by means of noninvasive testing, such as echocardiography. When the level of clinical suspicion is high, right-heart catheterization can provide a definitive diagnosis.

Targeted therapies have helped improve treatment of PAH. However, patients with scleroderma and PAH tend to have more modest responses than do patients who have other forms of PAH.

Characterizing the Disease

More than half of all deaths in patients with SSc occur directly as a consequence of the disease.2 Of those deaths, 35% result from pulmonary fibrosis, followed by PAH and cardiac causes, which account for about 25% each. As compared with other types of PAH, disease associated with SSc and other connective tissue disorders (CTDs) has an especially ominous phenotype. PAH associated with CTDs has a more favorable hemodynamic profile and right ventricular echocardiographic findings than does idiopathic PAH.3

However, CTD-PAH is associated with a higher prevalence of pericardial effusions, worse performance on the 6-minute walk test, higher B-type natriuretic peptide (BNP) levels, and lower diffusing capacity of carbon monoxide (DLCO). Moreover, patients with PAH and CTD have significantly worse rates of 1-year survival (86% vs 93%, P<0.0001) and freedom from hospitalization (67% vs 73%, P=0.03) than do patients who have idiopathic PAH.3

Patients with SSc-PAH have hemodynamics similar to those of patients with systemic lupus erythematosus (SLE), mixed CTD, or rheumatoid arthritis. However, SSc-PAH is associated with higher levels of BNP, low DLCO, and worse 1-year survival rates.3 Several key differences distinguish SSc-PAH from idiopathic PAH. Patients with SSc-PAH have significantly lower pulmonary artery systolic pressure (P<0.004), pulmonary artery pressure (P=0.002), and pulmonary vascular resistance index (P=0.026) than do patients with idiopathic PAH.4

The lower survival rate reflects more severe right ventricular impairment. Even at lower pressures, right ventricular systolic volume is more impaired than in patients who have idiopathic PAH.5 Scleroderma alters the intrinsic mechanics of the right ventricle.

A substantial proportion of patients with SSc-PAH also develop diastolic dysfunction in the left ventricle. The dysfunction leads to increased stiffness, which contributes to PAH and adversely affects left ventricular anatomy and function.4

Early Diagnosis

The most widely used noninvasive imaging to diagnose suspected PAH is transthoracic Doppler echocardiography (TTE). Used primarily to estimate pulmonary artery systolic pressure, TTE also provides functional and structural information. Clinical guidelines for PAH include caveats about the potential for false-positive and false-negative results.6 With clear instructions about studying the right heart, the value of TTE can be improved.

The correlation between TTE and right-heart catheterization for measuring systolic pulmonary artery pressure varies widely. The accuracy of TTE for estimating systolic pulmonary artery pressure deteriorates as the echocardiogram becomes increasingly abnormal. TTE provides no information about the extent of abnormality.

The value of stress echocardiography for evaluation of patients with SSc-PAH depends on the definition of an abnormal rise in pressure during exercise. No consensus exists about what constitutes an abnormal increase in systolic pulmonary artery pressure. Moreover, a rise in pulmonary artery pressure during exercise has no value without knowledge about pulmonary blood flow.

BNP is perhaps the single most useful clinical parameter to assess in patients with suspected PAH. Measuring BNP will not differentiate between right- and left-sided cardiac disease. However, an abnormal BNP measurement can focus clinical attention on the heart.

A nationwide prospective screening study in France employed an algorithm based on symptoms (primarily dyspnea), Doppler echocardiography, and right-heart catheterization.7 Investigators applied the algorithm to 599 patients who had SSc but no severe pulmonary function abnormalities. Only patients with known or suspected PAH by echocardiography were referred for right-heart catheterization.

Of 33 patients with suspected PAH, catheterization confirmed the diagnosis in 18 patients and revealed left ventricular dysfunction in three others. The remaining 12 patients had no evidence of PAH. The 18 patients with PAH confirmed by right-heart catheterization all had early-stage disease, associated with pulmonary artery pressure of 30 mm Hg and total pulmonary resistance of 524 dynes × second/cm5. The same measurements in patients with known PAH revealed mean values of 49 mm Hg and 1,007 dynes × second/cm5.

Almost 85% of the patients with newly diagnosed PAH had dyspnea as compared with 27% of the patients without PAH (P<0.0001). They also had a significantly lower DLCO (P<0.0004). The presence of these two factors should increase clinical suspicion of PAH.

Results of the French study emphasized the limitations of Doppler echocardiography. A substantial number of patients did not have PAH despite abnormalities on Doppler, emphasizing that treatment should not begin solely on the basis of Doppler echocardiography results but should await confirmation of PAH by catheterization.
**Treatment**

Physicians have more treatment options for SSc-PAH than in the past.

The endothelin receptor antagonist bosentan has demonstrated efficacy in patients with SSc-PAH and idiopathic PAH. In a pivotal clinical trial, patients with SSc-PAH had improvement in the 6-minute walk test at 16 weeks, whereas placebo-treated patients had a deterioration in performance.\(^8\)

Subgroup analyses showed a consistent benefit for treatment with bosentan, although patients with SSc-PAH appeared to have a less robust response than did those with other subtypes.

Another analysis of data from the pivotal trial showed that treatment with bosentan was associated with a significantly longer time to clinical worsening ($P=0.0015$). An analysis limited to patients with SSc-PAH showed a similar difference between patients treated with bosentan and those randomized to placebo.

Sildenafil was evaluated in a 12-week randomized, placebo-controlled trial involving 278 patients with CTD-PAH (45% SSc-PAH).\(^9\) Patients treated with any of three doses of sildenafil had improved 6-minute walk distance, whereas patients in the placebo group had deterioration of exercise capacity. The proportion of patients who were in New York Heart Association class I at the end of the study ranged between 29% and 42% in the sildenafil groups compared with 5% in the placebo arm.

A meta-analysis of 10 randomized, controlled trials of oral therapies for PAH included bosentan, sitaxsentan (an endothelin receptor antagonist no longer on the market), and sildenafil.\(^10\) Overall, the analysis showed similar effects among the agents, as did a separate analysis limited to patients with CTD-PAH.

**Summary**

PAH is a frequent, life-threatening complication of SSc, and early diagnosis is essential to improve the odds of survival. Although targeted therapies have demonstrated efficacy in SSc-PAH, responses tend to be inferior to those seen in patients with other types of PAH, underscoring the importance of early recognition and treatment. Appropriate use of noninvasive imaging followed by right-heart catheterization represents a rational approach to diagnosis of SSc-PAH. Despite use of the term “hypertension” to describe the condition, arterial pressure is not the determining factor in PAH outcomes but instead is right ventricular function. Focusing on pressures is counterproductive. The focus should be directed at parameters that inform the functional status of the right ventricle.

Two other oral therapies have approved indications for PAH: the phosphodiesterase type 5 inhibitor tadalafil and the endothelin receptor antagonist ambrisentan.

The parenteral prostacyclin epoprostenol was evaluated in a 111-patient randomized trial involving patients with SSc-PAH.\(^11\) Patients received either epoprostenol or conventional therapy, and the primary end point was change in 6-minute walking distance. The epoprostenol group had an increase in walking distance within the first week, and the improvement continued to week 12 ($P<0.003$). Walking distance decreased in the group randomized to conventional care.

Lung transplantation remains an option for selected patients with PAH or pulmonary fibrosis associated with SSc. However, some transplant centers prefer not to perform the procedure on patients with PAH because of poorer outcomes, particularly increased early mortality risk.

---

**Biologic Therapies in the Management of Rheumatoid Arthritis**

---

---

---


TNF inhibitors are an effective treatment for PsA. Results with methotrexate have been minimal and mixed. New therapies and therapeutic strategies lie ahead and provide reason for optimism about more effective clinical management that will substantially improve disease control and patients’ quality of life.

References

Psoriasis Update: Efficacy and Emerging Safety Issues

CME Questions Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

1. __________ occurs more often in patients with psoriatic arthritis than in those with rheumatoid arthritis.
   A. Hyperuricemia
   B. Metabolic syndrome
   C. Lymphoma
   D. Pulmonary arterial hypertension

2. The Diabetes Control and Complications Trial provided one of the first clear demonstrations that clinical outcomes could be improved by applying the concept of __________, a strategy that also is beneficial in RA.
   A. Caregiver education
   B. Intensive monitoring of laboratory values
   C. Multidisciplinary clinical management
   D. Treating to target

3. In clinical trials in psoriasis, which one of the following is the accepted metric for demonstrating efficacy?
   A. ACR50
   B. CD10
   C. DAS28
   D. PASI75

4. The ________ combines joint counts, patient global assessment, and physician global assessment to measure disease activity in RA, without requiring testing for C-reactive protein or erythrocyte sedimentation rate, making it an attractive metric for use in routine clinical practice.
   A. ACR50
   B. CD10
   C. DAS28
   D. PASI

5. The stepped approach to the treatment of psoriasis __________.
   A. Compares favorably with the treat-to-target concept
   B. Is a novel concept currently being studied
   C. Is no longer considered an adequate strategy
   D. Is the standard of care

6. Studies of RA patients taking methotrexate demonstrate that adding __________ significantly reduces disease progression as shown on radiography.
   A. Any of the biologic agents currently approved for RA therapy
   B. Nonsteroidal anti-inflammatory drugs
   C. T-cell inhibitors
   D. Tumor necrosis factor inhibitors

7. In addition to tumor necrosis factor inhibitors, the biologic agents currently approved for use in rheumatoid arthritis include all but one of the following. The exception is:
   A. A B-cell–depleting agent
   B. An anti-CD 20 antibody agent
   C. An interleukin-1 receptor antagonist
   D. A T-cell blocker

8. Untreated pulmonary arterial hypertension in patients with scleroderma progresses __________ and is associated with a 1-year survival rate of __________.
   A. Rapidly; 25%
   B. Rapidly; 50%
   C. Slowly; 75%
   D. Slowly; 90%

9. Transthoracic Doppler echocardiography provides all but one of the following. The exception is:
   A. Estimation of pulmonary artery systolic pressure
   B. Existence of a cardiac abnormality
   C. Extent of a cardiac abnormality
   D. Information about the structure of the right side of the heart

10. All of the following oral agents except one are currently approved and available for the treatment of pulmonary arterial hypertension in systemic sclerosis (PAH-SSc) and idiopathic PAH. The exception is:
    A. Ambisentan
    B. Bosentan
    C. Sildenafil
    D. Sitaxsentan

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. Please print.

Name:

Specialty:

Degree: ☐ MD ☐ DO ☐ PharmD ☐ RPh ☐ NP ☐ RN ☐ BS ☐ PA ☐ Other

Affiliation:

Address: City: ______________ State: ______________ ZIP: ______________

Telephone: ______________ Fax: ______________

E-mail: ______________

CME CREDIT VERIFICATION

I certify that I have spent ______ hour(s)/______ minutes of actual time working on this CME activity. No more than 1.5 CME credit(s) will be issued for this activity.

COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

• Determining the optimum treatment choices for individual patients with RA.
• Current information about RA.
• Determining the optimum treatment choices for individual patients with RA.
• Treating SSc/PAH rapidly or aggressively to prevent early death or irreversible organ damage.
• Making ongoing modifications to treatment strategies for psoriasis in a timely enough manner to maximize patient outcome and satisfaction.

Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?

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

Please elaborate on your answer.

Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed on the left?

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

Please elaborate on your answer.

Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?

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

Please elaborate on your answer.

How certain are you that you will implement this change?

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

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

Were the patient recommendations based on acceptable practices in medicine?

☐ Yes   ☐ No

If no, please explain which recommendation(s) were not based on acceptable practices in medicine.

Did you think the articles were without commercial bias?

☐ Yes   ☐ No

If no, please list the article(s) that was (were) biased.

_____________________________________________________________

The University of Louisville thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients’ care.
A CONTINUING MEDICAL EDUCATION CONFERENCE

PERSPECTIVES IN RHEUMATIC DISEASES 2012™

September 28-29, 2012

Island Hotel Newport Beach, Newport Beach, CA

CHAIR
Daniel E. Furst, MD
Carl M. Pearson Professor of Medicine
Department of Medicine, Division of Rheumatology
David Geffen School of Medicine
University of California, Los Angeles (UCLA)

CO-CHAIRS
Kenneth B. Gordon, MD
Professor of Dermatology
Northwestern University’s Feinberg School of Medicine
Chicago, Illinois

Brian Mandell, MD, PhD
Professor and Chairman of Medicine
Department of Rheumatic and Immunologic Diseases
The Cleveland Clinic, Cleveland, Ohio

Join an outstanding faculty, representing the best in the field, and learn about the newest scientific therapies and research focused on improving patient care and enhancing your practice.

APPROVED FOR AMA PRA CATEGORY 1 CREDIT(S)™

For agenda and faculty updates go to
www.globalacademycme.com/rheumatology