Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes
Dear Colleague:

We are pleased to provide you with this CME monograph, *Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes.*

Primary care providers (PCPs) play a pivotal role in the management of rheumatoid arthritis (RA). Active PCP involvement through early diagnosis of RA and ongoing monitoring of RA patients is crucial to achieving successful outcomes. If treatment is not initiated in the early stages of the disease, many RA patients develop disabilities that compromise their ability to perform activities related to daily living.\(^1\) Fortunately, appropriate application of disease-modifying therapy, usually provided by rheumatologists, can reduce that potential for disability by more than 60%.\(^1\)

This monograph will assist PCPs in making a provisional diagnosis of RA, provide guidance regarding the referral of a patient to a rheumatologist, explain how to care for the patient while waiting for the rheumatologist to begin disease-modifying therapy, and describe some of the common comorbidities among RA patients.

Your commitment to patient care is crucial to improving the identification of RA in primary care and decreasing patients' long-term disability. We thank you for your continued dedication to furthering your clinical education and improving the care of your patients. We are confident that you will find the information in this monograph valuable to your practice, and we encourage you to share this information with other health care professionals.

Sincerely,

Michael E. Weinblatt, MD  
John R. and Eileen K. Riedman Professor of Medicine  
Co-Director, Clinical Rheumatology  
Division of Rheumatology, Immunology, and Allergy  
Brigham and Women's Hospital  
Boston, Massachusetts

Lauren G. Collins, MD  
Assistant Professor of Family and Community Medicine  
Jefferson Medical College of Thomas Jefferson University  
Philadelphia, Pennsylvania

References
Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes

ACTIVITY OVERVIEW
Primary care providers (PCPs) play an important role in the diagnosis and ongoing management of rheumatoid arthritis (RA), which is a progressive inflammatory disease of the joints that affects 1% of the US population. Symptoms typically include pain, stiffness, and swelling of the joints. Early diagnosis of RA is crucial to improved patient outcomes.

Standard treatment regimens use disease-modifying antirheumatic drugs (DMARDs), which include methotrexate and biologics such as anti–tumor necrosis factor agents. RA is most effectively managed through an active collaboration between a PCP and a rheumatologist. This monograph focuses on the role of PCPs in the diagnosis and management of RA and devotes particular attention to identifying situations when a rheumatologist should be consulted.

TARGET AUDIENCE
This activity is intended for PCPs involved in the diagnosis and management of patients suspected of having RA.

LEARNING OBJECTIVES
Upon completion of this activity, participants should be able to:
- Identify patients who have probable early RA and should be referred to a rheumatologist
- Employ the squeeze test to assist with diagnosis of RA
- Order appropriate laboratory tests when RA is suspected
- Incorporate simple screening techniques for RA into daily practice
- Order proper vaccinations for patients starting DMARD therapy
- Appropriately manage infections in patients receiving DMARD therapy
- Assess and aggressively reduce cardiovascular disease risk in RA patients

AUTHOR
Thomas Finnegan, PhD
Associate Medical Director
Curatio CME Institute
Exton, Pennsylvania

FACULTY REVIEWERS
Lauren G. Collins, MD
Assistant Professor of Family and Community Medicine
Jefferson Medical College of Thomas Jefferson
Philadelphia, Pennsylvania

Joan M. Von Feldt, MD, MSEd
Professor of Medicine
University of Pennsylvania
Department of Medicine
Rheumatology Division
Associate Chief of Staff—Education
Philadelphia VA Medical Center
Philadelphia, Pennsylvania

FACULTY STEERING COMMITTEE
Michael E. Weinblatt, MD–Co-Chair
John R. and Eileen K. Riedman Professor of Medicine
Harvard Medical School
Co-Director, Clinical Rheumatology
Division of Rheumatology, Immunology, and Allergy
Brigham and Women’s Hospital
Boston, Massachusetts

Clifton O. Bingham III, MD
Associate Professor of Medicine
Divisions of Rheumatology and Allergy and Clinical Rheumatology
Director, Johns Hopkins Arthritis Center
Director, Rheumatology Clinics
Johns Hopkins University
Baltimore, Maryland

Joyce P. Carlone, MN, RN, FNP-BC, CCRC
Nurse Practitioner
Division of Rheumatology
Emory University
Atlanta, Georgia

Mary Suzanne Cleveland, JD
Senior Analyst
Kansas Health Institute
Topeka, Kansas

Jeanne G. Cole, EdD, FACME
Director, Office of CME
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

Karen H. Costenbader, MD, MPH
Associate Physician
Division of Rheumatology, Immunology, and Allergy
Brigham and Women’s Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Paul P. Doghramji, MD, FAAFP
Medical Director for Health Services at Ursinus College
Family Physician, Collegeville Family Practice
Collegeville, Pennsylvania

Daniel Duch, PhD
Medical Director
Curatio CME Institute
Exton, Pennsylvania

David S. Kountz, MD, MBA, FACP
Senior Vice President
Medical and Academic Affairs
Jersey Shore University Medical Center
Associate Professor of Medicine
Robert Wood Johnson Medical School
Neptune, New Jersey

ACCREDITATION
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME).

Jefferson Medical College of Thomas Jefferson University is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION
Jefferson Medical College of Thomas Jefferson University designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

METHOD OF PARTICIPATION
There are no fees for participating in this CME activity. To receive credit during the period June 2011 to June 30, 2012, participants must (1) read the learning objectives and disclosure statements, (2) study the educational activity, and (3) complete the posttest and activity evaluation, including the certificate information section. The posttest and evaluation can be accessed at the end of the activity OR completed online at http://jeffline.jefferson.edu/jeffcme/RAPID. To obtain a certificate, participants must receive a score of 70% or better on the posttest. Please e-mail any questions to jeffersoncme@jefferson.edu or call (888) JEFFCME.

DISCLOSURE
Jefferson Medical College of Thomas Jefferson University endorses the Standards of the ACCME and the Guidelines for Commercial Support. Every effort has been made to encourage the faculty to disclose any commercial relationships or personal benefit with commercial companies whose products may be discussed in this educational tool. Disclosure of a relationship is not intended to suggest or condone bias in any presentations but is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

Release date: June 30, 2011
Expiration date: June 30, 2012
Estimated time to complete activity: 1 hour
Faculty/Faculty Steering Committee

Clifton G. Bingham III, MD, has disclosed the following financial interests and/or affiliations:
Grant/Research Support: BMS, Genentech, Roche, UCB
Consultant: Celgene, Centocor Ortho Biotech Inc., Flexion, Genentech, Merck & Co., Inc., Roche, UCB
Joyce P. Carlone, MN, RN, FNP-BC, CCRC, has disclosed the following financial interests and/or affiliations:
Consultant, Product/Spokes Bureau, Other: UCB
Mary Suzanne Cleveland, JD, has declared no financial interests and/or affiliations.
Lauren G. Collins, MD, has declared no financial interests and/or affiliations.
Karen H. Costenbader, MD, MPH, has declared no financial interests and/or affiliations.
Paul P. Doghrmanji, MD, FAAFP, has declared no financial interests and/or affiliations.
David S. Kountz, MD, MBA, FACP, has disclosed the following financial interests and/or affiliations:
Consultant: NICOx, Novartis
Joan M. Von Feldt, MD, MSEd, has disclosed the following financial interests and/or affiliations:
Consultant: UCB
Michael E. Weinblatt, MD, has disclosed the following financial interests and/or affiliations:
Grant/Research Support: Abbott Laboratories
Consultant: Abbott Laboratories, Centocor Ortho Biotech Inc., Pfizer/Wyeth
Jefferson Medical College of Thomas Jefferson University

Jeanne G. Cole, EdD, FACME, Director, Office of CME, has disclosed no relevant financial relationships.
Curatio CME Institute

Daniel Duch, PhD, Medical Director, has disclosed no relevant financial relationships.
Thomas Finnegan, PhD, Associate Medical Director/Medical Writer, has disclosed no relevant financial relationships.
Jonathan S. Simmons, ELS, Senior Managing Editor, has disclosed no relevant financial relationships.

CONTENT DISCLAIMER

The information presented in this enduring material is for continuing medical education purposes only and is not meant to substitute for the independent medical judgment of a physician regarding diagnosis and treatment of a specific patient’s medical condition. The views or opinions expressed in the resources provided do not necessarily reflect those of Thomas Jefferson University, Thomas Jefferson University Hospital, the Jefferson Health System or staff, Curatio CME Institute, Abbott Laboratories, Centocor Ortho Biotech Inc., or Pfizer Inc.

CURATIO CME INSTITUTE POLICY ON PRIVACY AND CONFIDENTIALITY

Curatio CME Institute makes every effort to protect the privacy of RAoutlook.org users; user information is used only to maintain records as required by the American Medical Association (AMA) and the ACCME. Curatio CME Institute does not require individuals to register to use RAoutlook.org; registration is only required for physicians, health care professionals, and other users to participate in and receive CME/CE credit for accredited educational programs hosted on RAoutlook.org.

Curatio CME Institute is required by the AMA and the ACCME (and occasionally by other accrediting organizations) to collect user information that will allow Curatio CME Institute to issue a CME/CE certificate. Curatio CME Institute is required to keep this information on file for up to 6 years. The information is stored in a secure database and used only to verify individual participation in a CME/CE activity and to reissue a certificate if a user’s original certificate is lost or misplaced.

Information gathered through RAoutlook.org will not be released to any other company or organization for any purpose; this information remains confidential. At the end of the mandatory 6-year period, these records will be permanently destroyed.

Curatio CME Institute uses Web site tracking software to determine how RAoutlook.org is used. This information helps Curatio CME Institute determine the best strategies for improving RAoutlook.org and better meeting the needs of its users. This software does not identify individual users. If you have any questions about RAoutlook.org or any policies of Curatio CME Institute, please contact raoutlook@curaticme.com.

THOMAS JEFFERSON UNIVERSITY PRIVACY POLICY

Thomas Jefferson University (Jefferson) has created this statement to demonstrate Jefferson’s commitment to on-line privacy. It discloses Jefferson information-gathering and dissemination practices for this website.

You may visit the Jefferson website without submitting any information about yourself. For each visitor to the Jefferson website, Jefferson server automatically recognizes only the visitor’s IP address. Jefferson does collect aggregate information on what pages are visited in order to assess and improve the content of the Jefferson website. Jefferson will not, however, set any “cookies” to track visitor’s identification or use of the site without prior notification. The Jefferson website may log the IP addresses of visitors, but only to administer the site and diagnose problems with the Jefferson server. IP addresses are not used to identify individuals. Jefferson has appropriate security measures in place in our physical facilities to protect against the loss, misuse or alteration of information that Jefferson has collected from the Jefferson site.

If you send us e-mail or subscribe to one of Jefferson’s on-line publications, you will be asked to submit information about yourself. Jefferson will use this information to reply to your message or forward the requested material. Jefferson does not share this information with any other partners, affiliates, vendors, members of the Jefferson Health System, or other organizations.

This site contains links to other sites. Jefferson is not responsible for their privacy practices or content. Please note that Jefferson will not respond to any question concerning a specific medical or health condition. If you submit such a request, you will receive a standard response that you should consult with your own health care professional. Of course, Jefferson will not intentionally share the content of this type of an email with any third party. Due to the nature of electronic communications, however, Jefferson cannot and does not provide any assurances that the contents of your e-mail will not become known or accessible to third parties. WE URGE YOU NOT TO PROVIDE ANY CONFIDENTIAL INFORMATION ABOUT YOU OR YOUR HEALTH TO US VIA ELECTRONIC COMMUNICATION. If you do so, it is at your own risk.

If Jefferson information practices change at some time in the future, Jefferson will post the policy changes to the Jefferson website to notify you of these changes.

ACKNOWLEDGMENT

This program is supported by educational grants from Abbott Laboratories, Centocor Ortho Biotech Inc., and Pfizer Inc.
Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disease characterized by the progressive destruction of synovial joints. The joint damage and pain associated with RA significantly reduce patient quality of life. RA patients often have difficulty performing activities of daily living (ADLs; eg, cleaning, bathing) and instrumental activities of daily living (IADLs; eg, shopping, socializing, and maintaining employment). Half of patients with RA are unable to perform at least one ADL. Work productivity is also negatively affected by RA and worsens as disease severity increases. In addition, the systemic effects of RA contribute to a 5-to-15-year reduction in life expectancy, with mortality rates of 2.4 and 2.5 per 100 person-years for men and women, respectively. The total annual societal cost (including direct and indirect costs to patients, caregivers, and employers, as well as quality-of-life deterioration and premature mortality) of RA has been estimated at $39.2 billion.

Early diagnosis and initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) is essential to achieving optimal clinical outcomes, a fact that gives primary care providers (PCPs) a critical role to play in minimizing the impact of RA. Because they are likely to see patients at the first stages of symptom development, PCPs are in the best position to recognize RA in its earliest stages and refer patients to a rheumatologist for confirmation of the diagnosis and initiation of DMARD therapy. Patients who receive early treatment experience significant improvement in quality of life, a reduction in work disability, and a slowing in the progression of joint damage.

Developed for PCPs, this monograph describes a simple strategy for making an early provisional diagnosis of RA, discusses current therapies for treating RA patients, and outlines the key role of PCPs in the ongoing comanagement of RA patients with rheumatologists and other health care professionals.

### EPIDEMIOLOGY OF RA

More than 1.3 million people in the United States have been diagnosed with RA. Women are affected about 2 to 4 times more often than men. RA onset generally peaks between 40 to 60 years of age, but it can begin early in childhood and is common in young women of childbearing age. Joint damage occurs most rapidly during the first several years of the disease, but progression and severity varies greatly between patients. In up to 11% of cases, surgery is required to repair damaged joints.

### MECHANISMS OF DISEASE

The etiology of RA is still not well understood. It is currently believed that an interaction between environmental factors or triggers (such as a viral infection or tobacco use) and genetic factors that influence RA susceptibility initiate an abnormal autoimmune inflammatory response. Smoking is the best-studied environmental factor involved in the development of RA. One early study found that among patients positive for rheumatoid factor (RF), those who smoked were at a greater risk of developing RA if they had HLA-DR shared epitope genes.

Once the autoimmune response is triggered, cytokines such as interleukin-1 and tumor necrosis factor-α (TNF-α), are released from macrophage-like synoviocytes, resulting in synovitis. The release of cytokines, in turn, regulates the expression of chemokines and adhesion molecules that promote the influx of immune cells such as B cells, T cells, monocytes, macrophages, and mast cells into the synovium. Bone erosion occurs when monocytes differentiate into osteoclasts following exposure to both macrophage colony-stimulating factor (M-CSF) and receptor activation of nuclear factor kappa-B ligand (RANKL), which are localized to synovial tissue. Like bone, cartilage is destroyed as a consequence of RA, but through a mechanism that involves the release of proteases from synovial fibroblasts, neutrophils, and chondrocytes.

### RECOGNIZING RA IN ITS EARLY STAGES

After RA has been triggered, clinical symptoms caused by inflammation develop over weeks to months. In early RA, joint swelling and pain are caused by tissue edema and fibrin deposition, which result from the autoimmune response. At this early stage, a diagnosis of provisional RA may be made by PCPs and the patient referred to a rheumatologist for confirmation of the diagnosis and initiation of DMARD therapy. The most common presentation of RA is insidious pain, stiffness, and swelling of the small peripheral joints (metacarpophalangeal [MCP], metatarsophalangeal [MTP], and proximal interphalangeal [PIP]) and wrists. However, the large joints may be affected first. With disease progression, new joints may become involved. RA is not caught early and treatment is not started within 4 to 6 months of diagnosis, RA can lead to progressive joint damage and increase the risk for later disability. If treatment is not started within 6 months of the first appearance of symptoms, the odds of long-term disability increase. A recent European study followed 1,674 early-RA patients over 6 years to examine the effect of delayed diagnosis on patient outcomes. Those who were diagnosed more than 12 weeks after onset of symptoms experienced a 1.3-fold higher rate of joint destruction compared to those diagnosed earlier. In addition, delay in diagnosis was associated with a hazard ratio (HR) of 1.87 in not achieving DMARD-free remission. The authors defined DMARD-free remission as fulfillment of the following criteria for at least 1 year: (1) no current DMARD use, (2) no swollen joints, and (3) classification as DMARD-free remission by the patient’s rheumatologist.

### DIAGNOSING RA

A diagnosis of RA should be considered when a patient reports symptoms consistent with the onset of RA (ie, spontaneous onset of one or more swollen joints, morning stiffness lasting more than 45 minutes, and diffuse joint pain) to his or her PCP. While taking a detailed history, the PCP should ask specific questions about the nature of the patient’s symptoms to determine whether a provisional diagnosis of RA is warranted. Examples of pertinent questions include:
A provisional diagnosis of RA includes a consideration of three criteria (Figure 2):30:

1. **Swollen or tender joints:** The number and location of swollen or tender joints is the most important indicator of possible RA. The likelihood of RA increases as the number of affected joints increases. Often, the small joints of the hands and feet are involved, and the squeeze test is a good, quick, and simple screening procedure (Figure 1). In the squeeze test, the PCP firmly grasps the region of the second to fifth metacarpals or metatarsals, squeezing laterally and noting the presence or absence of joint tenderness as expressed by the patient. If the patient expresses discomfort or pain during the squeeze test, the test is considered positive. RA typically—but not always—affects joints symmetrically on the body.

2. **Duration of symptoms for 6 or more weeks:** Insidious onset of symptoms over 6 or more weeks is more likely to be caused by an inflammatory arthritis such as RA. Symptoms for many years without obvious deformity argues against the diagnosis of RA.

3. **Laboratory tests:** Certain laboratory tests are used to distinguish RA from other inflammatory arthritides. RF and anti-cyclic citrullinated peptide (anti-CCP) antibody are possible signs of RA. Whereas the presence of RF has long been used in the diagnosis of RA, anti-CCP antibodies recently have been found to be more specific than RF in discriminating RA from other diseases.31-33 and the presence of both anti-CCP and RF is highly indicative of RA.30,34 Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are part of the acute-phase response that accompanies inflammation and are useful as serological measures of inflammation that are predictive of joint disease and functional disability.35,36 Abnormally high levels of ESR and CRP suggest an inflammatory process, possibly RA or other inflammatory arthritis, in the absence of other known inflammatory conditions.

If multiple joints are swollen and tender, the squeeze test is positive, and/or any of these laboratory tests are abnormal, a provisional diagnosis of RA should be made and the patient referred to a rheumatologist for confirmation as soon as possible. In addition, if the patient does not meet the first two criteria but has at least one swollen or tender joint and a positive RF or anti-CCP test, he or she should still be referred to a rheumatologist for examination. The rheumatologist will make a definitive diagnosis of RA using the recently revised criteria of the American College of Rheumatology (ACR).30

If the patient does not meet any of these criteria, he or she may still have RA. It is, however, less likely, and it is therefore less urgent for the patient to be seen by a specialist. In these cases, it is important to rule out other potential causes of inflammatory arthritis (such as hepatitis or Lyme disease) and consider referral to a rheumatologist if the diagnosis remains unclear. Common diagnostic challenges include the presence of nonspecific symptoms such as pain, stiffness, fatigue, depression, and inconclusive laboratory results.31

Once a patient is given a provisional diagnosis of RA and referred to a rheumatologist, the PCP should obtain a laboratory workup that includes a complete blood count (CBC), RF, anti-CCP antibody, antinuclear antibody test, ESR, CRP, hepatitis B and C serology, Lyme titer, parvovirus antibody, and comprehensive metabolic panel. A tuberculosis skin test (purified protein derivative [PPD]) should be performed, and x-rays of the hands, wrists, feet, and chest can be considered (Table 1).30,37 The goal of x-ray testing is not to make a diagnosis but to document the extent of cartilage and bone destruction, as well as the progression of bony erosions as the disease progresses.
Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes

Table 1. Initial laboratory tests for patients with joint pain.

<table>
<thead>
<tr>
<th>Nonbiologic DMARD</th>
<th>Primary Benefits</th>
<th>Common Adverse Effects</th>
<th>Rare Adverse Effects</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Well-tolerated once-weekly medication; “gold standard” for managing RA; administered with folic acid; slows radiographic damage</td>
<td>Teratogenicity, nausea; diarrhea; alopecia; fatigue; lassitude; headache; elevated LFTs</td>
<td>Hepatotoxicity; pneumonitis; cytopenias</td>
<td>CBC,* ALT, albumin every 4–8 weeks</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>For moderate to severe disease, effective for slowing radiographic damage</td>
<td>Teratogenicity, diarrhea, nausea, alopecia, elevated LFTs, hypertension</td>
<td>Severe hepatotoxicity; pneumonitis; cytopenias, peripheral neuropathy, interstitial lung disease, rash</td>
<td>CBC,* ALT, albumin every 4–8 weeks</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Effective for slowing radiographic damage in mild to moderate disease</td>
<td>Nausea (improved with enteric coated formulation), diarrhea, rash (avoid in sulfa allergic) elevated LFTs, reduction in sperm count (reversible)</td>
<td>Hemolytic anemia, fever, hepatoxicity</td>
<td>Check G6PD before use, CBC,* ALT, albumin every 4–8 weeks</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Effective for mild disease and in combination with methotrexate</td>
<td>Nausea, rash, skin/hair discoloration, anorexia</td>
<td>Retinopathy, neuromyopathy (very rare)</td>
<td>Eye examination at least yearly</td>
</tr>
</tbody>
</table>

Table 2. Selected nonbiologic DMARD therapies for the treatment of RA


RA THERAPY

Once RA is diagnosed, early treatment is essential to minimize joint damage. Before the patient is seen by the rheumatologist, the PCP can prescribe certain medications to relieve pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically used for short-term management of RA but are sometimes associated with cardiovascular events and gastrointestinal (GI) bleeding. GI bleeding is particularly important to look for, as patients receiving NSAIDs are at an increased risk for this adverse event and this complication can occur without obvious symptoms. Therefore, gastroprotective therapies are often concurrently administered with NSAIDs. Low-dose corticosteroids (eg, ≤10 mg prednisone) are another therapeutic option that should also be given with GI protection; they can be used as a bridge therapy until DMARDs begin to demonstrate efficacy. A short-term course of corticosteroids has minimal side effects in most patients, though long-term low-dose corticosteroids have significant side effects, including osteoporosis, cataracts, and immunosuppression.

In most cases, the rheumatologist works with the patient and the PCP to develop a treatment plan. The PCP has an important role in monitoring the patient after therapy is started. DMARDs form the basis of long-term RA management and are the most effective treatment option for altering the natural course of RA and reducing disease severity, disability, mortality, and RA-specific complications (such as cardiovascular events). The increased use and availability of DMARD therapies may be at least partially responsible for the decreasing rate of orthopedic surgeries among patients with RA.

Traditional or nonbiologic DMARD therapies (eg, methotrexate, leflunomide, sulfasalazine) have been used successfully for decades to treat RA, and most require a minimal level of monitoring that includes a CBC panel and liver function tests (LFTs) (Table 2). Biologic DMARDs differ from conventional DMARDs in their ability to target specific components of the immune response involved in the pathophysiology of RA, such as TNF, T lymphocytes, B cells, and interleukin-6 (IL-6) (Table 3). Because biologics reduce immune function, it is important to be vigilant for signs of infection. Additionally, anti-TNF therapies require tuberculosis screening with a PPD, and IL-6 inhibitors may raise cholesterol and require lipid screens.
Table 3. Selected biologic therapies for the treatment of RA  

<table>
<thead>
<tr>
<th>Mechanism of Action/ Biologic DMARD</th>
<th>Primary Benefits</th>
<th>Common Adverse Effects</th>
<th>Rare Adverse Effects</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis factor-α inhibitors: adalimumab (SC), certolizumab pegol (SC), etanercept (SC), golimumab (SC), infliximab (IV)</td>
<td>Effective in moderate to severe disease; slows radiographic damage</td>
<td>Injection- or infusion-site reactions; Increased risk of bacterial infection</td>
<td>Rarely, opportunistic infection; reactivation of TB; lupus-like reactions; possible increase in lymphoma not yet determined; demyelination; hepatitis B reactivation</td>
<td>TB screening including PPD prior to therapy, periodic CBC*, LFTs, infection</td>
</tr>
<tr>
<td>T-cell costimulatory blockade: abatacept</td>
<td>Effective in patients who are nonresponsive to MTX and in patients who have not responded to TNF-α antagonists; slows radiographic damage</td>
<td>Mild to moderate infusion reactions; increased risk of bacterial infection</td>
<td>Infecions; possible increased risk for cancer</td>
<td>PPD before use, infection</td>
</tr>
<tr>
<td>B-cell depletion: rituximab</td>
<td>Effective in long-standing, active RA with inadequate response to TNF-α antagonist therapy when used in combination with MTX. Efficacy may persist many months after infusion</td>
<td>Mild to moderate infusion reactions; increased risk of bacterial infection</td>
<td>Severe infusion reactions. Medications and supportive care measures should be available during infusion; repeat administration may be associated with more patients with lower immunoglobulin levels</td>
<td>CBC and platelet counts should be obtained at regular intervals; more frequently in patients who develop cytopenias</td>
</tr>
<tr>
<td>IL-6 blockade: tocilizumab</td>
<td>Effective for RA patients who have not responded to biologic DMARDs</td>
<td>Infections, infusion reactions, increased lipids, neutropenia rare, elevated LFTs</td>
<td>Neutropenia, colonic perforation</td>
<td>PPD before use, CBC, LFTs, lipids, lipid-lowering drugs</td>
</tr>
</tbody>
</table>

*CBC includes a platelet count in all cases listed.

CBC, complete blood count; ALT, alanine aminotransferase; DMARD, disease-modifying antirheumatic drug; IV, intravenous; LFT, liver function test; MTX, methotrexate; RA, rheumatoid arthritis; SC, subcutaneous; TB, tuberculosis

**MONITORING DISEASE AND TREATMENT**

Once a patient has been diagnosed with RA and placed on a treatment regimen, it is important that all health care providers involved in the patient’s care schedule regular follow-up visits to monitor disease progression, adverse events, and changes in the patient’s general health. The role of the PCP in monitoring a patient with RA includes obtaining regular laboratory tests, monitoring for infections, and conducting routine screening for malignancies.

Respiratory infections, as well as other infections, are a major concern for patients with RA, since both the condition and the therapies used to treat it increase risk. Methotrexate pneumonitis, a noninfectious complication seen in patients on methotrexate, is another concern patients who present with dyspnea and cough (See Table 2). Patients receiving anti-TNF therapies are at an especially high risk of developing opportunistic infections, including mycobacterial, fungal, or viral (especially herpes zoster) infections, as well as skin and soft tissue infections. Antibiotics should be initiated promptly in patients with suspected bacterial infections. PCPs should be vigilant for infections that are severe enough to warrant a discussion with the patient’s rheumatologist. In some cases, after consultation with the rheumatologist, a PCP may stop DMARD therapy until the infection is over.

Septic arthritis should be considered in an RA patient who experiences isolated monoarthritis when all other joints are stable or who has swelling and tenderness in a joint that has undergone total replacement. This condition may be difficult to diagnose, as patients may not always present with a fever or an elevated white blood cell count.

To reduce the incidence of infections, patients with RA should continue to receive certain vaccinations, despite the finding that RA treatments may blunt the immune response to some vaccines, such as those against hepatitis B, pneumococcus, and influenza. The ACR guidelines for the use of biologic and nonbiologic therapy for RA specifically call for vaccination against pneumococcus, hepatitis B, and influenza in RA patients receiving methotrexate or biologics. Vaccination against herpes zoster may be given to patients taking methotrexate but should be avoided in patients receiving biologic therapy. In addition, all live virus vaccines should be avoided in patients receiving biologic therapy.
COMORBID CONDITIONS

The inflammatory nature of RA places patients at greater risk of developing several comorbid conditions. Cardiovascular disease (CVD) is among the most serious comorbidities related to RA. Several studies have shown that RA patients have at least twice as likely to have a myocardial infarction (MI), and almost six times more likely to have an unrecognized MI, than patients without RA.

Further, a prospective cohort study of 114,342 women who participated in the Nurses Health Study indicated that the risk of MI increases with the length of time from diagnosis. A portion of this increased risk is due to the disease itself, as it has been found that many traditional risk factors such as diabetes, high blood pressure, alcohol use, or ischemic heart disease are not increased in RA patients. However, atherosclerosis does occur more commonly in RA patients than in those without RA, and it may play a role in precipitating cardiovascular events and maintaining the inflammatory state of RA.

DMARD therapy may decrease cardiovascular risk in some patients. A recent study examined the records of 10,156 patients enrolled in the Consortium of Rheumatology Researchers of North America RA (CORONA) registry. Three study cohorts were defined based on mutually exclusive drug use categories: TNF antagonists, methotrexate, and other nonbiologic DMARDs. After adjusting for age, gender, cardiovascular risk factors, and RA disease characteristics, the researchers determined that patients using a TNF antagonist experienced a reduced risk of the primary composite cardiovascular end point (the primary study outcome was a composite of nonfatal MI, transient ischemic attack, or stroke and cardiovascular-related death; hazard ratio [HR] 0.39, 95% confidence interval [CI] 0.19–0.82) compared with users of nonbiologic DMARDs.

The risk reduction associated with TNF antagonists was also observed for nonfatal cardiovascular events (HR 0.35, 95% CI 0.16–0.74). Methotrexate, on the other hand, was not associated with a reduced risk (HR 0.94, 95% CI 0.49–1.80). Prednisone use was associated with a dose-dependent risk increase (P=0.04). The authors concluded that TNF antagonist use was associated with a reduced risk of cardiovascular events in patients with RA.

Another concern for patients with RA is the risk of malignancy. The risk of developing non-Hodgkin’s lymphoma and lung cancer is greater in patients with RA than in individuals without the disease. Several case studies and a small prospective study (N=25) have suggested that patients with RA who are receiving methotrexate may have an elevated risk of developing Epstein-Barr virus–associated lymphomas. There is currently a lack of agreement as to the relationship between anti-TNF administration and the development of malignancy. Some studies have found that anti-TNF therapy is associated with a greater risk of developing lymphoma and skin cancer. In contrast, patient database analyses and a meta-analysis concluded that the use of anti-TNF therapies was not associated with an increased risk of cancer, including lymphoma and nonmelanoma skin cancer.

CONCLUSIONS: PRACTICAL LEARNING POINTS

RA is a complex disease that requires cooperation between the PCP and rheumatologist to minimize the effect of the disease on a patient’s quality of life and overall health status. The best practices for the management of RA include:

- Early provisional diagnosis of RA by PCPs
- Early rheumatology referral to enhance the early and accurate diagnosis of RA and early initiation of DMARD therapy
- Collaboration and comanagement of RA patients by PCPs and rheumatologists
- Improved monitoring of RA to screen for cardiovascular disease, malignancy, and infection
- Appropriate vaccination of RA patients to reduce the risk of infection

References

Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes

POSTTEST

Please note your answers on the Posttest Answer Sheet on the following page.

1. Which of the following is required for a provisional diagnosis of RA?
   a. At least one swollen or tender joint
   b. Symptoms lasting 9 or more weeks
   c. Positive rheumatoid factor (RF) test
   d. Positive anti-citrullinated protein (anti-CCP) antibody
   e. X-rays showing joint damage

2. What effect does disease-modifying antirheumatic drug (DMARD) therapy have on RA?
   a. Reduce inflammation within joints
   b. Reduce pain and swelling of joints
   c. Improve function
   d. Decrease the risk of cardiovascular disease
   e. All of the above

3. Which of the following DMARDs targets B cells?
   a. Rituximab
   b. Golimumab
   c. Adalimumab
   d. Etanercept
   e. Certolizumab pegol

4. Which of the following vaccines is recommended for RA patients receiving methotrexate or biologic DMARDs?
   a. Human papillomavirus
   b. Meningococcus
   c. Influenza (injection)
   d. Rubella
   e. Diptheria, pertussis, tetanus (DPT)

5. RA patients are at least twice as likely to have a myocardial infarction and almost six times more likely to have an unrecognized MI as those without RA.
   a. True
   b. False

6. Which of the following statement is true?
   a. Corticosteroids may be used instead of traditional or biologic DMARD therapy in most RA patients
   b. Patients receiving anti–tumor necrosis factor therapy have a very high risk of lymphoma
   c. The anti-CCP antibody test is more specific than RF for RA
   d. RA cannot be diagnosed until at least 3 months after symptom onset
   e. Most patients with RA do not require therapy with biologic DMARDs to achieve remission

7. A 58-year-old patient was diagnosed with RA 10 years ago. Her RA is well controlled on methotrexate 17.5 mg every week and supplemented with oral folate 1 mg daily. You should aggressively screen for which of the following RA comorbidities?
   a. Anemia
   b. Bacterial vaginosis
   c. Cardiovascular disease
   d. Colon cancer
   e. Diabetes

8. A 42-year-old woman presents with pain in her feet for the last 7 weeks. Upon examination, there is swelling in the second to fifth metacarpals on her left hand and in the metatarsals on both of her feet. What is the best/recommended next step?
   a. Do nothing and wait for 3 more months to re-examine the patient
   b. Prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) and wait another month to see if the swelling and pain abates
   c. Order blood work, including RF, and refer patient to a rheumatologist only if the patient is positive for RF
   d. Make a provisional diagnosis of RA, prescribe NSAIDs for short-term symptomatic relief, and refer to a rheumatologist for further evaluation
   e. Make a provisional diagnosis of RA, prescribe infliximab, and refer to a rheumatologist

For the next two questions, please use this brief case description:

A 50-year-old man presents with pain in his hands for the last 6 weeks. Upon examination, you obtain a positive result when using the squeeze test across his metatarsophalangeal joints. You make a provisional diagnosis of RA and refer to a rheumatologist.

9. Which of the following laboratory tests should you order in addition to making the referral?
   a. Hemoglobin A1c
   b. Anti-CCP
   c. Fasting plasma glucose
   d. Low-density lipoprotein (LDL) cholesterol
   e. Thyroid panel

10. Which of the following prescriptions should be considered while the patient is being referred to a rheumatologist?
    a. NSAIDs
    b. High-dose corticosteroids
    c. Infliximab
    d. Allopurinol
    e. Rituximab
Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes
(Code: FMXX11RAP/MONO)

Release date: June 30, 2011 • Expiration date: June 30, 2012

Please refer to the Method of Participation section in the front of this monograph for additional information.

Complete this activity and request credits online at: http://jeffline.jefferson.edu/jeffcme/RAPID (or you may complete and submit the form below).

PARTICIPANT INFORMATION

PLEASE PRINT CLEARLY. Complete all items to receive credit for this program.

E-mail (required to receive CME certificate)

Specialty (please check one):

☐ FP  ☐ GP  ☐ IM  ☐ Ob/Gyn  ☐ Pediatrics  ☐ Rheumatology  ☐ Other ____________________________

Medical profession (please check one):

☐ Physician  ☐ NP  ☐ PA  ☐ Nurse  ☐ RN  ☐ Other ____________________________

Last Name ______________________________________ First Name ____________________________ MI _____

Mailing Address ____________________________________________________________________________

City ______________________________________________________________________________________

State _____ ZIP __________________

Telephone  ☐ Work  ☐ Home  ☐ Cell ____________________________________________________________

Web ID: _______ _______ _______ _______ (Please provide the last four digits of your Social Security number as your Web ID. This is how you will access your CME transcript)

POSTTEST ANSWER SHEET

Circle only one answer per question.

1. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
2. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
3. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
4. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
5. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E

6. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
7. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
8. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
9. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E
10. ☐ A  ☐ B  ☐ C  ☐ D  ☐ E

EVALUATION

Rate the extent to which

<table>
<thead>
<tr>
<th></th>
<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overall objectives of this activity were met</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Individual objectives of this activity were met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Identify patients who have probable early rheumatoid</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>arthritis (RA) and should be referred to a rheumatologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Employ the squeeze test to assist with diagnosis of RA</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Order appropriate laboratory tests when RA is suspected</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Incorporate simple screening techniques for RA into daily</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Primary Care Management of Rheumatoid Arthritis: Making the Diagnosis and Optimizing Outcomes

e. Order proper vaccinations for patients starting disease modifying antirheumatic drug (DMARD) therapy
f. Appropriately manage infections in patients receiving DMARD therapy
g. Assess and aggressively reduce cardiovascular disease risk in RA patients

3. You were satisfied with the overall quality of this activity
4. Content was relevant to your practice
5. Participation in this activity changed your knowledge / attitudes
6. You will make a change in your practice as a result of participation in this activity
7. The activity presented scientifically rigorous, unbiased, and balanced information
8. Content was free of commercial bias

If you believe the content exhibited commercial bias, please describe the specifics. ____________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________

PERFORMANCE SELF-REFLECTION

1. How many patients with joint pain and stiffness do you typically see in a week?
   - 0
   - 1–5
   - 6–10
   - 11–15
   - 16–20
   - 21–25
   - >25
   - I do not see patients.

2. How many years have you been in practice?
   - 0–5
   - 6–10
   - 11–15
   - 16–20
   - 21–25
   - >25

Please take a moment to reflect on your current and planned use of the practice strategies discussed in this monograph. You will not be graded on these responses; however, responses are required to earn credits. In the table below, please indicate (on the left side) how often you currently use each of the listed strategies and (on the right side) how often you now plan to use these same strategies as a result of your participation in this CME activity.

<table>
<thead>
<tr>
<th>Clinical Practice Strategies</th>
<th>Your Current Use</th>
<th>Your Planned Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Use a focused physical examination when you suspect RA</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
</tr>
<tr>
<td>b. Early referral to a rheumatologist when RA is suspected</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
</tr>
<tr>
<td>c. Use of RA patient monitoring strategies such as monitoring for RA flares and reviewing patient immunizations</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
</tr>
<tr>
<td>d. Coordinating patient care with a relevant specialist to ensure the best quality care</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
<td>Always (5) Often (4) Sometimes (3) Not Often (2) Never (1)</td>
</tr>
</tbody>
</table>
• What information remains unclear?
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

• Questions or comments regarding this activity
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

☐ I do not want to receive information about future educational activities.

PARTICIPANT STATEMENT FOR CERTIFICATION:
Time needed to complete this activity:  ☐ 0.25 h  ☐ 0.5 h  ☐ 0.75 h  ☐ 1.0 h
I hereby state that I have completed this activity independently.
Signature ___________________________________________ Date ______________________

HOW TO RETRIEVE YOUR CERTIFICATE
Certificates for this activity are only available online. Credits earned for this activity can be retrieved online at the Jefferson Electronic Transcripts and Certificates site (http://jeffline.jefferson.edu/jeffcme/JeffETC/). Credits are posted to the JeffETC website weekly on Fridays. Online transcripts are accessed using the combination of your last name plus last four digits of your SSN ["WebID"]. This WebID is automatically created for you when you submit this form online or on paper. If submitting on paper, allow 4-6 weeks for this posting to appear. Credits for online submissions will be posted within 2 weeks of submission.

If you have questions, please contact:
Office of CME
Jefferson Medical College of Thomas Jefferson University
jeffersoncme@jefferson.edu
1 888 JEFF CME

Complete this process online at
http://jeffline.jefferson.edu/jeffcme/rapid

If you prefer to submit this form on paper, please mail to
Curatio CME Institute
100 Campbell Boulevard
Suite 103
Exton, PA 19341

OR
Fax
(610) 363-7410