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#### Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Identify and address barriers to diagnosis and improved outcomes for rheumatoid arthritis (RA) in the primary care setting
- Demonstrate the importance of an early and accurate diagnosis of RA
- Examine appropriate RA patient management through a collaborative team approach
- Describe the monitoring of potential adverse events and benefits of primary care management of RA patients

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#### Target Audience

This newsletter has been designed to meet the educational needs of primary care clinicians who are interested in learning about the diagnosis and management of rheumatoid arthritis.

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# THE JOURNAL OF FAMILY PRACTICE

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## Management of rheumatoid arthritis: A primary care perspective

**R**heumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by inflammation of the synovial joints.

Early diagnosis and treatment within the first few months of disease initiation is critical in preventing joint damage and disease progression.<sup>1</sup> However, patients frequently experience symptoms of RA for an average of 9 to 12 months before a diagnosis is made, and they often wait additional months for a rheumatologic referral.<sup>2</sup> The **Rheumatoid Arthritis Primary Care Initiative for Improved Diagnosis and Outcomes (RAPID)** is an initiative designed to educate primary care clinicians (PCCs) about the early diagnosis and treatment of RA. This supplement will use a case-based approach to assist PCCs in appropriate case identification and referral by presenting a brief overview of the immunologic processes underlying RA and relating the disease process to a simplified, differential diagnosis (see "Rheumatoid arthritis: etiology and pathogenesis, pathophysiology, and immunologic cascade," pp 66-67). Initial management of patients with appropriate radiographic and laboratory studies, as well as bridge therapy, will be discussed. Finally, appropriate long-term management of RA will be presented, including monitoring and management of potential complications and adverse effects (AEs) related to the disease process and RA treatment. This information is presented in an extended form in 3 newsletters produced by the RAPID initiative.<sup>3-5</sup>

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**CASE STUDY**

A woman with hand discomfort and aching feet  
 A 50-year-old woman presents to her PCC with 2 years of notable “hand discomfort.” She also complains of aching feet when walking, pain when taking her wedding ring off and putting it on, and general fatigue. Upon questioning by the PCC, the patient noted that her hands and feet feel particularly “stiff,” most notably for the first 1 or 2 hours after she awakens in the morning. She also remarked that she sometimes has difficulty turning faucets and holding a toothbrush firmly. Finally, she recalled that she has had a hard time opening jars in the morning and believes that she may have spilled her coffee once, due to discomfort in holding the cup.

■ **Epidemiology, risks, and early signs of RA**

RA affects approximately 2.1 million people in the United States,<sup>6</sup> with a worldwide prevalence between 0.5% and 1.0%.<sup>7</sup> Compared with men, women have a 2- to 4-fold higher prevalence.<sup>8</sup> The peak age of onset for RA is generally 30 to 55 years, but juvenile rheumatoid arthritis and elderly-onset RA (in people older than 65 years) also occur.<sup>7</sup>

Approximately 39% of adults with arthritis report that their physical activities are limited because of their condition; arthritis and other rheumatic conditions are the leading cause of disability in the United States.<sup>6</sup> Patients with RA are more than 7 times as likely to have greater-than-moderate disability as their age- or sex-matched individuals.<sup>9</sup> RA-related disability can result in unemployment because of pain, impaired physical function, and transportation difficulties. An individual may be unable to do housework or home repairs, garden, or engage in physical activities or hobbies. Further, disability in RA is linked with increased mortality. The Health Assessment Questionnaire (HAQ; available at: [http://aramis.stanford.edu/downloads/HAQ37\\_pack.pdf](http://aramis.stanford.edu/downloads/HAQ37_pack.pdf)) disability index, which is used to follow RA patients, is the strongest clinical predictor of mortality, with a change of 1 standard deviation in the HAQ resulting in an odds ratio for mortality of 2.3.<sup>4,10</sup>

**TABLE 1**

**What should you ask the patient?**

- What hurts as you get out of bed in the morning?
- How long does it take to feel as limber as you are going to feel for the day?
- When is your pain the worst (AM or PM)?
- Do you smoke?
- Do any members of your family have RA?
- Can you:
  - Turn faucet handles?
  - Hold a hairbrush/toothbrush?
  - Dress/bathe independently?
  - Fix your own breakfast?
  - Walk outdoors on flat ground?
- What are the things you cannot do because of your symptoms?

Adapted from Ramey DR, et al. In: *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1996:227-237.

In the early stages of RA, patients will experience some degree of joint stiffness, especially in the morning after awakening, or other diffuse aching. Joint stiffness may accompany or precede joint swelling or pain. Joint swelling, which is usually symmetrical, with tenderness upon palpation, is one of the key signs of RA.<sup>11,12</sup> **TABLE 1** lists a number of questions that can be useful in documenting the patient’s symptoms.<sup>13</sup> Although joint stiffness and swelling are not specific for RA, patients with RA will frequently complain of morning stiffness that lasts for at least 1 hour and often longer.<sup>11,12</sup>

**CASE STUDY**

**The “squeeze” test indicates RA**

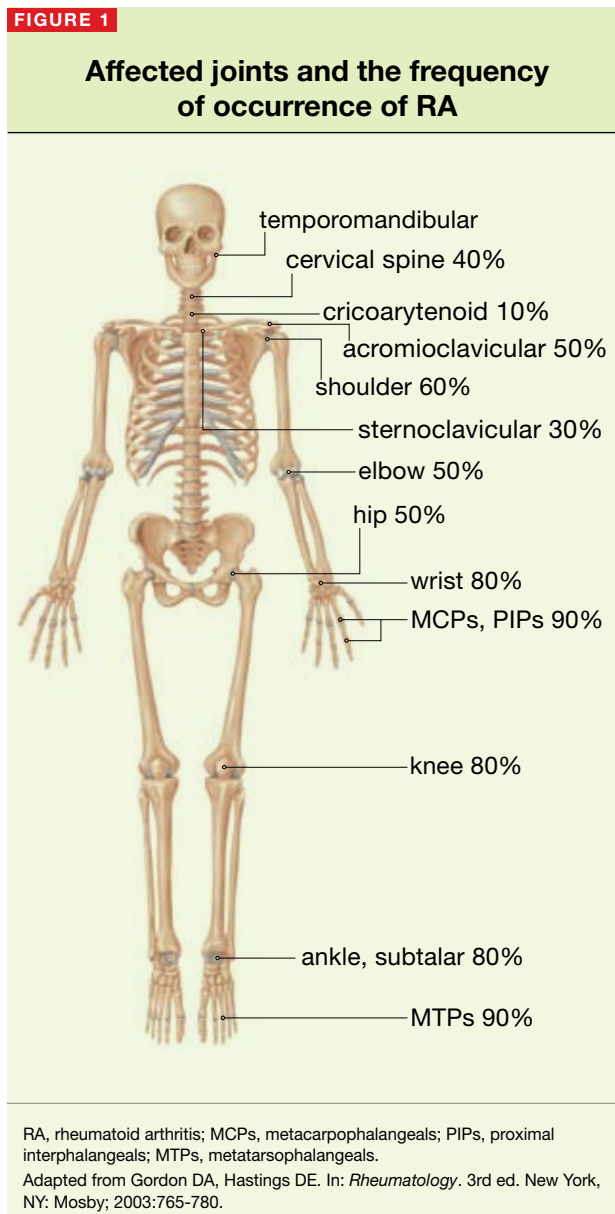
A physical examination of the patient’s hands shows swelling of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and swelling of the wrist. A “squeeze test” on the patient’s hands and feet indicates symmetrical tenderness and pain across the second to fifth metacarpals and across the metatarsals. Based on these indications, the PCC makes a provisional diagnosis of RA.

## ■ The diagnosis of early RA can be challenging

The importance of early diagnosis and treatment in RA outcomes was demonstrated by Lard and colleagues, who found that delaying treatment initiation by as little as 4 to 6 months could result in long-term joint damage.<sup>14</sup> The most common presentation of RA is insidious pain, stiffness and swelling of the small peripheral joints (MCP, metatarsophalangeal [MTP], and PIP) and wrist; in some cases, the large joints can be affected first. Swelling that results from thickening and edema caused by synovial effusions occasionally does not extend beyond the affected joint, and the effusion is sometimes difficult to detect in the smaller joints.<sup>11,12</sup> Range of motion is often limited. As RA progresses, joint damage progresses as well, and the involvement of other joints is not uncommon (FIGURE 1).<sup>11,12</sup>

Early-stage RA characteristically shows no overt clinical evidence of joint damage and/or no signs of cartilage or bone loss on plain film radiographs. At this stage, it is difficult to determine if the disease course will be mild or more severe. The diagnosis of RA at this stage can be challenging; onset may be acute or may take place over several months.<sup>3</sup> A squeeze test, which assesses tenderness or pain in response to squeezing across the second to fifth metacarpals or across the metatarsals, is used to examine for synovitis and possible RA (FIGURE 2).<sup>3,15-17</sup> The accepted symptoms for diagnosis of RA include the presence of at least 3 swollen or more arthritic joints (FIGURE 2), but a recent recommendation suggests that a provisional diagnosis and referral to a rheumatologist should be made on the basis of more than 1 swollen or arthritic joint, rather than 3 or more.<sup>15</sup> This would improve the odds of diagnosing RA at its earliest stages (FIGURE 3).

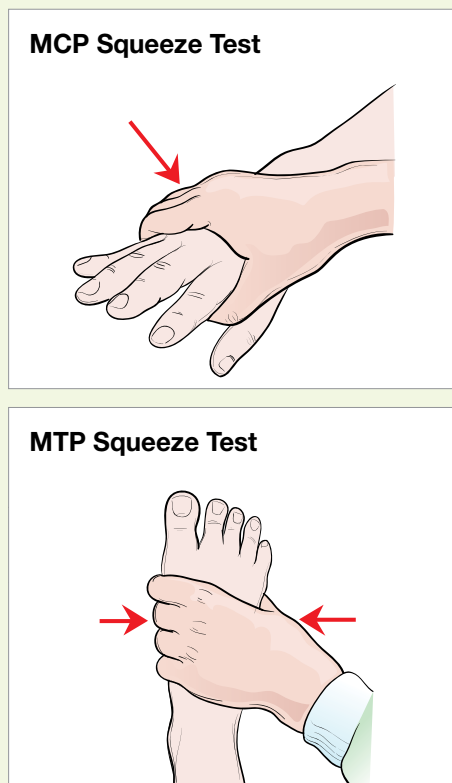
If PCCs can recognize these early signs and symptoms of RA in patients, they can make a provisional diagnosis of RA, after which the patient can be referred to a rheumatologist for confirmation and treatment with disease-modifying antirheumatic drugs (DMARDs; discussion follows). (A provisional diagnosis of RA does not have an ICD-9 code;



polyarthritides and/or polyarthralgias are diagnoses that can be billed.) It is important for the patient to see a rheumatology specialist within a few weeks of diagnosis, because early treatment improves outcomes.<sup>4</sup> In many areas of the United States, there is a delay in new patient appointments with rheumatology specialists, and a phone call from the PCC to the specialist can often facilitate an earlier appointment for a patient with newly suspected RA.<sup>4</sup> Early RA clinics are being established in some regions to address this problem.

**FIGURE 2**

**The MCP and MTP squeeze tests**



**With an initial diagnosis of RA, referral to a rheumatologist is advised if the patient has any of the following symptoms:**

- $\geq 3$  swollen joints
- Positive squeeze test across MCP/MTP joints
- Morning stiffness  $\geq 30$  minutes

MCP, metacarpophalangeal; MTP, metatarsophalangeal.

Illustration reproduced with permission from Emery P, Breedveld FC, Dougados M, et al. *Ann Rheum Dis*. 2002;61:290-297.

**Definitive diagnosis of RA by a rheumatologist is based on the following criteria:**

1. Morning stiffness
2. Arthritis in 3 or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

A patient has RA if at least 4 of these criteria are satisfied (criteria 1 to 4 must have been present for at least 6 weeks).

Arnett FC, Edworthy SM, Bloch DA, et al. *Arthritis Rheum*. 1988;31:315-324.

**CASE STUDY**

**Medication, lab tests, X-rays, and referral**

The PCC gives the patient prescriptions for a non-steroidal anti-inflammatory drug (NSAID) and a low-dose glucocorticoid. She tells the patient that she wants to refer her to a rheumatologist, and that the PCC will call the specialist to make sure the patient receives an early appointment. In the meantime, the PCC orders blood tests including blood chemistries, complete blood count (CBC), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). She also orders X-rays of the patient's hands, feet, and wrists. What is ordered should be the same as what is recommended below.

**■ Initial management of RA in primary care**

Once a preliminary determination of RA is made, NSAIDs and glucocorticoids may be prescribed before DMARDs are initiated by the rheumatologist, as well as during the early treatment period with DMARDs (FIGURE 4). Because DMARDs may take several months for their full effect to manifest, NSAIDs are helpful in providing partial relief of pain and stiffness at this early stage.<sup>15,18-20</sup> When prescribing NSAIDs, the gastrointestinal (GI), renal, and cardiovascular (CV) status of the patient should be considered, and patients should be monitored for side effects.

Glucocorticoids are potent suppressors of the inflammatory response in many diseases, including RA. Low-dose glucocorticoids have been shown, especially in the first 6 months after RA onset, to decrease the radiologic progression of joint damage and can be considered DMARDs.<sup>21</sup> Low-dose oral glucocorticoids (less than or equal to 10 mg prednisone/day or equivalent) and local injections of glucocorticoids are highly effective for relieving symptoms in patients with active RA, and may be used as a bridge therapy until other DMARDs with fewer side effects become effective.<sup>18-20</sup> However, due to their limited disease-modifying effects, they should be combined with DMARDs and not used as the primary or sole

RA treatment. Patients using glucocorticoids should be carefully monitored for AEs.

Nonpharmaceutical interventions also should be considered, beginning early in treatment as an adjunct to pharmacologic therapy.<sup>15,20</sup> Instruction in joint protection and a home program of strengthening and range-of-motion exercises are important in maintaining joint function.<sup>20</sup> Occupational therapy and hydrotherapy have been shown to have symptom-relieving effects.<sup>15</sup>

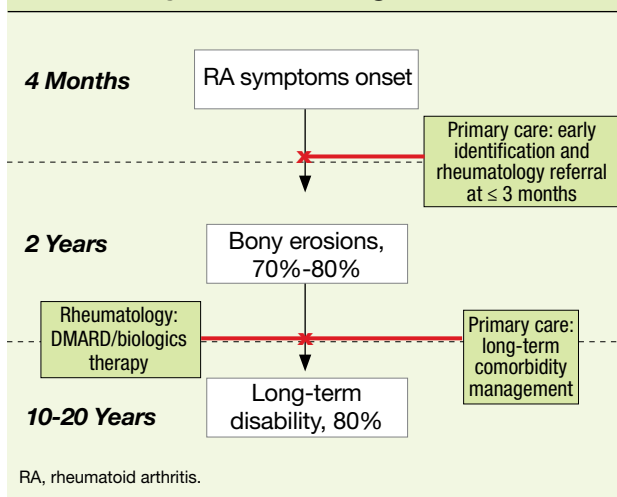
### ■ Laboratory investigation of RA

Laboratory investigation of suspected RA is important to confirm the diagnosis, rule out competing diagnoses, predict disease progression, and monitor disease activity. A more favorable disease course, characterized by remissions, is associated with prognostic factors such as age less than 40 years, acute onset in primarily a few large joints, short disease duration (less than 1 year), and no RF seropositivity.<sup>3</sup> A more severe disease prognosis is associated with insidious onset in combination with symptoms such as weight loss, fatigue and low-grade fever, rapid appearance of rheumatoid nodules, and seropositivity for RF (often present at high titers).<sup>22-24</sup> Although a high RF titer in the early stages of disease often indicates a worse prognosis,<sup>11,12</sup> RF is detected in fewer than 50% of patients during the first 6 months. If seropositivity develops, it is usually within the first year, and only 85% of patients are seropositive for RF during the course of their disease. It should also be noted that seropositivity for RF is not specific for RA; systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, cirrhosis, other liver disorders, such as hepatitis B and C, and certain malignancies can also be seropositive.<sup>11,12</sup>

Blood chemistry is tested to evaluate renal and liver function. Acute-phase reactants, such as CRP or ESR, are evaluated, and tests for anemia and thrombocytosis (a myeloproliferative disorder) also are conducted. Other tests for anti-CCP antibody, anti-nuclear antigen (ANA), and Lyme serologies can be conducted to either help in confirming or ruling out

FIGURE 3

### Primary care in management of RA



RA. However, negative laboratory test results in the presence of supportive clinical criteria do not negate the diagnosis.

The presence of anti-CCP antibodies has a higher specificity for RA than RF; they are found in up to 40% of RA patients who are negative for RF early in the disease. Anti-CCP antibodies may also be observed earlier in the disease course than RF and can more accurately predict the extent of erosive disease and joint damage.<sup>5</sup> Anti-CCP antibody testing also has limitations because not all RA patients are anti-CCP antibody positive. Additionally, patients with other inflammatory arthritis, such as psoriatic arthritis, can be anti-CCP positive.<sup>25,26</sup>

If a patient is homozygous for one of the major histocompatibility complex (MHC) alleles linked to RA susceptibility, a more severe disease outcome with extra-articular manifestations may be expected. However, these tests are rarely ordered.<sup>11,12</sup> Other results that may indicate a more severe disease prognosis include increased ESR and radiographic evidence of joint damage that manifests early in the disease process. Plain films can demonstrate early marginal erosions, but these are rarely diagnostic. Over time, radiography can delineate the characteristic pattern of joint abnormalities and the extent of joint damage caused by bony erosion and loss of cartilage,<sup>11,18</sup> thereby helping to determine the effectiveness of treatment.

**TABLE 2**

**DMARDs commonly used in North America for RA\***

DMARD/ biologic therapy	Primary benefits	Disadvantages	More common adverse effects	Rare adverse effects	Laboratory tests
Hydroxychloroquine	Effective for mild disease and in combination with methotrexate	Takes 3-6 months to become effective; no evidence of halting radiographic progression	Diarrhea; bloating; anorexia; rash	Retinopathy (if dosed too high); neuromyopathy	Yearly ophthalmologic exam
Sulfasalazine	Effective for mild-to-moderate disease; may be used in combination with other agents; slows radiographic damage	Contraindicated in patients who have sulfa allergies	GI effects; headache; rash	Cytopenias; hepatotoxicity	CBC every 2-4 weeks for 3 months, then every 3 months
Methotrexate	Well-tolerated once-weekly medication; gold standard for managing RA; administered with folic acid; slows radiographic damage	Contraindicated in potentially childbearing women	Nausea; diarrhea; alopecia; fatigue; lassitude; headache; elevated LFT levels	Hepatotoxicity; pneumonitis; cytopenias	CBC, ALT, albumin every 4-8 weeks
Leflunomide	For moderate-to-severe disease; slows radiographic progression	Greater cost; long half-life; contraindicated in potentially childbearing women	Diarrhea; nausea; alopecia; anorexia; rash; elevated LFT levels	Severe hepatotoxicity; pulmonary fibrosis	CBC, ALT, albumin every 4-8 weeks
Infliximab	Highly effective for moderate-to-severe disease; slows radiographic damage	High cost; administered with methotrexate; infused every 6-8 weeks after loading doses	ISRs (20%); increased risk for bacterial infection	Opportunistic infection; reactivation of TB; lupus-like reactions; possible increase in lymphoma not yet determined; demyelination	None unless patient also receiving other DMARDs
Etanercept	Highly effective for moderate-to-severe disease; slows radiographic damage	High cost; SC injections once or twice weekly	ISRs (37%); increased risk for bacterial infection	Opportunistic infection; reactivation of TB; lupus-like reactions; possible increase in lymphoma not yet determined; demyelination	None unless patient also receiving other DMARDs
Adalimumab	Highly effective for moderate-to-severe disease; slows radiographic damage	High cost; SC injections every other week or weekly	ISRs (20%) based on clinical trials; increased risk for bacterial infection	Opportunistic infections; reactivation of TB; lupus-like reactions; possible increase in lymphoma not yet determined; demyelination	None unless patient also receiving other DMARDs
Anakinra	Effective in subsets of patients with RA; can be used in patients with risk for TB who cannot use a TNF antagonist; slows radiographic damage	High cost; daily SC injections; ISRs are common; less effective than TNF antagonists at symptom relief and slowing radiographic progression	ISRs (70%) can be severe; increased risk for bacterial infection	Cytopenias	CBC monthly for 3 months then every 3 months
Abatacept	Effective in patients who are nonresponsive to methotrexate and in patients who have failed to respond to TNF antagonists; slows radiographic damage	High cost; administered as 30-minute infusions every 4 weeks	Mild-to-moderate infusion reactions; increased risk for bacterial infection (especially in patients with underlying lung disease)	Infections; possible increased risk for cancer	None unless patient also receiving other DMARDs
Rituximab	Effective in long-standing, active RA with inadequate response to TNF antagonist therapy when used in combination with methotrexate; efficacy may persist many months after infusion	Administered as 2 separate 3-4 hour infusions 2 weeks apart; administration of IV methylprednisolone or equivalent recommended minutes before infusion to prevent serious reactions; delay in clinical response	Mild-to-moderate infusion reactions; increased risk for bacterial infection	Severe infusion reactions; medications and supportive care measures should be available during infusion; repeat administration may be associated with more patients who have lower immunoglobulin levels	CBC and platelet counts should be obtained at regular intervals, and more frequently in patients who develop cytopenias

\*Biologic medications are listed in order of US Food and Drug Administration approval for use.

DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; LFT, liver function test; SC, subcutaneous; ISRs, injection site reactions; TB, tuberculosis; TNF, tumor necrosis factor; IV, intravenous; CBC, complete blood count; ALT, alanine aminotransferase; GI, gastrointestinal.

Used with permission from Bykerk VP, Keystone EC. *J Musculoskelet Med*. 2004;21:133-146; O'Dell JR. *N Engl J Med*. 2004;350:2591-2602; Bingham CO, Miner MM. *J Fam Pract*. 2007;59:S1-S8.

**CASE STUDY****Rheumatologist confirms RA**

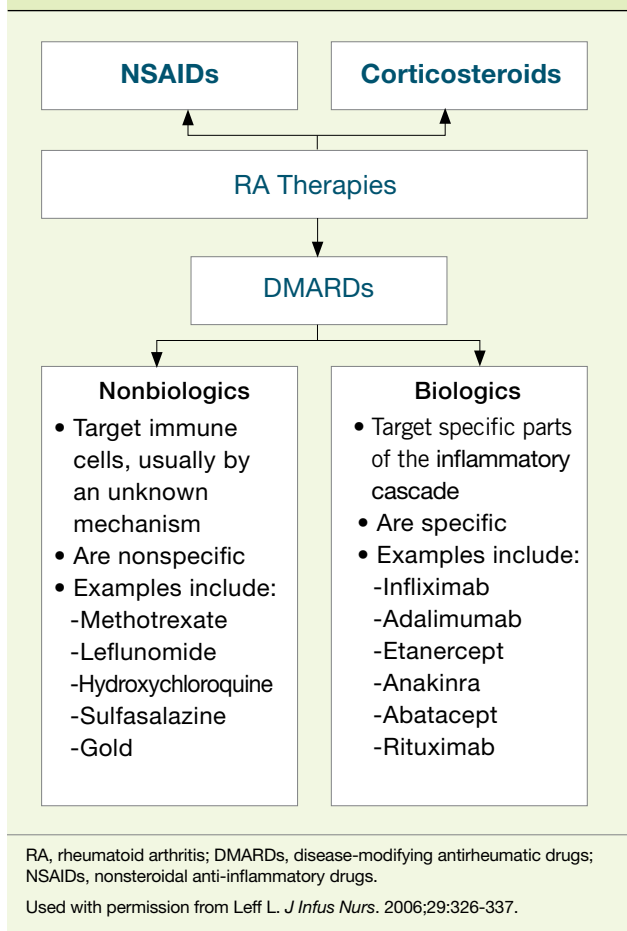
The rheumatologist examines the patient, reviews the laboratory data and X-rays, and makes a definitive diagnosis of RA. The patient is prescribed methotrexate. The rheumatologist also recommends a number of range and strength exercises that the patient can perform at home. At her next visit several months later, the patient reports improvement in morning stiffness and joint swelling, but her activities of daily living are still restricted, and the rheumatologist adds a biologic DMARD.

**How DMARDs are prescribed in RA**

Originally, DMARDs were withheld until erosions were clearly present;<sup>27</sup> however, early intervention with DMARDs is now standard.<sup>15,20,27</sup> The most common DMARDs used in North America are listed in **TABLE 2**.<sup>28</sup> Regular monitoring of disease activity and AEs will guide the decisions regarding DMARD choice and any needed changes in treatment strategy.<sup>15,20</sup>

DMARDs can be classified into 2 groups (**FIGURE 4**): the nonbiologics, which target immune cells in a nonspecific manner, and the biologics, which specifically target different parts of the immunologic cascade (**FIGURE 5**).<sup>18,27,29-31</sup>

**Nonbiologics.** DMARDs include drugs from many classes; they do not have many common properties other than the ability to improve inflammatory symptoms and slow the progression of joint erosions.<sup>27</sup> Most of these drugs were developed and used for other diseases, such as cancer, and were inadvertently found to treat RA. The traditional, nonbiologic DMARDs include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and gold salts.<sup>27,28</sup> These drugs can suppress inflammatory disease activity and produce quantifiable alterations in synovial tissue morphology.<sup>32</sup> They are still the cornerstone of most RA treatment regimens, especially as monotherapy; however, toxicity and inadequate response limit their use.<sup>33</sup> Often, these drugs, primarily methotrexate, are used in combination therapy with the newer biologic DMARDs.<sup>15,18,20</sup>

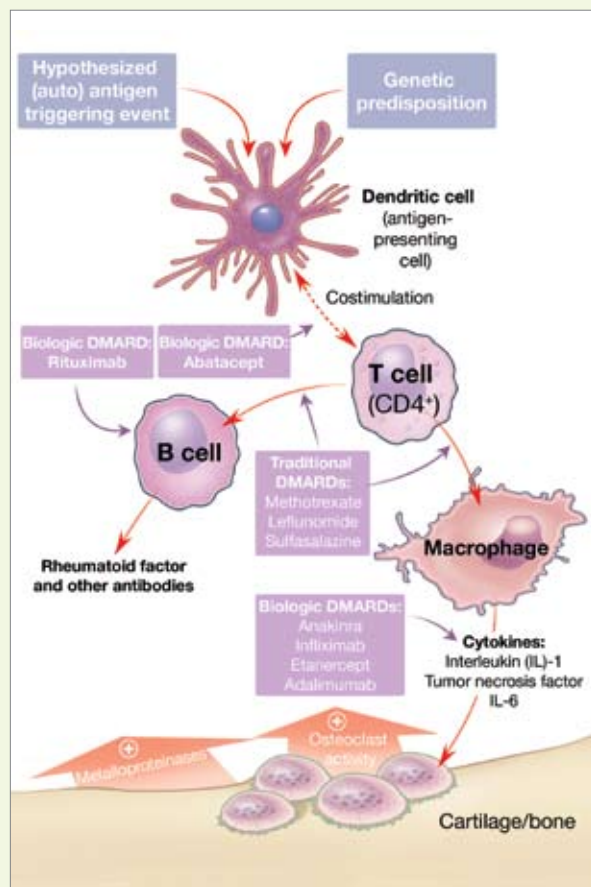
**FIGURE 4****The 3 main classes of therapy for treatment of RA**

**Methotrexate.** Methotrexate is usually the drug of first choice because it is most likely to induce a long-term response.<sup>15,18,34</sup> However, its mechanism of action in RA is not established. Methotrexate, a folate antagonist, was originally developed as an anticancer agent.<sup>34</sup> In addition to its antifolate action, methotrexate has been proposed to inhibit T-cell proliferation via effects on purine and pyrimidine metabolism; to inhibit transmethylation reactions required for T-cell cytotoxicity; to promote the release of adenosine, an endogenous anti-inflammatory mediator; and to interfere with glutathione metabolism, and hence, alter the recruitment of monocytes to the inflamed joint.<sup>34</sup>

In patients with RA, early trials indicated that methotrexate was an effective therapy and was useful

**FIGURE 5**

**The mechanism of action for treatment of rheumatoid arthritis**



Overview of the inflammatory process and the mechanism of action of drugs used to treat rheumatoid arthritis.

Adapted from Gaffo A, et al. *Am J Health Syst Pharm.* 2006;63:2451-2465.

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an enzyme necessary for the production of DNA and RNA, thereby suppressing proliferation of lymphocytes.<sup>36</sup> Leflunomide, which is administered orally at dosages of 10 to 20 mg/day, has been found to be very effective when used in combination with methotrexate.<sup>19,28</sup> Like methotrexate, leflunomide can cause liver toxicity and bone marrow suppression.

**Hydroxychloroquine.** Hydroxychloroquine was originally developed to prevent malaria, and was introduced as a therapy for RA in the 1950s.<sup>19</sup> Hydroxychloroquine may act either by interfering with tumor necrosis factor (TNF) release from macrophages, or by diminishing the presentation of antigens to CD4<sup>+</sup> T cells.<sup>37,38</sup> However, it can take up to 6 months before hydroxychloroquine is effective, and it has not been shown to halt radiographic progression of bony erosions.<sup>28</sup> Hydroxychloroquine has been found to be effective in mild RA, or used in combination with methotrexate.<sup>28</sup> It is usually well tolerated, but its rare dose-related retinal toxicity requires all patients to be monitored at least yearly by an ophthalmologist.<sup>39</sup>

**Sulfasalazine.** Sulfasalazine was developed in the 1930s to treat RA; its active ingredients consist of salicylate combined with a sulfa antibiotic.<sup>40</sup> Although this drug counters inflammation and is used to treat several other conditions, its mechanism of action in RA is not understood. Similar to hydroxychloroquine, it is effective for RA patients with mild-to-moderate RA and is used in combination with methotrexate.<sup>28</sup> It is contraindicated in patients with sulfa allergies and can cause bone marrow suppression and liver toxicity.

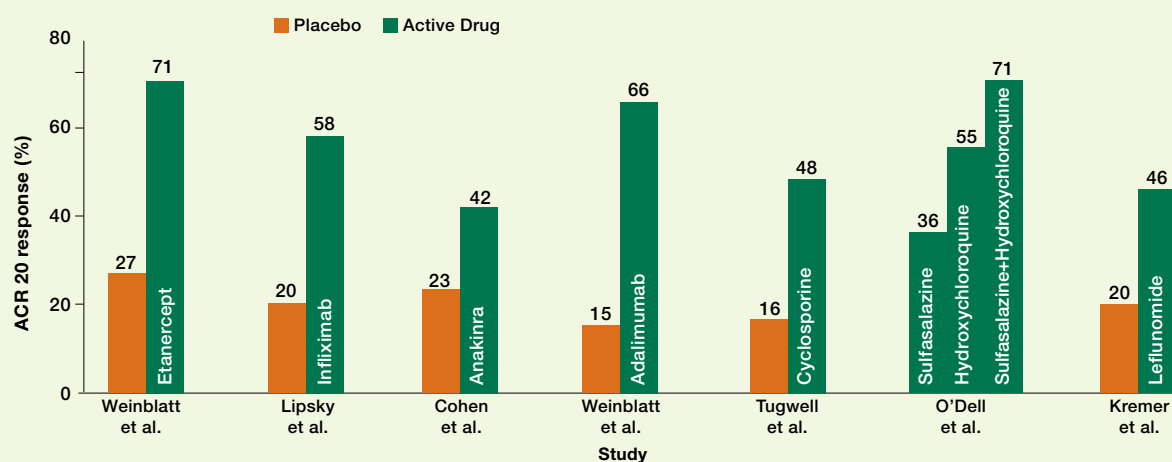
**Gold.** Since the 1920s, gold commonly has been used as a DMARD for RA. It is administered as either an oral form (auranofin) or as an injectable (chrysotherapy). Its mechanism of action is not well understood, and it can take many months before it becomes effective.<sup>28</sup> Side effects differ according to the route of administration; for gold injections, proteinuria, thrombocytopenia, and neutropenia should be monitored before each injection, as kidney damage and decreased white blood cell count may occur.<sup>28,41</sup>

in patients who were refractory to other agents.<sup>34</sup> Low-dose, weekly methotrexate treatments were found to be relatively well tolerated, particularly when compared with other DMARD agents (TABLE 2). Methotrexate is usually given in combination with daily folic or folinic acid, which has been shown to decrease AEs, such as mouth ulcers and anemia.<sup>35</sup>

**Leflunomide.** Leflunomide is considered an alternative to methotrexate as a monotherapy for patients who either cannot tolerate methotrexate or are having an inadequate response.<sup>20</sup> It suppresses immune cells by inhibiting dihydroorotate dehydrogenase,

FIGURE 6

## Responses to drug therapy in 7 studies involving patients receiving methotrexate



All the patients in these studies were already receiving methotrexate, to which the other medication was added. Responses were measured in terms of an improvement of at least 20% in symptoms, as defined by the American College of Rheumatology (ACR 20). Numbers above the bars are response rates.

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**Biologics.** The biologic DMARDs were developed to target specific immunologic components that are believed to be involved in the pathogenesis of RA, specifically, TNF (infliximab, etanercept, adalimumab), interleukin (IL)-1 (anakinra), costimulation of CD4<sup>+</sup> T cells (abatacept), and B cells (rituximab) (FIGURE 5).<sup>18,20,29,42</sup> This class of drugs has been demonstrated to be efficacious in both early and late disease, but, due primarily to cost, has been recommended as a second-line therapy after trying the traditional DMARDs.<sup>15,18,20</sup> The biologic DMARDs are also used in combination therapy with methotrexate.

**Anti-TNF agents: infliximab, etanercept, adalimumab.**

These 3 agents target TNF. Infliximab, which is an anti-TNF monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding to its cell-surface receptor.<sup>30,43</sup> Similarly, adalimumab is a recombinant monoclonal antibody that also binds to TNF- $\alpha$  and prevents binding to its receptor.<sup>29</sup> Etanercept is a fusion protein composed of 2 recombinant soluble TNF receptors. It binds to TNF- $\alpha$ , competing with the biologic receptor, and thereby blocking interactions with its biologic target by effectively lowering the free concentration of TNF.<sup>30</sup> As a result,

TNF is prevented from activating metalloproteinases that erode bone (FIGURE 5 and BOX, pp 66-67). In a review of randomized controlled trials of adalimumab, etanercept, and infliximab, the 3 anti-TNF agents were found to be effective treatments: they improved symptom control and physical function, and slowed radiographic changes in joints. The numbers needed to treat (NNTs) to effect an ACR response compared with placebo were ACR 20: adalimumab 3.6 (confidence interval [CI] 3.1 to 4.2), etanercept 2.1 (CI, 1.9 to 2.4), and infliximab 3.2 (CI, 2.7 to 4.0). No significant differences were found in NNT between the 3 agents.<sup>44</sup> All 3 agents have been found to be effective in patients with moderate-to-severe RA but have a relatively high cost.<sup>28</sup> Infliximab is given by intravenous infusion; etanercept and adalimumab are self-administered by subcutaneous injection.<sup>19</sup> TNF antagonists increase patient risk of developing infections, such as tuberculosis (TB),<sup>45</sup> and ongoing research suggests that they may increase the risk of some malignancies as well.<sup>46</sup> For patients treated with anti-TNF antibodies, the number needed to harm (NNH) was 154 (95% CI, 91-500) for 1 more malignancy in a 6- to 12-month period. For serious infections, the

Continued on page 70a

## Rheumatoid arthritis: Etiology, pathogenesis,

The etiology of RA is still fundamentally unknown.<sup>1</sup> RA has been linked to both genetic susceptibility and environmental influences. Siblings of affected individuals are 2 to 4 times more likely to develop RA than unrelated individuals.<sup>2</sup> Genes in the MHC have been linked with RA,<sup>2,3</sup> and studies have identified other potential genetic markers that may confer susceptibility to RA independently of the MHC.<sup>2</sup> Environmental influences such as infectious agents have also been associated with RA. The evidence is most strong for smoking, which is associated with anti-CCP-positive, RF positive RA.<sup>4</sup>

It has been suggested that RA may be precipitated when some unidentified environmental or biologic trigger, such as a viral infection, initiates an abnormal autoimmune inflammatory response in the synovium of patients who have a genetic predisposition to the disease.<sup>5,6</sup> This inflammation is central to the pathophysiology of RA, and clinical symptoms caused by inflammation develop over weeks to months.<sup>6-8</sup> In early RA, tissue edema and fibrin deposition are prominent, leading to joint swelling and pain.<sup>6-8</sup> The synovial lining becomes hyperplastic, and the synovium, which is normally only 1 to 2 cells deep, thickens to 10 or more cells. The primary cells in this thickened synovium are type A and type B synoviocytes.<sup>7</sup> T cells, B cells, macrophages, neutrophils, and plasma cells infiltrate the sublining. Synovial-vessel endothelial cells develop into high endothelial venules during these early stages. At this point, the patient may complain of aches, especially in the affected joints, and a preliminary diagnosis of RA may be made by the PCC. If appropriate treatment is started, progression to later stages of RA can be substantially slowed or prevented.

If RA is not treated in its early stages, irreversible bone and cartilage loss can occur (FIGURE, THIS PAGE).<sup>9</sup> A proliferating pannus forms that is associated with the early erosion of cartilage and bone.<sup>6,7</sup> Matrix metalloproteinases are produced; these enzymes degrade the connective-tissue matrix and are believed to be the primary mediators of joint damage in RA.<sup>7</sup> Extensive angiogenesis occurs in the pannus. MRI studies have found evidence of erosions at 4 months after onset in 45% of the patients examined, again reinforcing the need for early detection.<sup>10</sup>



**Figure.** Interphalangeal joint abnormalities. Osseous erosions are evident at the radial and ulnar aspects of the PIP joint of the second finger (arrows). Soft-tissue swelling and loss of interosseous space are additional findings. Marginal erosion is also seen on the middle phalanx at the distal interphalangeal joint (open arrow).

With permission from Theodorou DJ, Theodorou SJ, Resnick D. *Rheumatology*. 3rd ed. New York, NY: Mosby; 2003:801-810.

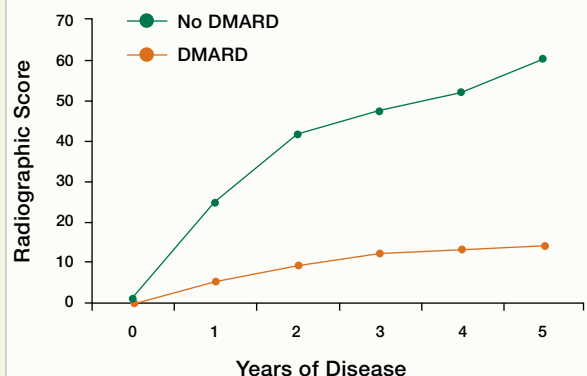
DMARDs are now considered the cornerstone of RA therapy, and the primary goal is to achieve remission.<sup>11</sup> They are associated with a decrease in radiographic progression (Figure, p 67), and act by blocking or inhibiting different aspects of the immune response.<sup>12</sup> The immunologic events underlying joint damage are becoming better known, and are leading to new, effective treatments for RA. Central to the

# pathophysiology, and immunologic cascade

whole immunologic response is the CD4<sup>+</sup> T cell, a T helper cell.<sup>6,7,13,14</sup> Initiation of the immune response in RA may begin when an antigen or autoantigen is presented to a CD4<sup>+</sup> T cell by way of a dendritic cell (antigen-presenting cell). This results in costimulation of the CD4<sup>+</sup> T cell. Antigen-activated CD4<sup>+</sup> cells in turn stimulate B cells and macrophages.<sup>6,7,13,14</sup> B cells release RF, as well as other autoantibodies, and a number of cytokines.<sup>15</sup> RF is immunoglobulin directed against other immunoglobulins. It is not known whether these autoantibodies are themselves pathogenic, but their presence does correlate with more severe, erosive, and destructive arthritis.<sup>16</sup> Cytokines are small, secreted proteins that mediate and regulate the humoral and cellular immune responses, as well as the activation of phagocytic cells. Activated macrophages release the cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), which in turn activate type B synoviocytes to produce high levels of metalloproteinases.<sup>17</sup> TNF- $\alpha$  is also responsible for the systemic symptoms of RA, including

fatigue, malaise, arthralgias, and low-grade fevers, of RA.<sup>10</sup> This cascade leads to increased osteoclast activity and the characteristic bony erosions.<sup>6,7</sup>

## DMARDs are associated with a decrease in radiographic progression



Combination of results from several studies to show the effects of DMARDs on radiographic progression of RA.

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NNH was 59 (95% CI, 39-125) in a 3- to 12-month treatment period.)<sup>46</sup>

**IL-1 receptor antagonist: anakinra.** Anakinra is a recombinant human IL-1 receptor antagonist that binds to the IL-1 receptor but has no biologic activity. By blocking IL-1 from binding to its receptor, it eliminates the intracellular responses initiated by IL-1.<sup>29,30</sup> Because anakinra has a short (~6-hour) half-life in plasma, it must be administered daily by subcutaneous injection.<sup>30</sup> Although it is less effective than TNF antagonists, it can be used in patients who are at risk of TB.<sup>28</sup> It is also the drug of choice for periodic fever syndromes.

**Abatacept.** Abatacept is a recombinant fusion protein that inhibits co-stimulatory signals while maintaining antigen recognition.<sup>31</sup> By binding on the T-cell surface, it acts upstream from other biologic agents and can directly modulate T cell function. In several clinical trials, abatacept was found to significantly reduce disease activity in patients with RA, and it was well tolerated.<sup>47,48</sup> It is administered by infusion every 4 weeks; mild-to-moderate infusion reactions and infections are the most common AEs but occur rarely (21%).<sup>19,29</sup>

**Rituximab.** Rituximab is a monoclonal antibody that targets and destroys both normal and malignant B cells; it was approved in 2006 in combination treatments with methotrexate for patients with RA that is refractory to the anti-TNF therapies.<sup>49,50</sup> In combination with methotrexate, it has been shown to be efficacious in treating RA.<sup>49,50</sup> It is administered in 2 separate infusions, 2 weeks apart; infusion reactions are the most common AEs.<sup>19,49</sup> Rituximab has caused severe infusion reactions, which were fatal in some cases.<sup>29</sup> Medications and supportive care measures should be available during infusion, if medically indicated.

**Combination therapies.** In treating RA, current clinical guidelines call for using methotrexate as the DMARD of first choice.<sup>15,18,20,28</sup> However, the advent of biologic DMARDs in the last decade has

presented an opportunity for improved therapy. The use of a combination of methotrexate and other DMARDs is now fairly common, and the combinations have been found to be efficacious (FIGURE 6).<sup>18,51-57</sup>

#### CASE STUDY

#### Prognosis is good for this patient with RA

The patient follows the instructions of the rheumatologist in regard to DMARD therapy and nonpharmacologic therapy. She feels well: her morning stiffness lasts for less than 15 minutes, and she is able to put in a full day at work, without restricting her activities. Because of her family history of heart disease, and now with the increased risk of atherosclerotic cardiovascular disease (CVD) secondary to her RA, the PCC carefully evaluates her CV risk, and institutes statin therapy. She arranges follow-up visits with her PCC in addition to her rheumatologist to monitor disease progress. Her overall prognosis is good.

#### Potential complications related to RA

RA is a systemic illness, and patients need careful monitoring for potential complications resulting from RA or its treatment. The mortality rate in RA patients is generally higher than that observed in the general population, although the actual causes of mortality are the same.<sup>58</sup> CVD is the most common cause of death.

Fever is a warning sign that requires careful watching in RA patients. Studies estimate that the risk of serious infections in patients with RA is 6 to 9 times greater than that seen in normal populations.<sup>59</sup> Fever may result from the disease process itself, from ordinary infection (eg, upper respiratory or urinary tract), from serious infection, or from malignancy. When monitoring RA patients who are taking steroids, methotrexate, leflunomide, or biologics, especially anti-TNF therapy, PCCs should consult with the rheumatologist in case of any infections. These therapies may contribute to an increased infection rate, and fever may more commonly reflect serious pathology

than in non-RA patients.<sup>60</sup> In patients with a total joint replacement, swelling and tenderness in the joint should be carefully monitored because RA patients may not mount a febrile response, and the white blood count may not be elevated.

To prevent some common infections, influenza and pneumococcal vaccinations are recommended, although titers may be lower. There is no evidence-based medicine that these vaccinations should be given prior to starting therapy or that there is an exacerbation or precipitation of rheumatic disease from the vaccinations. However, live vaccines (including the zoster vaccine for shingles) should be avoided in patients on steroids, and other immunosuppressive therapies, including methotrexate, leflunomide, and biologics due to T cell-mediated dysfunction.<sup>61,62</sup>

Increased incidence of GI bleeding has been reported and may be explained by NSAID treatment in RA patients who take these drugs for longer periods and at higher doses than the general population. In addition, RA patients are often treated with steroids.<sup>63</sup> Some experts believe, however, that RA patients experience an increased risk for GI bleeding beyond that attributable to NSAID and steroid use.<sup>60</sup>

A high index of suspicion of CVD is necessary in RA patients, because atypical, silent chest pain and sudden death are more common. On average, CVD occurs 10 years earlier in RA patients than in the general population without RA,<sup>64-69</sup> with the relative risk (RR) of CVD about 2 to 4 times that of age- and sex-matched controls.<sup>64</sup> This increased risk is not explained by traditional risk factors such as smoking, lipids, hypertension, or diabetes mellitus, because, after adjusting for these factors, the RR is still 3.2.<sup>64</sup> Patients with RA and persistent inflammation as measured by CRP level and ESR may be considered to have an additional risk factor for disease, and therefore, require more aggressive CVD management.<sup>60</sup>

RA patients also have a 2- to 3-fold risk of lymphoproliferative disease, especially diffuse large B cell lymphoma.<sup>10,46,70-74</sup> Epstein Barr virus-associated lymphomas are increased in patients on methotrexate. Chronic inflammation may be responsible for the increased lymphoma risk. Lung cancer is also more common in patients with RA, but this may be due to cigarette smoking, which is a common risk factor. Anti-TNF medications also may be associated with increased risk of lymphoma, skin cancer, and other solid malignancies.

In patients taking methotrexate, dyspnea and a cough could be methotrexate pneumonitis. Neck pain with focal motor neurologic signs could result from cord compression, such as C1-C2 subluxation. Rheumatoid eye disease may present as a painful red eye that is usually not photosensitive.

## ■ Summary

The role of the PCC in early diagnosis and referral of RA is critical to optimal disease outcomes. If the PCC can recognize the early signs and symptoms of RA and facilitate early diagnosis, referral to a rheumatologist, and treatment, the result will be a decrease in RA severity, disability, mortality, and RA complications.<sup>28</sup> Patients who fit the clinical criteria should be referred to a rheumatologist after no longer than 3 months of potentially consistent symptoms, or earlier if the clinician strongly suspects that RA is causing the patient's symptoms. As in the patient in our case study, RA patients who are identified and treated early can achieve remission on medications and have a much better prognosis. Early intervention in conjunction with some of the newer and more effective treatment options should result in continued decline in the rates of lower-extremity orthopedic surgical procedures. Controlling the RA inflammatory response also may decrease cardiac and malignancy risks. ■

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