

The Impact of Inflammation on the Safety and Efficacy of Therapeutic Agents

A CME Symposium held during the 25th
Congress of Clinical Rheumatology

Arthur Kavanaugh, MD (Chair)
Director, Center for Innovative Therapy
Professor of Medicine
Division of Rheumatology, Allergy, and Immunology
University of California San Diego
La Jolla, CA

Christopher Ritchlin, MD
Professor of Medicine
Director, Translational Immunology Center
University of Rochester Medical Center
Rochester, NY

Nora Singer, MD
Assistant Professor, Department of Pediatrics
Division of Infectious Diseases, Immunology, and Rheumatology
Case Western University
Cleveland, OH



Jointly sponsored by Interstate Postgraduate Medical Association and MEV Healthcom, Inc.
Supported by an educational grant from Roche.



Introduction

The availability of biologic agents for the treatment of rheumatoid arthritis (RA) has greatly improved patient symptoms and quality of life, and lessened structural damage. At the same time, newer insights from basic studies in immunology and inflammation have elucidated mechanisms underlying joint inflammation, cartilage damage, and bone resorption. With a better understanding of the inflammatory pathways in clinical disease, and with new biologic agents able to target these pathways, clinicians are increasingly able to offer patients treatments with superior efficacy, a greater potential for disease remission, and lower toxicity.

This activity examines the present and future impacts on clinical medicine that follow from an advanced understanding of inflammation. In his presentation, "Insights from the Bench," Christopher Ritchlin, MD, discusses key interactions between inflammatory cells and cytokine networks in RA; immune and bone cell cross-talk, leading to alterations in bone remodeling; and new research into the link between lymph node dynamics and RA flare.

Clinical management of rheumatoid arthritis is often complicated by coexisting conditions such as infection and cardiovascular disease. In her clinically based presentation, Dr. Nora Singer adopts a case management approach to addressing "Comorbidities in RA Patients."

The therapeutic armamentarium for rheumatologists is expanding. In his presentation, Program Chair Arthur Kavanaugh, MD, provides a timely analysis of studies that have determined the relative "Safety and Efficacy of New and Emerging Agents in Rheumatoid Arthritis."

CME Information

Release date: September 30, 2009

Expiration date: September 30, 2010

Estimated time to complete this activity: 1.5 hours.

Learning Objectives

- Choose treatment options considering inflammatory pathways underlying clinical disease.
- Select treatment options that improve outcomes and reduce toxicity for RA patients with comorbid conditions.
- Evaluate the efficacy and safety of new and emerging agents for the treatment of patients with rheumatoid arthritis.
- Consider how new therapies may change RA treatment.

Target Learners

This activity is intended for rheumatologists.

Faculty

Arthur Kavanaugh, MD (Chair)

Director, Center for Innovative Therapy
Professor of Medicine
Division of Rheumatology, Allergy, and Immunology
University of California San Diego
La Jolla, CA

Christopher Ritchlin, MD

Professor of Medicine
Director, Translational Immunology Center
University of Rochester Medical Center
Rochester, NY

Nora Singer, MD

Assistant Professor, Department of Pediatrics
Division of Infectious Diseases, Immunology, and Rheumatology
Case Western University
Cleveland, OH

Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Interstate Postgraduate Medical Association (IPMA) and MEV Healthcom, Inc. IPMA is accredited by the ACCME to provide continuing medical education to physicians.

Credit Designation

IPMA designates this continuing medical education activity for a maximum of *1.5 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of participation in the activity.

Commercial Support

This program is supported by an educational grant from Roche.

Method of Participation

Physician learners will participate in this educational activity by reading this education content, completing the post-test and evaluation. Learners must complete a post-test and evaluation and receive a passing score of 70% or more on the post-test. This activity should take 1.5 hours to complete.

IPMA-Faculty Planning Disclosure Statement

As a provider dedicated to independent education and accredited by the ACCME, IPMA must ensure balance, independence, objectivity, and scientific rigor in all its educational activities. It is the policy of IPMA to require the disclosure of the existence of any significant financial interest or any other relation a faculty member, planner, or a sponsor has with either the commercial supporter of this activity or the manufacturer(s) of any commercial product(s) discussed in an educational presentation.

Faculty Disclosures

Arthur Kavanaugh, MD, *Consultant* — Roche, Abbott, Centocor, UCB, Genentech; *Research* – Roche, Abbott, Centocor, UCB, Genentech.

Christopher Ritchlin, MD, *Consultant* — Centocor, Amgen, Abbott, Bristol-Myers Squibb; *Research* – Centocor.

Nora Singer, MD, *Speaker's Bureau*— Abbott; *Consultant* – Abbott, Vienna Medical.

Planner Disclosures

Mary W. Ales, Investment — Amgen.

No other planners or staff in the position to influence the content of this activity had any relationships with relevant commercial interests to disclose.

Writer

Barbara L. Jones, MA, reported no relevant commercial relationships.

Independent Reviewers

John F. Schneider, MD, PhD – nothing to disclose.

Alan J. Bridges, MD – *Speaker/Teacher* – Abbott Laboratories, Biogen, Bristol-Myers Squibb, Genentech, Inc.

Disclosure of Off-Label Use

Some of the information contained herein may cite the off-label use of drugs. Consult the approved package insert(s) for complete prescribing information. Tocilizumab, orelizumab, ofatumumab, epratuzumab, tamarinib, ustekinumab, apilimod, pamipimod, alefacept, efalizumab, natalizumab, belimumab, ABT-874, and denosumab are investigational drugs not approved by the FDA.

On April 3, 2009, when the “live” symposium took place, certolizumab pegol and golimumab were not approved. As of this publication, they received FDA approval.

Disclaimer

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that the faculty members are expressing the views of IPMA or MEV Healthcom, Inc.

Peer Review

This activity was peer-reviewed by physicians in the target audience group.

Privacy Policy

At IPMA, we care about providing you with tools and information to manage and protect your online privacy. IPMA retains records solely to comply with ACCME record-keeping policies. We will not share your information with any other organization. We will keep you informed of our CME activities.

Contact IPMA, P.O. Box 5474, Madison, WI 53705. Phone 877-292-4489 or Fax 608-231-9045. Please e-mail cmehelp@ipmameded.org if you do not want to receive any communications from us.

Table of Contents

Insights From the Bench	5
Cytokine Targets in RA.....	5
Biologic Activities of IL-6 in RA	5
The IL-6-Hepcidin Axis and Anemia of Inflammation.....	6
Understanding Bone Erosion in Rheumatic Diseases.....	6
Exploring Mechanisms of RA Flare	6
Management of Comorbidities in RA Patients	7
Case: RA Patient With Cardiovascular Risk	7
Genetic Risk and Comorbidities.....	7
Predictors of Mortality in RA	7
Considerations in the Treatment of Patient SJ	8
Effects of Anti-RA Therapies on Cardiac Risk Factors	8
Prevention, Secondary Prevention, and Treatment of RA.....	8
Case: RA Patient With Recurrent Infections.....	9
Efficacy of Pneumococcal and Influenza Vaccines in RA	9
Efficacy and Safety of New and Emerging Agents	10
TNF Inhibitors	10
Therapeutic Options in Patients Refractory to TNF- α Inhibitors.....	11
Safety of Biologic Therapy Over 10 Years	11
Emerging Immunomodulatory Therapies	11
The Promise of Tomorrow With Biologics in RA.....	12
Audience/Faculty Questions and Answers	12
References	13
Evaluation	17
Post-test	18

Insights From the Bench

Traditionally, rheumatoid arthritis (RA) has been defined by clinically useful criteria that have not been based on disease etiology or pathogenesis.¹ Until quite recently, this information was not available. Recent advances have allowed for a better understanding of the role of cytokine regulation. This, along with the development of cytokine-based therapy, has enabled rheumatologists to gain insights into the inflammatory processes in RA.

Scientists have learned that adaptive immunity appears to play an important role in the etiology of RA. And, although the entire process is not yet fully understood, Klareskog et al, in 2008,¹ proposed a 3-stage etiologic model that is “supported by the data,” according to speaker Christopher Ritchlin, MD (Figure 1).

Three-stage etiologic model for the development of chronic rheumatoid arthritis.¹

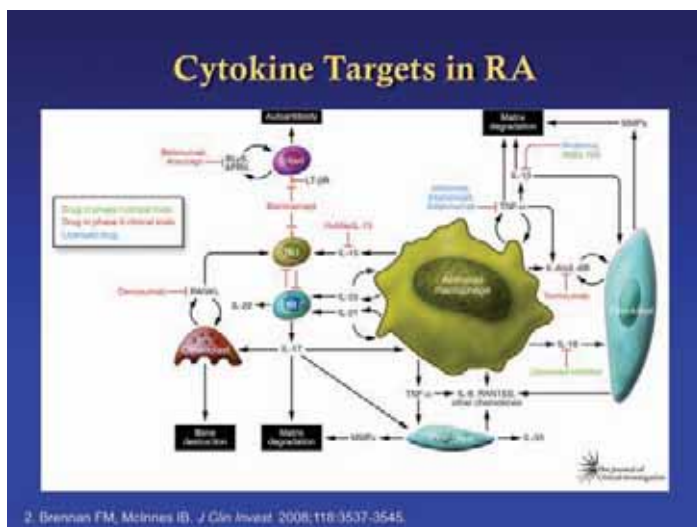
According to this model, at stage 1 (Immune response), environmental risk factors such as smoking may induce “citrullination” (post-translational modification of arginine in a protein into citrulline) of proteins in the lungs. In genetically susceptible individuals (eg, HLA-DR SE-positive), altered antigen uptake, processing, and presentation could lead to the production of antibodies to citrullinated protein antigens (ACPA).¹

At stage 2 (Pathologic inflammatory response), an unspecified arthritis develops, accompanied by citrullination of proteins in the joints.¹

During stage 3 (Chronic rheumatoid arthritis), citrullinated proteins, along with an influx of immune cells and the production of cytokines and autoantibodies, perpetuate joint inflammation into chronic RA.¹

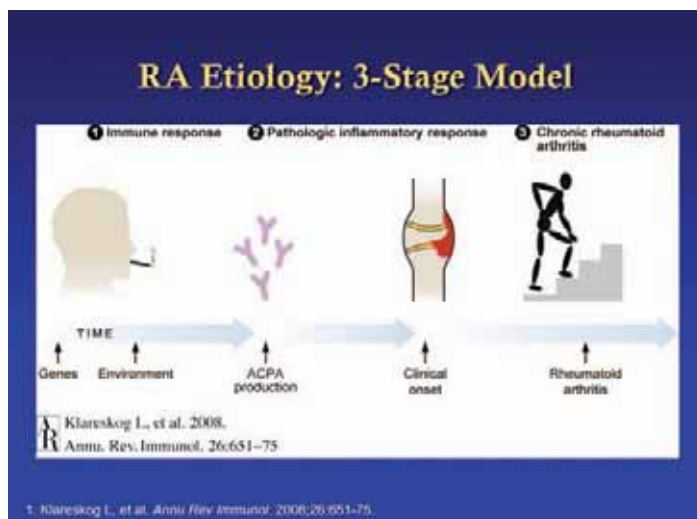
A major feature of this etiologic model of RA is that antibodies to the citrullinated proteins occur before the onset of the disease.¹ As Dr. Ritchlin explained, recruitment of ACPA from the circulation results in the formation of immune complexes. Clinically, ACPA thus represent a “relatively specific” diagnostic tool for RA, since they were present in about 60% of an early RA cohort, but only about 2% of the general population.¹

Figure 2. Cytokine Targets in RA.



Cellular interactions believed to be important in RA pathogenesis and the interactions of macrophages, T cells, B cells, and nonhematopoietic cells (fibroblasts, connective tissue cells, and bone).²

Figure 1. RA Etiology: 3-Stage Model.



Three-stage etiologic model for the development of chronic rheumatoid arthritis.¹

Cytokine Targets in RA

Meanwhile, in between the production of anti-CCP (cyclic citrullinated peptide) and clinical onset, “...a lot of interactions are going on in the immune system and in the immune system’s relationship to bone and cartilage,” Dr. Ritchlin continued.

Studies to elucidate the central effector pathways in RA show that a number of cytokines that are active in the joints of patients with RA play essential roles in processes that result in inflammation, articular destruction, and comorbidities common in RA patients (Figure 2).²

For example, the RA synovial membrane contains activated B cells and T cells, plasma cells, mast cells, and activated macrophages. Host tissue cells (eg, activated synovial fibroblasts, chondrocytes, and osteoclasts) are also involved. Their actions, and the effects that follow, include mediating cartilage and bone destruction and perpetuating inflammation.² Dr. Ritchlin noted, “At the center of all this is the activated macrophage, which releases a variety of key cytokines such as tumor necrosis factor (TNF)-alpha, interleukin-6 (IL-6), IL-15, IL-18. Each may have important roles in RA. We also know that the fibroblasts acted upon by released cytokines, particularly IL-6, results in the release of metalloproteinase and subsequent cartilage destruction.”

In its role in the pathogenesis of RA, TNF-α induces the production of other proinflammatory cytokines, including IL-1 and IL-6, and the production and release of chemokines that attract leukocytes from the blood into inflamed tissue.² As one of its many roles, TNF helps to drive angiogenesis and the accumulation of leukocytes and activation of endothelial cells. Along with IL-6, it also drives hepcidin. These critical actions lead to cartilage destruction and bone resorption.²

Biologic Activities of IL-6 in RA

Through a series of diverse activities, the pleiotropic cytokine IL-6 contributes to systemic and local symptoms in RA. Scientists have also demonstrated that this cytokine plays a key role in the shift from acute to chronic inflammation, a finding that may establish a place for IL-6 in the development of RA.³

Among its complex actions and downstream effects, IL-6 is also

involved in inducing the acute-phase response, represented by fever, anemia of chronic disease, elevated C-reactive protein (CRP), serum amyloid, and other acute-phase proteins (Table 1).³

IL-6 also mediates varied effects on immune cells. In RA, IL-6 induces B-cell differentiation and antibody formation, which may stimulate the production of autoantibodies like rheumatoid factor (Table 1).³ Other effects include induction of T-cell activation and differentiation and macrophage differentiation, all of which are important to the induction of matrix metalloproteinases, which may result in cartilage damage.³

The IL-6-Hepcidin Axis and Anemia of Inflammation

Experiments from the past few years have determined a role for hepcidin (a liver-derived peptide regulator of iron homeostasis) as a key mediator of hypoferremia in inflammation.⁴ Dr. Ritchlin explained that inflammatory macrophages release IL-6, which acts on hepatocytes to release hepcidin. Hepcidin blocks the release of macrophage iron and intestinal iron absorption, which can lead to anemia.⁴ (TNF release can also lead to increased IL-6 levels.) Other inflammatory cytokines did not stimulate the production of hepcidin; notably, TNF- α inhibited it.⁴

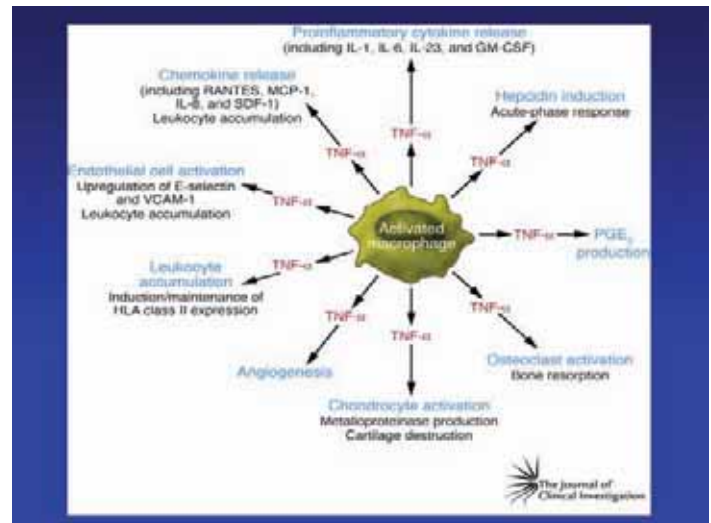
Understanding Bone Erosion in Rheumatic Diseases

Osteoimmunology, which is the study of the interaction of the immune system with the skeleton, is an active area of current scientific inquiry.⁵ Beyond extending the basic understandings of inflammatory processes and explaining their links to disease, the work has clinical potential. “By altering the timing in which these inflammatory cells are released into the circulation and to the tissues, there may be a way for us to influence therapy for rheumatoid arthritis,” Dr. Ritchlin said. In a 2009 review of leading concepts in osteoimmunology, the authors demonstrate how molecular regulation of osteoclast formation and its control by proinflammatory cytokines has helped to forge an understanding of the mechanisms of bone erosion in rheumatic diseases.⁵

Studies in osteoimmunology flow from 3 key areas of focus: 1) regulation of bone remodeling by the immune system; 2) the interaction between inflammation and bone formation; and 3) bone and bone marrow as a niche for immune cells.⁵

As part of a complex process of immune system regulation of bone remodeling, Dr. Ritchlin said, tumor necrosis factor (TNF) and interleukin (IL)-1, IL-6, and IL-17, increase the expression of RANKL (receptor activator of nuclear factor-kappa B ligand), to

Figure 3. TNF- α Actions Relevant to Pathogenesis of RA.



The biologic actions of TNF- α , produced mainly by activated macrophages in the inflamed synovial membrane tissue in patients with RA.²

support osteoclastogenesis in the joints.⁵ He noted, “Th1 and Th17 release a variety of these key molecules [eg, TNF, IL-1, IL-6, IL-17], and in combination with RANK ligand and macrophage colony-stimulating factor (M-CSF), osteoclasts are formed from osteoclast precursors.” Regulatory T (T-reg) cells, on the other hand, inhibit osteoclast formation through the release of CTLA4 (cytotoxic T-lymphocyte antigen 4).⁵

The hope is that these studies, along with advanced inquiries into bone loss in rheumatic disease and osteoimmunologic aspects of bone formation (how immune activation controls bone formation), will guide the development of new therapies that can target skeletal damage more specifically and effectively.⁵

Osteoimmunologic studies in mechanisms of immune activation and bone formation are expected to aid in tailoring new therapies that can target skeletal damage more specifically and effectively.⁵

Exploring Mechanisms of RA Flare

Another line of inquiry into understanding the pathophysiologic mechanisms in RA seeks to explain why, when RA patients are doing well for a period of time, some suddenly begin to experience severe joint pain and stiffness. According to promising research, joint flare may result from impaired lymphatic drainage. Therapies

Table 1. Biologic Activities of IL-6³

IL-6 Activity	Presentation
Acute-phase response	Fever, anemia, elevated CRP
B-cell differentiation	Anti-CCP, rheumatoid factor (RF) production
T-cell activation and differentiation, macrophage differentiation	Inflammatory immune response
Activation of endothelial cells	Leukocyte recruitment
Synoviocyte proliferation and osteoclast activation	Synovial pannus formation
Matrix metalloproteinases (MMP) induction	Joint and cartilage damage

directed at maintaining lymphatic flow could thus result in sustained remission. In their work to identify signals that result in RA flare, Dr. Ritchlin and colleagues are training their focus on the role of B cells and dendritic cells (DCs).

Dendritic cells are highly efficient antigen-presenting cells that appear to be crucial to the regulation of most adaptive immune responses.⁶ Many DCs in lymph nodes “mobilize, with antigen in tow,” from the peripheral tissues and proceed to drain to downstream lymph nodes via a network of lymphatic tissues. Such insights help to explain how DCs initiate and organize immune responses.⁶

To observe this process at close range, engineers working with Dr. Ritchlin designed MRI coils that can visualize joint structures. The MRI images of the knees of TNF transgenic mouse models provided detailed views of the draining popliteal lymph node, and also showed synovial volume and size. CT scans of bony structures provided detailed views of the patella and the talar bone, along with information regarding synovial proliferation and joint destruction. “The really striking finding was the presence of a large draining popliteal lymph node in the inflamed knee,” Dr. Ritchlin said. “When the lymph node collapses just prior to the flare, there is a massive increase in synovial tissue, a decline in the size of the lymph node, and marked destruction of the patella.”

Histopathologic studies revealed differences involving B cells and led to the group’s coining of the phrase “toilet bowl hypothesis” to describe their observations. “In the mouse model that did not have a flare, there was a normal distribution of B cells in the

periphery of the node and what appeared to be normal flow,” said Dr. Ritchlin. But with the lymph node collapsed, followed by a flare, “a migration of B cells from the periphery to the center of the node was observed, and this was associated with compromised flow through the node.”

When the mice were treated before the onset of a flare, however, the investigators found that the flare could be avoided. “If you use an antibody to a chemokine (CXCL13), which is expressed by dendritic cells in the center of the lymph node, B cells did not migrate centrally from the periphery,” Dr. Ritchlin reported. Depletion of B cells in the TNF transgenic mouse also significantly lessened arthritis flare.

These studies greatly extend understanding of the role of B cells in the TNF transgenic mouse model. Importantly, RA patients demonstrated similar lymph node dynamics. “In one of our RA patients with active RA, synovitis was evident before the onset of a flare, but went down after treatment. So did the size of the node.”

Dr. Ritchlin explained that therapeutic implications arise from each of these areas of investigation. Cytokine pathways mediate inflammation and damage in RA. New and emerging targets include IL-6, IL-15, IL-17, IL-18, IL-23, and RANKL. Th 17 cells promote osteoclastogenesis. Agents targeting this population may limit both synovitis and bone erosion. Joint flare may result from impaired lymphatic drainage, a novel disease mechanism. And therapies directed at maintaining lymphatic flow could result in sustained remission in RA.

Management of Comorbidities in RA Patients

Case: RA Patient With Cardiovascular Risk

SJ is a 29-year-old male package delivery employee. He complains of increased joint swelling in his hands and knees over a period of 5 months, and has a 3-month history of morning stiffness and foot soreness lasting until noon. He says that these symptoms are interfering with his ability to perform his job because he is no longer able to hold the clipboard steady when asking customers to sign for a package.

SJ is married with one child. He smokes a pack of cigarettes per day. Weekends, he drinks a beer and may also have a cocktail. SJ attributes a recent 20-pound weight gain to dropping out of a twice-weekly basketball game and discontinuing running on a daily basis. His physician has indicated that unless he loses weight, he'll likely need to begin an antihypertensive medication.

SJ's father was disabled from the police force at the age of 48 due to a massive myocardial infarction and is currently being treated for hypertension and hyperlipidemia. His maternal grandmother has RA that developed in her 60s. His mother is healthy.

American College of Rheumatology (ACR) recommendations would point to starting the patient on methotrexate,⁷ said speaker Dr. Nora Singer. But a poll of the audience suggested that clinical decision-making varies. Some clinicians would choose a different disease-modifying antirheumatic drug (DMARD) because of SJ's alcohol intake. Some indicated a preference for starting a biologic plus a DMARD, and others would choose a biologic.

Genetic Risk and Comorbidities

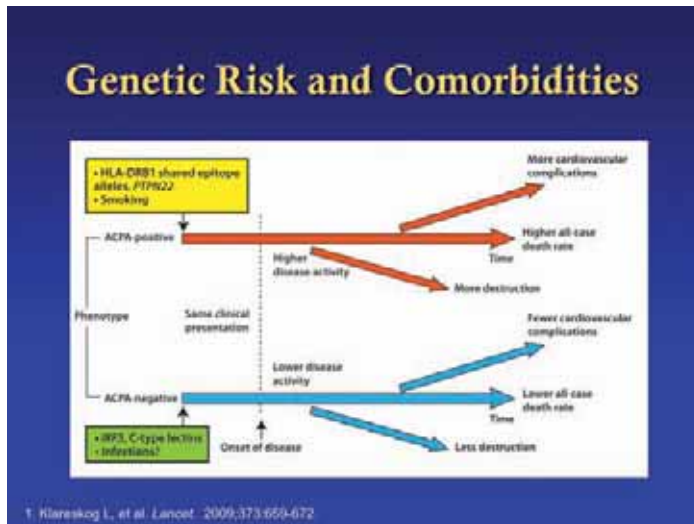
Among several considerations in managing this patient, one is genetic risk. RA is considered a complex genetic disease in which several genes, environmental and chance factors act in concert.⁸ Recent data from several sources indicate that in addition to the HLA DRB1, PTPN22 risk alleles are associated with a subset of RA that is defined by the presence of ACPA or rheumatoid factor, or both.⁸ A firmly established environmental risk factor for RA is cigarette smoking, which also appears to contribute to genetic susceptibility to RA (Figure 4).⁸

Two disease subsets (ACPA-positive and ACPA-negative) are associated with different genetic and environmental risk factors. Even with the same or similar clinical presentation, these two subsets may have different levels of disease activity.⁸ “As we begin to ask who we're treating and how quickly we're treating them, we need to be able to subset patients because we know that rheumatoid arthritis is very much a heterogeneous disease,” Dr. Singer said. As this patient illustrates, cardiovascular disease is an important co-factor in treatment decisions.

Predictors of Mortality in RA

Standard mortality ratios in RA are 1.5- to 1.6-fold higher than in the general population, and slightly higher in noninception cohorts (1.6-1.7).⁹ Despite improvements in the therapeutic armamentarium, attributable causes of death have been quite stable over the past 60 years. Cardiovascular disease remains the most common cause, accounting for about 40% of deaths in

Figure 4. Genetic Risk and Comorbidities.



Longitudinal course of RA, showing the contributions of genetic risk and comorbidities.⁸

patients with RA, according to numerous published reports from the US and Western Europe.⁹ The most significant predictors of premature mortality in patients with RA from epidemiologic data, Dr. Singer said, appear to be older age, male sex, comorbidities, poor patient and physician global estimates of status, and poor functional status as assessed by physical measures and patient reports.⁹

The established RA patient has an average of 2 or more comorbid conditions.¹⁰

According to a 2007 analysis of data from the National Data Bank for Rheumatic Diseases (NDB), on average, the established RA patient has 2 or more comorbid conditions.¹⁰ Specific morbidities that are increased in RA are lung disease, myocardial infarction, fracture, stroke, and diabetes.¹⁰

In addition to affecting prognoses and outcomes, comorbidities have measurable effects on quality of life (QOL). In this analysis, the number of comorbid conditions was directly related to QOL rankings.¹⁰

Considerations in the Treatment of Patient SJ

Effects of anti-RA therapies on cardiac risk factors

The same cytokines that are involved in RA are also implicated in coronary artery disease and may contribute to pathogenesis of both, according to Dr. Singer. Paradigms such as activated or oxidized LDLs stimulating macrophages to produce proinflammatory cytokines suggest that “what is going on in the joint might also be going on in the heart,” said Dr. Singer. Could the use of biologic anti-RA therapies have impacts, positive or negative, on risk markers in heart disease?

Activated immune cells in plaque produce inflammatory cytokines interferon- γ , IL-1, and TNF, which induce production of IL-6. IL-6, in turn, stimulates the production of acute-phase reactants, including C-reactive protein (CRP), serum amyloid A, and fibrinogen, especially in the liver.¹¹ IL-6 is known to be important in lipid metabolism.

Biologic agents affect cardiac parameters differently (Table 2). TNF- α inhibitors reduce inflammation and modify lipids. Short-term infliximab therapy, for instance, produced a significant increase in high-density lipoprotein cholesterol levels.¹² Co-stimulatory inhibitors appear to reduce inflammation in the context of therapeutic response and might also reduce cardiac disease markers, Dr. Singer suggested. B-cell inhibitors show similarly positive effects on inflammatory parameters, but with an apparent cautionary note—evidence that statins may confirmationally change patients’ ability to express CD20, according to a recent article in the oncology literature.¹³ In the setting of statin use, therefore, Dr. Singer indicated that “there are concerns that the efficacy of a B-cell depleter such as rituximab¹⁴ may be reduced.” With IL-6 receptor inhibition, increases in total cholesterol and low-density lipoprotein cholesterol have been seen.¹⁵ (TNF inhibitors may be contraindicated with Class 3 or 4 heart failure.⁷)

Prevention, Secondary Prevention, and Treatment of RA

The precise trigger or set of triggers for the onset of clinical RA are not yet fully explained. In a smoker such as the patient SJ, however,

cessation may delay the disease pathogenesis or attenuate it, Dr. Singer noted. More citrullinated proteins results in more drive to produce autoantibody, and the autoantibody participates in disease pathogenesis and treatment of undifferentiated arthritis in high-risk individuals. The PROMPT trial (PRObable rheumatoid arthritis Methotrexate versus Placebo Treatment) suggested that in CCP-positive patients but not in CCP-negative patients, initiation of methotrexate in undifferentiated arthritis delays the onset of RA.¹⁶

For the patient SJ, therefore, who is experiencing clinical onset of RA, secondary prevention measures apply, including smoking cessation, weight loss, and osteoporosis prevention. The aims of therapy are to prevent joint destruction, to “compete against time” because time in RA means joint damage, and to prevent complications and comorbidities.

SJ was started on a traditional DMARD and then advanced to a combination of DMARD (or biologic if he failed to have a good EULAR response). Risk reduction measures, in addition to ongoing disease control, included smoking cessation, weight control, management of dyslipidemia, exercise, and screening.

Table 2. Effect of Class on Cardiac Comorbidities.

Biologic	Inflammatory parameters	Potential or Known CV adverse effects	Effect on lipids
TNF- α inhibitors	Reduced if response to therapy	May be contraindicated in CHF Class III/IV	controversial ⁷
Co-stimulatory inhibitors	Reduced if response to therapy	none	no data
B-cell depleters/inhibition	Reduced if response to therapy	none	Statins may alter CD20 expression and effects of Rituximab in B-cell depletion ¹³
Anti-IL6/IL6R inhibition	Reduced if response to therapy	none	Increase cholesterol, LDLs

5. Garcia SP, et al. Ann Rheum Dis. 2009;67:895-898.

6. Winarska M, et al. PLoS Med. 2008;5:0502-0517.

(Timing of screening procedures remains controversial, and the impact on disease activity versus bone health, Dr. Singer said, “needs to be studied prospectively.”)

Case: RA Patient With Recurrent Infections

GN is a 56-year-old woman with a 10-year history of rheumatoid arthritis whose disease is controlled with a combination of methotrexate and TNF- α inhibitor. Her complaint is that each winter she seems to spend more time off her RA therapy than on it because she contracts sinus infections. Last winter, she was hospitalized for 2 weeks with pneumonia. GN wants to know if anything can prevent her sinusitis and pneumonia, and to what extent her RA medications are contributing to her recurrent infections.

This is a relatively common therapeutic dilemma in patients receiving immunosuppressive therapy. Pneumococcal pneumonia is the leading cause of pneumonia in the United States.¹⁷ In patients with RA, the leading cause of death is bacterial infection: 15%-25% of deaths are from pneumonia.¹⁸

Current guidelines recommend vaccination against pneumococcal disease for individuals aged 2 to 64 years with chronic illnesses and all person aged 65 years or older.¹⁸ The approved 23-valent polysaccharide pneumococcal vaccine accounts for more than 90% of strains that produce pneumococcal disease.¹⁸ However, the vaccination rate against influenza in RA patients offered immunosuppressive therapy is low—56% in one report. After this report, and 2 years later, 49% of patients >65 years were more likely to have received pneumococcal vaccination (compared with 24% of those <65 years).¹⁹ Patients contribute to the trend of underimmunization, Dr. Singer pointed out. They may decline vaccination for reasons such as being unsure of the need, adverse effects or RA flare with a previous vaccination, or because they had heard bad reports relating to the vaccination.

According to Dr. Singer, proper management of this patient should include screening for risk factors including smoking history. (Smoking contributes to a breakdown of protective barriers against sinus infection.) Additional screening tests might include serum immunoglobulins and immunoglobulin subclasses. Patients lacking in immunoglobulins or in certain subclasses may have more difficulty fighting infection. In select patients with particular problems with recurrent infection, screening for pneumococcal titers may be appropriate.

Efficacy of Pneumococcal and Influenza Vaccines in RA

Several studies provide evidence that RA patients mount a good response to the influenza and pneumococcal vaccines.

In a study of 205 patients, 184 patients with psoriatic arthritis, stratified by whether or not they received methotrexate (MTX),

randomly assigned to etanercept or placebo, and given 23-valent pneumococcal vaccine, underwent analysis of their antibody response to the vaccine. Approximately 20% in each group did not show a 2-fold response to any of 5 antigens.²⁰ Logistic regression analysis identified older age (≥ 47 years) as an independent risk factor predictive of an attenuated vaccine response, along with MTX use.²⁰ (Etanercept was not predictive of poor response in these patients.²⁰)

RA patients treated with TNF inhibitors alone (without MTX) showed better immune responses to 23-valent pneumococcal vaccine than patients receiving a combination of TNF inhibitor plus MTX, in a study to compare treatments. RA patients given MTX alone had the lowest immune responses.²¹

By contrast, in an ASPIRE substudy (Active controlled Study of Patients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset), investigators comparing responses to pneumococcal vaccine in 70 patients with early RA who added infliximab to MTX 3 mg/kg and 6 mg/kg with that of patients receiving MTX alone, found no significant difference between groups. All groups has lower responses to the vaccine than would be expected in a normal population.¹⁸ Only 20% to 25% of patients in all treatment groups responded to 6 or more different serotypes; roughly 80%-85% responded to at least one serotype.¹⁸ Thus, the addition of the TNF inhibitor to MTX did not appear to affect response to vaccination.

Equivalent protection followed administration of pneumococcal vaccine to RA patients receiving adalimumab (85.9%) or placebo (81.7%).²²

RA patients treated with rituximab generally had poorer serologic responses to influenza vaccination, however,²³ Dr. Singer noted, suggesting that “We’re better off vaccinating prior to treating with rituximab, even though there may be some chance patients will respond post-rituximab.”

Influenza vaccination is recommended in the United States for persons age 50 and older,²⁴ but in Europe, it is recommended for individuals beginning at age 60 or older.²⁵ Dr. Singer commented that most studies have been performed with inactivated flu vaccine; prospective studies with live attenuated virus administered intranasally have not been performed. Currently, use of biologics are considered a contraindication to live attenuated vaccines.⁷

In summary, Dr. Singer stated that RA patients should be counseled to receive vaccination against pneumococcus and influenza since most patients mount some immune response to both immunizations. A workup for specific antibody deficiency may be appropriate if infections recur. Patients who are actively infected warrant the consideration of an interruption of therapy. Patients should be alerted to these potential situations and educated about when they should ask their rheumatologists about holding off therapy.

Efficacy and Safety of New and Emerging Agents

In a 1998 editorial in the *Journal of Rheumatology*, Dr. Arthur Kavanaugh and colleagues Drs. Stanley Cohen and John Cush bemoaned the “disappointing life cycle of new biologic therapies in rheumatoid arthritis.”²⁶ Referring to the recent introduction of TNF inhibitors, they asked rhetorically whether the long-term utility of this new class of biologics would prove to provide “tangible benefit” for patients with RA. In old Texas parlance, they asked “Will that dog hunt?,” after a series of long-term disappointments had emerged from clinical trials. By 2004, Dr. Kavanaugh said, it was clear that this class of drugs had revolutionized rheumatology practice, having “dramatically improved patient outcomes.”²⁷

TNF Inhibitors

In 2009, Dr. Kavanaugh finds, the status of TNF inhibitors includes a number of “knowns.”

- Inhibition of a single key cytokine can be effective, a marvel, given the overlap and redundancy in the immune system.
- Most patients respond [to therapy] with improvements in signs and symptoms. Some enter into “remission.” (The meaning of remission, however, is currently in flux.)
- Clinical efficacy requires continued therapy. That is, the disease is not being “cured.”
- There may be a window of opportunity for cure, however, particularly in early rheumatoid arthritis.
- TNF inhibitors improve quality of life and functional status, in addition to slowing disease progression seen on x-ray. For these reasons, a TNF inhibitor plus methotrexate is the gold standard for patients with established refractory disease (and some might argue the gold standard for patients with early rheumatoid arthritis).
- In primary or secondary TNF failure, switching to another TNF is a reasonable option. (Also effective could be a switch to biologics with alternative modes of action [B-cell-targeted therapies, T-cell-targeted therapies, other cytokine-targeted therapies]).
- However, no synergy and an increase in side effects has been seen in studies into combinations of biologic therapies (eg, TNF/IL-1, TNF/T cell).
- Long-term safety data might justify “guarded optimism,” Kavanaugh stated. More than 2 million patients have been treated with TNF inhibitors for Crohn’s disease (CD), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile rheumatoid arthritis (JRA), psoriasis, and ulcerative colitis (UC).
- Safety issues are more often target-related than agent-related, including serious/opportunistic infections (eg, TB), risk of cancer (lymphoma), lupus-like reactions, and infusion-site reactions.
- Recent efficacy has been demonstrated in AS, psoriasis, PsA, and CD.
- Negative data have been generated in congestive heart failure, Wegener’s, polymyalgia rheumatica/temporal arteritis (PMR/TA).

Clinical responses to TNF inhibitors reflect the heterogeneity of this disease. Whether assessed by swollen/tender joint count, erythrocyte sedimentation rate (ESR), or Health Assessment Questionnaire (HAQ) score, patient responses are not bimodal; that

is, a clear distinction between responders and nonresponders is not found. Instead, responses are representative of a continuum, implying that multifactorial mechanisms are at work.²⁸

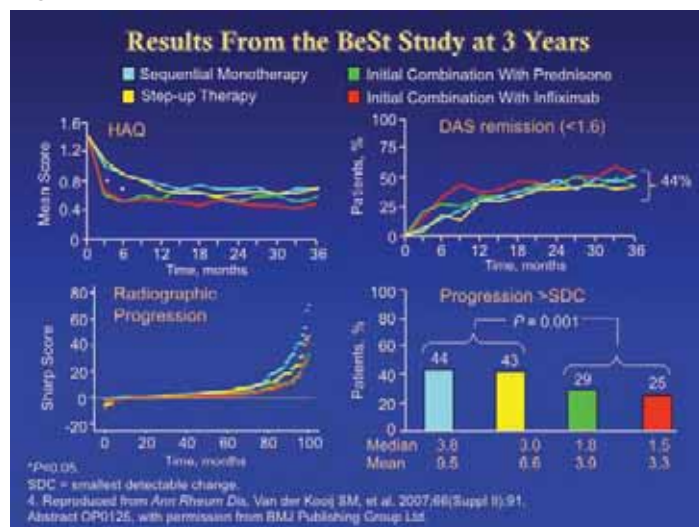
The BeSt study (Behandel-Strategieën) in early RA illustrates this point, offering insights into the potential for improving responses in early disease, and perhaps achieving remissions. BeSt investigators evaluated 4 therapeutic approaches and tested the concept of treating-to-goal—identifying the optimal strategy to prevent damage and preserve function.²⁹ BeSt was a single-blind, randomized trial comparing 4 treatment strategies, including sequential substitution monotherapy (Group 1); step-up, add-on combination therapy (Group 2); initial combination therapy with a short course of high-dose prednisone (Group 3); and initial combination therapy with TNF inhibitor infliximab (Group 4).²⁹ At 3 years, treatment strategies guided by Disease Activity Score (DAS) resulted in sustained clinical and functional benefit for almost half of study patients. Patients who were initially treated with a TNF inhibitor plus methotrexate required significantly fewer changes in treatment regimen vs. patients who received sequential monotherapy, step-up therapy, or initial combination therapy with prednisone (Figure 5).³⁰ (Five-year data, now available, are similar.)

The BeSt data raised the provocative question of whether aggressive early treatment might enable RA patients to discontinue therapy. Dr. Kavanaugh pointed out that roughly 15% of patients in all treatment groups achieved remission over about one year. Follow-up data will determine the persistence of these remissions.

It might be reasoned that patients who do not succeed with initial TNF therapy will respond to another TNF inhibitor. According to results from a recent meta-analysis of 31 studies, efficacy after switching between TNF inhibitors appears to be lower following a primary inadequate response.³¹

According to results from a 2008 meta-analysis of 31 studies, efficacy after switching between TNF inhibitors appears to be lower following a primary inadequate response.³¹

Figure 5. Results From the BeSt Study at 3 Years.



Therapeutic Options in Patients Refractory to TNF- α Inhibitors

T-cell-directed therapy is an alternative for patients who experienced an inadequate or unsustained response to TNF inhibitor therapy. Abatacept was studied in this patient group in the 6-month ATTAIN study (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders).³² After 6 months, ACR 20 responses in the abatacept group were 50.4% and 19.5% in the placebo group ($P < 0.00$). ACR 50 and ACR 70 responses were also higher for patients receiving abatacept than placebo (20.3% vs. 3.8%, $P < 0.001$; and 10.2% vs. 1.5%, $P = 0.001$, respectively). Adverse events rates were 79.5% in the abatacept group and 71.4% in the placebo group. The incidence of serious infections was 2.3% in each group (abatacept and placebo).³²

In the 24-week REFLEX study (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) with B-cell depleter rituximab, patients who were refractory to anti-TNF therapy achieved ACR 20, 50, and 70 responses similar to those in the ATTAIN study with abatacept. At week 24, significantly more ($P < 0.0001$) rituximab-treated patients than placebo-treated patients achieved ACR 20 responses (51% vs. 18%), ACR 50 responses (27% vs. 5%), and ACR 70 responses (12% vs. 1%). Most adverse events occurred with the first rituximab infusion, and were mild to moderate. The rate of serious infections was 5.2 per 100 patient-years in patients treated with rituximab and 3.7 per 100 patient-years in the placebo group.³³

The two trials produced results consistent with what many rheumatologists have observed in their clinical experience. Dr. Kavanaugh: “Even though [compared with ATTAIN] the REFLEX study differed in design, drugs, times and locale...this is what we expect with patients who had been on a TNF inhibitor—a little bit lower response...but a level of response I think we would like to see.”

Safety of Biologic Therapy Over 10 Years

The most complete picture of safety of biologic agents consists not just of double-blind, placebo-controlled studies, but case series, registries, and even anecdotes. When these sources are compiled, Dr. Kavanaugh said, the adverse event of greatest concern to most rheumatologists with these agents is serious infections.

That said, an assessment of drug safety in treated RA patients is

more complicated than study results alone suggest. Safety is not “monolithic.” A true assessment must take into account not just the drug but the patient’s status. In this regard, important safety insights were drawn from a 2009 published analysis of more than 19,000 patients exposed to adalimumab in 36 global clinical trials over 10 years, for multiple immune-mediated inflammatory diseases (RA, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, psoriasis, and juvenile idiopathic arthritis).³⁴ Overall, RA patients with severe active refractory disease experienced different effects than did those with early rheumatoid arthritis. Burmester et al, authors of this analysis, concluded that the safety profile of a drug such as adalimumab “...is likely influenced by a combination of drug-based toxicity, disease inherent risks for certain serious adverse events, and baseline patient characteristics.”³⁴

Emerging Immunomodulatory Therapies

Potential future therapies are emerging from investigations with number of biologic targets in inflammatory disease (Table 3). Early data vary in terms of real promise. Disappointing negative data have been seen with the p38 MAP kinase inhibitor, pamapimod. Results from a 12-week, double-blind, methotrexate-controlled study in patients with active RA showed an initial drop in CRP, followed by a rebound approximately to baseline, suggestive of a counter-regulatory effect following an initial positive performance.³⁵

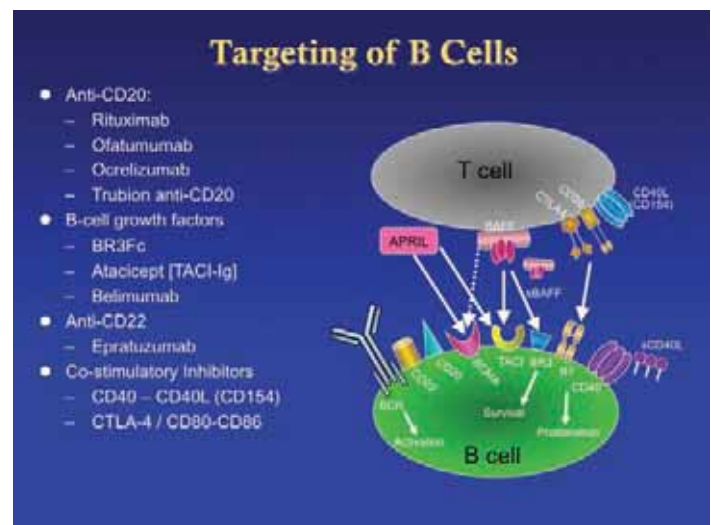
The IL-6 inhibitor tocilizumab (TCZ) is being studied in a large development program enrolling more than 4,000 RA patients to date. Overall, the data show “very consistent improvements in signs and symptoms in terms of ACR 20/50/70,” Dr. Kavanaugh noted. The 24-week OPTION study (tOcilizumab Pivotal Trial in methotrexate Inadequate respONDers) compared tocilizumab at 2 doses—4 mg/kg and 8 mg/kg, or placebo, in 623 patients with moderate to severe RA. Methotrexate was held stable at pre-study doses.³⁶ By week 24, significantly more tocilizumab-treated patients had an ACR20 response than did patients receiving placebo ($P < 0.0001$ for both tocilizumab groups vs placebo).³⁶ Similarly, significantly more patients receiving tocilizumab showed ACR50 and ACR 70 responses compared with placebo ($P < 0.0001$ for both tocilizumab groups vs placebo for both ACR50 and ACR70).³⁶

The 24-week RADIATE study (Research on Actemra Determining efficacy after Anti-TNF failures), reported at the ACR Annual Meeting in 2008 showed that patients were 9 times more likely to achieve an ACR20 response at week 24 with TCZ 8 mg/kg

Table 3. Emerging Immunomodulatory Therapies.

Emerging Immunomodulatory Therapies	
Anti-TNF-α – Golimumab – Certolizumab pegol – TACE inhibitors (?)	Antiadhesion therapy – Alectacept – Etanercept – Natalizumab
Anti-interleukin-1 – IL-1 TRAP – sIL-1RI Fc fusion protein – Anti-IL-1 mAb – ICE inhibitors	B-cell inhibitors – Anti-BLyS – Ocrelizumab – Ofatumumab – TACI-Ig
Anti-interleukin-6 – Tocilizumab	Small molecule – JAK-3 inhibitor – SYK kinase inhibitor – P38 MAP kinase inhibitors
Anti-interleukin-15 Anti-interleukin-17	Anti-RANKL – Denosumab

Figure 6. Targeting of B Cells.



and 4 times more likely with TCZ 4 mg/kg, than were controls ($P < 0.0001$).³⁷

Evidence that IL-6 may play an important role in joint damage and structural integrity in RA emerged from the LITHE study.³⁸ LITHE (Tocilizumab safety and THE prevention of structural joint damage trial) was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of TCZ plus MTX versus MTX alone in preventing structural joint damage and improving physical function and clinical disease activity over 2 years. At a 1-year ITT analysis, data showed that significantly more patients treated with tocilizumab (4 mg/kg or 8 mg/kg, plus MTX) experienced no progression of structural joint damage from baseline, compared with placebo.³⁸ LITHE is the fifth phase III study with TCZ, after the OPTION, TOWARD, RADIATE, and AMBITION trials.

A variety of B-cell targets that are under current examination build upon the data with rituximab, showing that it is effective in the treatment of patients with RA, including those who have previously received TNF inhibitor therapy (Figure 6). The efficacy

and safety of other B-cell targets remain to be established. “We might find very different efficacy and very different toxicity,” Dr. Kavanaugh said.

Among numerous T-cell targets are IL-12 and IL-23, which share a common p40 subunit that is the target of the monoclonal antibody, ustekinumab, and ABT-874. Both are generating excitement in the dermatology community, but “it makes sense that it could be effective in rheumatoid arthritis,” says Dr. Kavanaugh, especially for patients in whom TNF therapy has not been effective.

The Promise of Tomorrow with Biologics in RA

Ongoing investigations of a variety of new biologic targets will likely result in adding new treatment options in the near or intermediate term. To optimize their therapeutic value, Dr. Kavanaugh cautioned that it will be important to “gain a clear understanding of safety issues that in biologics may well relate to immune-modulating effects or to other target-specific properties.”

Audience/Faculty Questions and Answers

The data and case studies emerging from this presentation generated a series of questions from the audience which were addressed by one or more of the presenters.

QUESTION: Should we be lowering CRP as much as possible [in patients with cardiac risk factors] or aim for the normal range?

DR. SINGER: I don't think we know the answer. I think we need to engage with our cardiology colleagues [to answer this question]. I do not particularly target a lower than normal CRP. I am more likely to use a disease measure such as DAS28 to try to achieve low disease activity, and then look for dyslipidemias.

QUESTION: Could you comment on [whether] the ACR said that [use of] methotrexate is or is not a contraindication to herpes zoster vaccination (Zostrix)?

[Editor's Note: In June 2008, the CDC Advisory Committee on Immunization Practices issued recommendations for the prevention of herpes zoster, with new directives relevant to patients with rheumatic disease receiving immunosuppressive therapy. The recommendation states that zoster vaccination is indicated in all immunocompetent persons >60 years of age, provided they have no contraindications].³⁹

DR. KAVANAUGH: [This announcement was reported] in the [ACR] hotline³⁹ because it was a very important topic, but it's not based on a wealth of evidence that suggests that this is the safest way to go.

DR. SINGER: In general, we give patients notes that say “no live attenuated vaccine,” but for adults on methotrexate who are interested in getting Zostrix, I've not discouraged it.

QUESTION: An RA patient has been on methotrexate for 3 years. A TNF inhibitor was added 6 months ago. The DAS score dropped to 3.6 on the combination therapy, and the therapy was well-tolerated. What do you do with the patient at this point: change to a different TNF inhibitor; maintain the current one for 3 more months; discontinue and add rituximab; discontinue TNF inhibitor and add abatacept; or discontinue the TNF inhibitor and add anakinra?

DR. KAVANAUGH: Most people would continue therapy for another 3 months. There are data now to support this. We think of the TNF inhibitors as having a very quick response, yet when you look at the people in the BeST study, about a third who were

not ACR responders at 3 months became ACR responders by 6 months. So there's certainly support for that [continuing for 6 months], and I think it fits nicely with what we see in the clinic.

QUESTION: Is evidence being gathered on people who have been on rituximab and didn't completely respond and went back on a TNF blocker? And [is there] evidence that might provide a safety basis for considering combination therapy?

DR. KAVANAUGH: I refer to what we have to do in the clinic as “unintentional combination therapy.” Right now there's no single [source of data] that I'm aware of. As patients run the gamut of therapies, it's important for all of us to collect information so that we can begin to answer important questions like that.

QUESTION: Studies show that, for any TNF inhibitor, [given] with methotrexate, patients have better Sharp T scores. But if the patient is doing well clinically, shall we skip the methotrexate because Sharp scores would be better?

DR. KAVANAUGH: That's a good philosophical question. I'm going to flesh it out to consider a patient in remission on methotrexate with no tender joints, maybe one swollen joint, low sed rates and low CRP. You get an x-ray, and the radiologist sees a new erosion that wasn't there 2 years ago. I personally would bring it up to the patient, but I would be very hard-pressed to push therapy if the patient is doing that well.

QUESTION: I have a patient who, with or without methotrexate and TNF therapy, is doing very well in every clinical aspect. In this instance, can I stretch the [dosing] interval [beyond what is recommended in the labeling]?

DR. KAVANAUGH: I think that experiment is being done by patients all the time. However, it would be very tough to do this because you're going beyond what the drug's half-life would dictate.

QUESTION: I was going to comment on that same phenomenon. A number of patients drop out of your practice, because they have gotten well.

DR. KAVANAUGH: Absolutely. In an analysis of that from the CORRONA database, we found that there is [a group of] people who stop TNF inhibitor therapy and don't flare right away. Benefit persists way beyond what you would expect from the pharmacokinetics.

QUESTION: Can you comment on your strategies for stopping or continuing anti-TNF and methotrexate [in the circumstance of] elective surgery?

DR. KAVANAUGH: I look at the individual patient. The more I'm worried [about the patient], the further away [from surgery] I'll recommend stopping the drugs. If the patient is a diabetic on steroids getting foot surgery, I'm going to recommend stopping several half-lives away. In a young, healthy person with a clean surgery and a very low inherent risk, I may advise stopping closer to the time of surgery. Worldwide, recommendations vary. Some indicate [stopping therapy] 2 weeks [prior to surgery]. Some recommend 4 weeks, and some [guidelines] are half-life-based. I will not recommend restarting the immunosuppressor again until the surgeon is happy with the wound healing.

QUESTION: What do you recommend as the target LDL level for patients with RA?

DR. SINGER: I think it depends on family risk factors and on the HDL levels. Probably 90% of serum lipoprotein values are not based on cholesterol intake but rather on heredity. We have a poor understanding of [whether there is] an absolute target level, just as we have a poor understanding of the suppressive level of vitamin D for an RA patient, versus a preventative level for an osteoporotic patient. That information is coming, however. We do know that for males, if total cholesterol increases from about 200 to 240, there's about a 3-fold increase in risk of heart disease.

References

1. Klareskog L, Rönnelid J, Lundberg K, Padyukov L, Alfredsson L. Immunity to citrullinated proteins in rheumatoid arthritis. *Annu Rev Immunol*. 2009;26:651-675.
2. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest*. 2008;118:3537-3545.
3. Cronstein BN. Interleukin-6; a key mediator of systemic and local symptoms in rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007;65(suppl 1):S11-S15.
4. Andrews NC. Anemia of inflammation: the cytokine-hepcidin link. *J Clin Invest*. 2004;113:1251-1253.
5. Schett G. Osteoimmunology in rheumatic diseases. *Arthritis Res Ther*. 2009;11:210 (doi:10.1186/ar2571).
6. Randolph GJ, Ochando J, Partida-Sanchez S. Migration of dendritic cell subsets and their precursors. *Annu Rev Rheumatol*. 2008;26:293-316.
7. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59:762-784.
8. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet*. 2009;373:659-672.
9. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol*. 2008;26(suppl 51):S35-S61.
10. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21:885-906.
11. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695.
12. Garces SP, Parreira Santos MJ, Vinagre FMR, Roque RM, da Silva JAC. Anti-tumour necrosis factor agents and lipid profile: a class effect? *Ann Rheum Dis*. 2008;67:895-896.
13. Winiarska W, Bil J, Wilczek E, et al. Statins impair antitumor effects of rituximab by inducing conformational changes of CD20. *PLoS Med*. 2008;5:0502-0517.
14. Remicade (infliximab) [package insert]. Malvern, PA: Centocor, Inc; 2006.
15. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibitor therapy. *Mod Rheumatol*. 2009;19:12-19.
16. Van der Helm-van Mil AH, Detert J, le Cessie S, et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. *Arthritis Rheum*. 2008;58:2241-2247.
17. National Heart Lung and Blood Institute. National Institutes of Health. What causes pneumonia? www.nhlbi.nih.gov/health/dci/Diseases/pnu/pnu_causes.html. Accessed June 11, 2009.
18. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. *J Rheumatol*. 2007;34:952-957.
19. Doe S, Pathare C, Kelly AC, Heycock CR, Binding J, Hamilton J. Uptake of influenza vaccination in patients on immunosuppressant agents for rheumatological diseases: a follow-up audit of the influence of secondary care. [Letter to the editor] *Rheumatology*. 2007;46:715-724.
20. Mease PJ, Ritchlin CT, Martin RW, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol*. 2004;31:1356-1361.
21. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology*. 2006;45:106-111.

22. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. *J Rheumatol*. 2007;34:272-279.
23. Gelinck LBS, Teng YKO, Rimmelzwaan GF, van den Bemt BJJ, Kroon FP, van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. [Letter] *Ann Rheum Dis*. 2007;66:1402-1403.
24. Centers for Disease Control and Prevention. MMWR. Prevention and control of seasonal influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. 2009;58(RR-8):1-52. <http://www.cdc.gov/mmwr/pdf/rr/rr5808.pdf>. Accessed August 31, 2009.
25. van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. *Vaccine*. 2000;21:1780-1785.
26. Kavanaugh A, Cohen S, Cush J. Inhibitors of tumor necrosis factor in rheumatoid arthritis: will that dog hunt? [Editorial]. *J Rheumatol*. 1998;25:2049-2053.
27. Kavanaugh A, Cohen S, Cush JJ. The evolving use of tumor necrosis factor inhibitors in rheumatoid arthritis. *J Rheumatol*. [Editorial]. 2004;31:1881-1884.
28. Van Vollenhoven RF, Klareskog L. Clinical responses to tumor necrosis factor alpha antagonists do not show a bimodal distribution. *Arthritis Rheum*. 2003;48:1500-1503.
29. Weisman MH. Progress toward the cure of rheumatoid arthritis: the BeSt study. [Editorial]. *Arthritis Rheum*. 2005;52:3326-3333.
30. Van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis*. 2007;66:1356-1362.
31. Nalysnyk L, Xu Y, Williams K, et al. Treatment of rheumatoid arthritis after failure of TNF antagonists: a systematic review and meta-analysis. *Ann Rheum Dis*. 2008;67(suppl II):326.
32. Genovese MC, Becker J-C, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis α inhibition. *N Engl J Med*. 2005;353:1114-1123.
33. Cohen SB, Emery P, Greenwald MW, et al, for the REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006;54:2793-2806.
34. Burmester GR, Mease P, Dijkmans BAC, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis*. Published online Jan 15, 2009 as 10.1136/ard.2008.102103.
35. Cohen SB, Cheng T-T, Chindalore V, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. *Arthritis Rheum*. 2009;60:335-344.
36. Smolen JS, Beaulieu A, Rubbert-Roth A, et al, for the OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet*. 2008;371:987-997.
37. Emery P, Keystone E, Tony H, et al. Tocilizumab (TCZ) rapidly and significantly improves outcomes in patients with rheumatoid arthritis (RA) who have inadequate response (IR) to TNF antagonists (The RADIATE study). Program and Abstracts of the American College of Rheumatology (ACR). 2008 Annual Scientific Meeting. Abstract 1209.
38. Kremer J, Fleischmann R, Brzezicki J, et al. Tocilizumab inhibits structural joint damage, improves physical function, and increases DAS28 remission rates in patients who respond inadequately to methotrexate: The LITHE study. *EULAR* 2009. Abstract OP-0157.
39. American College of Rheumatology Hotline. Herpes zoster (shingles) vaccine guidelines for immunosuppressed patients. August 1, 2008. www.rheumatology.org. Accessed June 24, 2009.

Evaluation

LEARNING OBJECTIVES

After completing this activity, learners should be able to:

- Choose treatment options considering inflammatory pathways underlying clinical disease.
- Select treatment options that improve outcomes and reduce toxicity for RA patients with comorbid conditions.
- Evaluate the efficacy and safety of new and emerging agents for the treatment of patients with rheumatoid arthritis.
- Consider how new therapies may change RA treatment.

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 sponsorship of the Interstate Postgraduate Medical Association and MEV Healthcom, Inc. Interstate Postgraduate Medical Association is accredited by the ACCME to provide continuing medical education for physicians.

Interstate Postgraduate Medical Association designates this educational activity for a maximum of *1.5 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity. Your certificate will be e-mailed within 3 weeks of receipt of this post-test and evaluation.

Release date: September 30, 2009

Expiration date: September 30, 2010

Estimated time to complete this activity: 1.5 hours

After reading the publication, please log on to www.ipmameded.org/CCR2009 or complete and return this form to:

IPMA
P.O. Box 5474
Madison, WI 53705
Phone: 608-231-9045
Fax: 877-292-4489
www.ipmameded.org

YOUR CONTACT INFORMATION:

E-mail Address: _____

Name: _____

Degree: (MD, DO, etc.) _____

Phone Number: _____

Street Address 1: _____

Street Address 2: _____

City: _____ State: _____ ZIP Code: _____

Specialty: _____

- Physician Resident Other (List below)

EVALUATION

Please rate this CME activity according to the scale below:

5 = Excellent

4 = Very Good

3 = Good

2 = Fair

1 = Poor

Extent to which learning objectives were met:

Choose treatment options considering inflammatory pathways underlying clinical disease.

5 4 3 2 1

Select treatment options that improve outcomes and reduce toxicity for RA patients with comorbid conditions.

5 4 3 2 1

Evaluate the efficacy and safety of new and emerging agents for the treatment of patients with rheumatoid arthritis.

5 4 3 2 1

Consider how new therapies may change RA treatment.

5 4 3 2 1

Was this publication free of commercial bias? Yes No

If no, please explain.

What is the greatest challenge in your rheumatology practice?

What other topics would aid your knowledge and practice of rheumatology?

Post-Test

To receive your CME credit, please complete the post-test below.

Credit will be issued by the Interstate Postgraduate Medical Association for participants who correctly answer at least 70% of these questions. Participants who do not achieve a passing score on the post-test will have the opportunity to retake the test one time. A CME certificate will be mailed within approximately 3 weeks of receipt of your completed registration, post-test, and evaluation.

Circle the appropriate response to each question or incomplete statement. Only one answer is correct.

1. In the setting of statin use, what concern has recently emerged regarding use of the B-cell depleter, rituximab?
 - A. The effectiveness of rituximab may be reduced.
 - B. The dosing of rituximab may require adjustment.
 - C. The side effects of the statin may be increased.
 - D. The efficacy of the statin may be reduced.
2. What was an important, clinically relevant finding from the LITHE study with the IL-6 inhibitor, tocilizumab?
 - A. Increases in total cholesterol
 - B. Efficacy after TNF inhibitor failure
 - C. Prevention of structural joint damage
 - D. Long-term disease control
3. What statement best summarizes the current state of knowledge about combining biologic therapies to treat RA patients?
 - A. Combination regimens of biologics have not been studied.
 - B. Combinations of biologics deliver no synergies and increase side effects.
 - C. Combinations of biologic agents with different modes of action may be effective in some patients who have failed other therapies.
 - D. Combinations of biologic agents may help to prolong disease remissions.
4. Which emerging immunomodulatory therapy has shown negative results of an initial drop in CRP followed by a rebound approximately to baseline, representing a possible counter-regulatory effect?
 - A. Anti-IL-17
 - B. Golimumab
 - C. p38 MAP kinase inhibitor
 - D. IL-1 TRAP
5. Which of the following represents an early immune response that might occur in RA-susceptible individuals who are smokers?
 - A. Production of antibodies to citrullinated protein antigens
 - B. Joint inflammation similar to chronic RA
 - C. Citrullination of protein in the joints
 - D. Production of cytokines and autoantibodies
6. The BeSt study produced which of the following clinically valuable conclusions?
 - A. Patients who were initially treated with sequential monotherapy required significantly fewer changes in treatment regimen than patients who received a TNF inhibitor plus methotrexate.
 - B. Patients who were initially treated with initial combination therapy with prednisone required significantly fewer changes in treatment regimen than patients who received a TNF inhibitor plus methotrexate.
 - C. Patients who were initially treated with a TNF inhibitor plus methotrexate required significantly fewer changes in treatment regimen than patients who were treated with sequential monotherapy, step-up therapy, or initial combination therapy with prednisone.
 - D. TNF inhibitors performed as well as second-line as first-line choices for RA patients.
7. Which class of biologic used to treat RA may be contraindicated in some patients with heart failure?
 - A. T-cell therapy
 - B. IL-6 inhibitors
 - C. B-cell depleter therapy
 - D. TNF inhibitors
8. What was the overall finding from an ASPIRE substudy comparing responses to pneumococcal vaccine in patients with early RA treated with either infliximab + MTX or MTX alone?
 - A. The addition of a TNF inhibitor to MTX did not appear to affect response to the vaccine.
 - B. Response to the vaccine was reduced in most RA patients receiving the combination of infliximab + MTX.
 - C. Response to the vaccine was improved when infliximab was added to MTX in RA patients.
 - D. The dose of MTX predicted patients' response to the pneumococcal vaccine in RA patients.

