Rheumatoid Arthritis: Diagnosis and New Therapeutic Options

Case Study and Commentary, Clarence W. Legerton III, MD, and Douglas C. Conaway, MD

Introduction

INTRODUCTION

Yogi Berra’s well-known maxim, “When you come to a fork in the road, take it!” applies to the treatment of rheumatoid arthritis (RA): that is, take some action quickly to control inflammation. It is known that inaction, or treatment undertaken too slowly, spells a poor outcome in RA. Approximately 0.5% to 2% of the North American population has RA [1]; 1 study has suggested that 20% of RA patients treated conservatively are severely disabled after 20 years of illness and that another 30% have died [2], some from ulcer complications of nonsteroidal anti-inflammatory drug (NSAID) treatment or drug treatment–related infections [3].

Information is incomplete about new treatments and their effect on altering these poor outcomes, but there are reasons to be optimistic. Evidence is mounting that earlier use of quick-acting second-line (disease-modifying) agents, singly or in combination, will prevent or slow disease-related morbidity. New agents with novel mechanisms of action, leflunomide (Arava) and etanercept (Enbrel), are now available, allowing more options for disease control. Selective cyclooxygenase-2 inhibitors may reduce the risk of NSAID ulcers and their complications, preventing treatment-related deaths.

This case study demonstrates the central role of the primary care physician (PCP) in diagnosing, managing, and appropriately referring patients who develop RA. It illustrates the hypothesis that PCPs can manage patients with RA who appear to have a good prognosis using simple therapies such as NSAIDs, hydroxychloroquine, tetracyclines, or low-dose corticosteroids that require minimal monitoring. Conversely, the case study suggests that RA patients who have indicators of a poor prognosis or who fail to respond quickly to initial simple therapies should be referred swiftly to a rheumatologist for care; quick control of the synovitis of RA with second-line agent therapy offers the hope of altering an otherwise poor long-term outcome. Finally, the case study addresses use of combination second-line agent therapy and use of newly available agents as options for those patients who fail to respond to single-agent treatment.

CASE STUDY

Initial Presentation

A 58-year-old woman presents to her internist with several months of joint pain.
History

The patient was well until 6 months ago when she noted the onset of joint pain, principally involving her hands, knees, and ankles. Over the past 3 months, these joint pains progressed in severity to the point that now she has pain most of the time. The patient notes that her hands swell and, upon specific questioning, reports pain in several proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints and admits to “dropping things” from her hands. She also has developed some pain on the plantar surface of her feet and complains that she walks “like an old lady” after arising in the morning. She adds that she doesn’t typically “loosen up,” particularly in her hands and knees, until about 2 1/2 hours after waking. She also has noticed fatigue and decreased exercise tolerance over recent months. She denies any significant hair loss, pain or redness in her eyes, back pain, or skin rashes.

Past medical history includes a total abdominal hysterectomy for uterine fibroids at age 42 and a history of shoulder pain 3 years ago which was felt to be “bursitis” and for which she received an injection in her shoulder with relief. She still occasionally has pain in her shoulder, but this has not been a particular problem in the last few months. She was diagnosed with a “stomach ulcer” 5 years ago after taking aspirin for acute low back pain; her abdominal symptoms resolved after therapy with a histamine-2-receptor blocker.

The patient has no known drug allergies. Medications include calcium carbonate, 500 mg daily; estrogen replacement therapy; and ibuprofen, 200-mg tablets as needed for headaches. She notes that if she takes more than 2 ibuprofen tablets she has “stomach upset.” For this reason she has been unable to tolerate ibuprofen regularly for relief of her increasing joint pain.

Family history is remarkable for an aunt with systemic lupus erythematosus (SLE).

The patient works as an administrative assistant for a local executive and her duties include general office work, including use of the phone and the computer. She has had some difficulty typing due to hand pain, especially in the morning, but then she seems to improve somewhat. She has not smoked tobacco in 10 years and she drinks alcohol socially.

Physical Examination

Physical examination reveals a woman who is afebrile with a normal blood pressure. Head and neck examination is unremarkable. Thyroid examination is normal. There is no lymphadenopathy. Pulmonary examination is normal on auscultation and percussion. Cardiovascular, abdominal, and neurologic examinations are within normal limits. Musculoskeletal examination reveals that her neck and lumbar spine are nontender and exhibit good range of motion. Both her ability to make a fist and her grip strength are decreased. Elbows, shoulders, and hips are normal. Knee examination reveals very small bilateral effusions without warmth, erythema, or tenderness. Range of motion is normal. Both ankles appear slightly swollen but are nontender and exhibit full dorsiflexion and plantarflexion.

Table 1. Distinguishing Inflammatory from Noninflammatory Arthritis

<table>
<thead>
<tr>
<th>Symptom/Findings</th>
<th>Noninflammatory</th>
<th>Inflammatory</th>
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<tbody>
<tr>
<td>Constitutional symptoms‡</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>&lt; 30 min</td>
<td>&gt; 60 min</td>
</tr>
<tr>
<td>Joint inflammation</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Extra-articular disease†</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Laboratory findings‡</td>
<td>Absent</td>
<td>Present</td>
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‡Elevated erythrocyte sedimentation rate, elevated C-reactive protein level, anemia of chronic disease, hypalbuminemia.

†Rheumatoid nodules, inflammatory ocular disease, or any extra-articular organ system involvement.

• What historical and physical examination points are important in the initial workup of a patient with joint pain?

• What are the leading diagnostic considerations in this patient?

Distinguishing Clinical Findings

Many illnesses are characterized by musculoskeletal pain. The development of an accurate differential diagnosis is centered on the physician’s ability to recognize and distinguish several key features from the history and physical examination. First, the distinction between articular and periarticular pain must be made. Periarticular musculoskeletal pain, such as bursitis and tendinitis, can mimic arthritis. Once the patient’s complaints are identified as articular, one must next ascertain whether the musculoskeletal complaints are part of a systemic inflammatory process (eg, RA) or part of a mechanical or noninflammatory one (eg, osteoarthritis). This distinction is the first and most important one made in the evaluation of a patient with musculoskeletal complaints. A number of features from the history and physical examination assist with this diagnostic challenge (Table 1).

Patients with systemic inflammatory illness will have constitutional symptoms, which may include fatigue, anorexia, low-grade fever, or weight loss. They also will have joint inflammation, which may manifest as swelling, erythema, warmth, and tenderness. These inflamed joints, in combination with the systemic inflammation, result in morning stiffness, usually lasting 1 hour or more. Taken together,
findings from the history alone are often sufficient to classify the patient as having a systemic inflammatory illness. In the case of the patient at hand, one would suspect a systemic inflammatory illness, as she describes joint swelling in multiple areas, notes constitutional features of fatigue and decreased activity, and suffers from more than 2 hours of morning stiffness.

The physical examination confirms the presence or absence of inflammatory disease. Joint inflammation is observed as joint swelling, tenderness, warmth, and perhaps erythema. Tenderness and soft tissue swelling are often the most sensitive clues to the presence of an inflammatory arthritis. Many extra-articular features, such as oral ulcers, skin rashes, pleural or pericardial effusions, or rheumatoid nodules, may indicate the presence of a systemic rheumatic disease.

Usually, a noninflammatory problem requires a symptomatic approach to therapy. Thus, the patient with rotator cuff disease, trochanteric bursitis, or osteoarthritis requires a treatment regimen drawn from analgesics, NSAIDs, physical therapy, heat or ice application, or injection therapy. On the other hand, systemic inflammatory disease carries the risk for more severe articular destruction and loss of function and therefore requires more aggressive therapy and perhaps earlier referral to a rheumatologist.

Narrowing the Differential Diagnosis

After determining the presence of a systemic inflammatory illness, the next step is to classify the patient’s type of arthritis. Most commonly, the number of involved joints is ascertained to classify the arthritis as involving 1 joint (monarticular), 2 to 4 joints (pauci- or oligoarticular), or 5 or more joints (polyarticular). Further refinement of the differential diagnosis can be made by defining characteristics such as symmetry, the pattern of progression (eg, additive or migratory), and, importantly, the distribution of involved joints. The case patient would be classified as having subacute (sever- ing stiffness.

SLE also may present as polyarticular and symmetrical arthritis. Lupus arthritis can be very painful but is the result of periarticular involvement more than synovitis. Although the joint deformities superficially resemble those of RA, the arthritis is not erosive and the deformities are reducible. Although the seronegative spondyloarthopathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis) may present in this fashion, they more typically result in an asymmetrical oligoarticular arthritis that has a predilection for larger joints. The absence of back pain, rashes characteristic of psoriasis or Reiter’s syndrome, inflammatory bowel disease, or other features seen in conjunction with HLA-B27–related diseases makes these illnesses less likely in this case.

Many other systemic autoimmune diseases may present with a symmetrical polyarticular process. Examples include systemic sclerosis (scleroderma), sarcoidosis, and polymyositis or dermatomyositis. The absence of other characteristic features, such as thickening of the skin, Raynaud’s phenomenon, pulmonary disease, or proximal muscle weakness, render these possibilities less likely. Similarly, the physician in this case would need to entertain the possibility of a systemic infectious disease, such as subacute bacterial endocarditis, Lyme disease, or viral hepatitis.

Clearly, the presence of a systemic inflammatory polyarthritis effectively rules out noninflammatory illness, such as osteoarthritis or fibromyalgia. The lack of Heberden’s or Bouchard’s nodes and involvement of joints not classically involved in primary osteoarthritis (MCP, wrists, and elbows) eliminate this possibility. Similarly, the presence of joint inflammation eliminates the fibromyalgia syndrome as a cause of this woman’s fatigue and pain.

- What diagnostic tests would be appropriate at this juncture?

Diagnostic Testing

Given the patient’s symmetrical inflammatory polyarthritis, with RA as the most likely diagnosis, initial evaluation of this patient can be very focused. A positive rheumatoid factor (RF) provides important prognostic information, although the diagnosis of RA can be made in the absence of a positive test. In a female of middle age with constitutional features of fatigue, screening for hypothyroidism by means of a highly sensitive assay for thyroid-stimulating hormone (TSH) would be reasonable. An erythrocyte sedimentation rate (ESR) will not assist with the diagnosis in this case, but rheumatologists would utilize an ESR in monitoring disease activity. However,
The internist orders tests for ESR, TSH level, and RF. For her arthritis, the patient is given a prescription for naproxen sodium, 500 mg twice daily with food. Risks of gastrointestinal (GI), hepatic, and renal disease from NSAIDs are discussed with the patient and she is instructed to take the naproxen with food and to remain upright for 30 minutes to 1 hour after taking it. An appointment is scheduled for 2 weeks later to review test results and evaluate response to therapy.

At her follow-up appointment, the patient reports that she took the naproxen for 3 days with some mild relief but then developed mild abdominal pain with some “heartburn,” and she discontinued the medication. However, she has had difficulty working at the computer due to increased pain in her hands over the last week and has resumed taking ibuprofen, even though the medication upsets her stomach. The internist reviews her test results with her, which are as follows: mildly elevated ESR (25 mm/hr), normal TSH level, elevated RF (55 IU/mL; normal, <20 IU/mL). He tells her that based on her history, physical examination findings, and laboratory results, he can make a definitive diagnosis of RA (Table 2). The patient asks whether this means she needs to see a rheumatologist.

Workup and Initiation of Treatment

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Is it reasonable to expect a PCP to manage RA?

Primary Care Management of RA

Treatment of patients with RA has undergone a revolution over the past couple of decades. Results of a number of long-term epidemiologic studies demonstrated increased morbidity and mortality among patients with RA, even among those receiving what was for the time aggressive therapy [2,5]. As a result, treatment of the patient with RA evolved to earlier use of disease-modifying agents, often in combination.

Several prognostic factors may help the PCP distinguish patients who might be expected to have milder disease from those who are likely to do poorly. Factors suggesting a poor prognosis include a high number of inflamed and swollen joints, positive serologic assay for RF, the presence of marginal erosions by radiography, extra-articular manifestations

Table 2. Criteria for the Classification of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
</tr>
<tr>
<td>2. Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, ankle, and MTP joint</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
</tbody>
</table>

NOTE. For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made. (Adapted with permission from Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:319.)
RHEUMATOID ARTHRITIS

of disease (nodules, scleritis, vasculitis), or evidence of systemic inflammation not responding quickly to treatments (manifested by prolonged morning stiffness, increased acute phase reactants, anemia of chronic disease, or hypoalbuminemia) [6]. Patients with these features should receive early and aggressive therapy by a rheumatologist (Figure).

The PCP may be comfortable initiating management for patients who lack poor prognostic factors. Treatment options might include nonpharmacologic as well as pharmacologic measures. Important among the former are physical and occupational therapy, as most patients present with hand involvement. A number of pharmacologic agents serve as treatment options for the PCP. Chief among these are NSAIDs, hydroxychloroquine, tetracyclines, and low-dose corticosteroids.

Reassessment of the patient after institution of therapy is critical. Patients who fail to respond adequately should be referred promptly to a rheumatologist. Factors that should prompt referral include persistent joint swelling (synovitis), inability to use joints, persistently elevated ESR or C-reactive protein level, severe fatigue, prolonged morning stiffness, or the development of extra-articular manifestations.

• Which therapies should a PCP be comfortable prescribing for a patient newly diagnosed with RA?

NSAIDs

Given their effectiveness and rapid onset of action, NSAIDs are often employed early in the management of patients presenting with inflammatory arthritis. By blocking cyclooxygenase (COX), NSAIDs inhibit the production of prostaglandins, which are involved in the inflammatory and pain responses in RA. Thus, the blockade of prostaglandins by NSAIDs results in both analgesic and anti-inflammatory activity.

While most patients will note improvements in pain and in markers of inflammation such as decreased joint tenderness and shortened duration of morning stiffness, NSAIDs alone are rarely sufficient as monotherapy. However, the degree of relief can be quite dramatic and sufficient in the patient with very mild disease. Most patients with active RA will require further therapy.

As suggested by the plethora of NSAIDs on the market, no one drug is universally superior to another and response is highly patient-dependent. Patients may benefit from a therapeutic trial of several different agents to determine the one to which they will respond maximally.

Salicylates

Salicylates are both inexpensive and demonstrably effective in the treatment of joint inflammation. As with the other NSAIDs, higher doses are required for anti-inflammatory effect, generally 3 to 6 g of aspirin daily to achieve serum levels of approximately 20 mg/dL. Limiting factors include the need for frequent dosing and the risk of adverse effects, especially GI intolerance and salicylate intoxication.

Nonacetylated salicylates, such as salsalate or choline magnesium trisalicylate, have much fewer GI side effects but are generally felt to be slightly less efficacious in their anti-inflammatory effects than aspirin or NSAIDs. Dosing is initiated at 1000 mg to 1500 mg twice daily and is increased based on serum salicylate levels. Dosing is usually limited by symptoms of salicylism, principally tinnitus.

Traditional NSAIDs

NSAIDs represent an advance over salicylates in the need for less frequent dosing and increased GI tolerability. For agents with longer half-lives, longer trials are needed to judge response. Most patients with RA should be continued on maximally tolerated doses for at least 2 weeks.

GI toxicity is the most serious adverse effect. Symptoms of dyspepsia occur frequently and may affect up to half of patients who take NSAIDs [7]. More serious adverse effects such as perforation, ulceration, and bleeding in the stomach or intestine occur at an incidence of 2% to 4% per year, accounting for 10,000 to 20,000 deaths annually [7]. The fact that both aspirin and NSAIDs inhibit platelet function contributes to the risk of GI ulceration and bleeding. Management of the patient on NSAIDs is difficult because up to 80% of patients with GI complications never have symptoms of pain [8]. Thus, neither the presence nor absence of symptoms can predict risk of complications in a given patient. Prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) [9] controlled trials, such as the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) [10] and data gathered from large databases [11], have identified risk factors for serious GI complications (Table 3). For example, the case patient has the significant risk factor of a previous gastric ulcer due to NSAIDs. Were she to be prescribed corticosteroids for her RA, additional risk factors would be present. The risk of ulcer complications increases with the number of risk factors present.

Chief among other serious adverse effects is nephrotoxicity. Patients with renal insufficiency, congestive heart failure, or other states in which renal perfusion is dependent upon prostaglandins are at risk for a decline in renal function, the development of edema, or the exacerbation of hypertension if prostaglandin synthesis is inhibited by NSAIDs. More rarely, NSAIDs may cause acute tubular necrosis, interstitial nephritis, or nephrotic syndrome. Less common effects seen in patients include hepatotoxicity, depression, difficulty concentrating, asthma, and anaphylaxis.
Figure. Incorporating prognostic factors into treatment decisions for rheumatoid arthritis. CREG = cross-reactive epitope group; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; PCP = primary care physician.
Selective COX-2 Inhibitors
The hypothesis adopted earlier this decade that 2 different isoforms of COX exist led to an intense search for agents selective in their mode of action. The prostaglandin products that are produced by COX contribute to the symptoms of inflammation. It has been hypothesized that COX-1 is constitutively present in a number of tissues and is principally responsible for homeostatic functions such as protection of the gastric mucosa, while COX-2 is induced in inflammatory states. Additionally, while COX-2 appears to be constitutively present in a few tissues (eg, brain, kidney), it is not constitutively present in the GI tract and is therefore not involved in the development of peptic ulcer disease. Agents selective for their inhibition of COX-2 over COX-1, therefore, should be anti-inflammatory but not ulcerogenic [12].

Two of these selective COX-2 inhibitors have been approved for treatment of osteoarthritis: celecoxib (Celebrex) and rofecoxib (Vioxx). Both drugs have been shown to be as effective as nonselective NSAID comparators in the treatment of pain due to osteoarthritis. For osteoarthritis, celecoxib is dosed at 100 mg twice daily or 200 mg daily, while rofecoxib is dosed at 12.5 mg daily and increased to 25 mg daily if needed [13,14]. Celecoxib also has been approved for treatment of RA at doses of 100 mg to 200 mg twice daily. Studies with rofecoxib in RA are ongoing.

As selective COX-2 inhibitors and nonselective COX inhibitors appear to have the same mechanism of action in treating inflammation (ie, inhibition of COX-2), one would expect to see equivalent efficacy. One would also expect a significant advantage from the lack of inhibition of COX-1, which would be expected to result in decreased GI toxicity. Indeed, significant reductions in endoscopically observed GI mucosal lesions are seen with both celecoxib and rofecoxib when compared to traditional NSAIDs [15]. In light of the fact that these drugs do not inhibit platelet function (ie, there is no COX-2 enzyme in platelets), their low incidence of observable GI ulceration is especially promising for a reduction in significant GI toxicity.

Whether these low rates of endoscopically observed ulcers translate into a decrease in clinically significant complications of bleeding, ulceration, and perforation remains to be seen as more patients are treated for longer periods of time in the postmarketing period. All available evidence from corporate-sponsored clinical trials and the early postmarketing period favors a very low incidence rate of serious GI complications. Thus, the development of these agents will only increase the earlier use of NSAIDs for RA and may well contribute to safer and earlier use of NSAIDs in other disorders such as osteoarthritis. To what extent these agents expand the use of NSAIDs to other populations who have been at significant risk for GI toxicity from NSAIDs such as the elderly, those with a history of peptic ulcer disease, or those on concomitant corticosteroids remains to be seen, but results are promising. The data are incomplete on COX-2 inhibitor use in patients with special considerations, such as patients on anticoagulants or those with varying degrees of renal insufficiency.

Hydroxychloroquine
Antimalarial agents, typified by hydroxychloroquine (Plaquenil), are safe and effective in the treatment of joint inflammation in RA. A classic example of a slow-acting antirheumatic drug, hydroxychloroquine therapy may require 2 to 4 months for clinical improvement to be noticed. The addition of hydroxychloroquine at 400 mg daily for 4 to 6 months, decreasing to 200 mg daily after initial response, is a reasonable therapeutic option in the patient who has only a partial response to NSAIDs. Hydroxychloroquine is a relatively safe drug, and a high percentage of patients are able to remain on the drug [16,17]. Hydroxychloroquine is often used in combination with other disease-modifying antirheumatic drugs (DMARDs), specifically methotrexate. The incidence of retinal toxicity is low, but some rheumatologists recommend semiannual ophthalmologic examinations for patients on hydroxychloroquine. Other adverse effects (hematologic) are so uncommon that most rheumatologists do not recommend routine screening.

Tetracyclines
Three randomized trials examining the effect of minocycline (100 mg twice daily) in patients with active RA have recently been published [18–20]. All have demonstrated a modest but significant reduction in the number of tender and swollen joints as well as a reduction in serum C-reactive protein levels and/or ESR with minimal adverse effects. The most common adverse events are related to central nervous system effects, especially dizziness. The mechanism of action of this class of antibiotics in the treatment of RA is uncertain. In addition to their antimicrobial effects, these agents have a number of anti-inflammatory properties, which could account for their efficacy in inflammatory diseases such as RA [21].
**Glucocorticoids**

Although the mechanism of action of exogenous glucocorticoids is complex, their anti-inflammatory and immunosuppressive effects are well understood. Soon after the discovery of corticotropin, glucocorticoids were shown to produce dramatic and rapid improvement in inflammatory arthritis. However, the development of significant adverse events was not recognized until later. In many ways, this balance between efficacy and toxicity has been at the center of the debate as to the appropriate use of glucocorticoids in RA.

There is good evidence that glucocorticoids are disease-modifying in RA. For example, prednisolone prescribed for 2 years to patients with RA at a constant dose of 7.5 mg each morning in addition to their other therapy for RA resulted in marked reduction of joint destruction as measured by radiographic erosions [22]. There is also good evidence that low doses of prednisone (less than 10 mg given once daily) have fewer adverse effects than higher doses previously prescribed. Saag et al [23] examined a historical cohort of patients with RA on prednisone at doses of less than 15 mg (or its equivalent) for at least 1 year. Adverse events were clearly dose-related, being especially frequent in patients treated with more than 10 mg daily.

Use of daily, low-dose prednisone is widely practiced. Most commonly, prednisone is begun early in the disease as a “bridge” to gain control of the patient’s joint inflammation until second-line agents (eg, methotrexate) become effective. Ideally, the prednisone is tapered down or off once the patient’s arthritis is suppressed by DMARD therapy, the consensus being that long-term therapy with drugs such as methotrexate is associated with fewer adverse effects than glucocorticoids. In reality, many patients obtain such significant relief from prednisone that they are unwilling to discontinue it. In this case, the lowest possible dose should be maintained, certainly no more than 5 to 7.5 mg given each morning. Inability to taper prednisone to doses of 5 mg per day or less should prompt referral to a rheumatologist.

Alternate-day dosing of prednisone is usually ineffective in the treatment of RA. The physician should recognize that alternate-day therapy does not significantly reduce the loss of bone that occurs with use of glucocorticoids. Because increased bone resorption occurs rapidly after the institution of glucocorticoids, measures for maintaining bone mineral density should be instituted simultaneously. Important among these are adequate calcium and, perhaps, vitamin D intake and estrogen replacement therapy. Additionally, weight-bearing exercise, avoidance of habits associated with osteoporosis (use of tobacco and excessive alcohol intake), and, ultimately, use of agents shown to be effective at preventing or treating corticosteroid-induced osteoporosis (alendronate and etidronate) should be considered [24,25].

**Internist’s Initial Management**

Because of the patient’s GI intolerance to NSAIDs, the internist suggests that she discontinue ibuprofen and begin taking celecoxib 200 mg twice daily. To improve her function at work, a steroid dose-pack is prescribed. A follow-up appointment is scheduled for 1 month later, at which time the internist will assess the patient’s response to treatment and potential need for referral to a rheumatologist. The patient is instructed to call if she experiences worsening of her symptoms.

- Is this appropriate initial pharmacotherapy for this patient?

Discontinuation of the ibuprofen due to dyspepsia is advisable, especially given her previous history of ulcer. There are several options for use of NSAIDs at this juncture. Prescription of one of the newer COX-2 agents is a reasonable approach based on the presence of several risk factors for more serious GI adverse events (history of “stomach ulcer” and concomitant use of corticosteroids). Alternatively, one could prescribe a nonselective COX-inhibiting NSAID along with misoprostol (200 µg 2 to 4 times daily), a synthetic prostaglandin that has been shown to prevent NSAID ulcer disease and complications such as bleeding and perforation [26].

Institution of corticosteroids at this juncture is also reasonable. Persistently active disease as manifested by painful and swollen joints and progressive difficulty performing her activities of daily living and her job warrant an increase in therapy, especially one which will rapidly improve her symptoms. However, a continuous low dose of prednisone (5 to 7.5 mg each morning) would have been preferable. The dose-pack will improve her symptoms rapidly, but her pain will recur once the dose-pack is completed.

- What additional therapeutic recommendations might have been appropriate at this time?

This patient’s internist might also consider several other therapies. With the institution of corticosteroids in a postmenopausal female, one must immediately consider therapies aimed at preservation of bone mineral density. She is already on estrogen therapy. Her calcium intake should be increased to approximately 1500 mg daily. The addition of vitamin D (400 to 800 IU daily) should also be considered depending on her nutritional status and degree of sun exposure. A dual-energy x-ray absorptiometry (DEXA) scan should be scheduled since she has several risk factors for osteoporosis.
(female sex, postmenopausal status, RA, glucocorticoid use, history of tobacco use). Further therapies will be based on the results of her DEXA scan and on her interest in taking additional medications to prevent glucocorticoid-induced osteoporosis.

Due to the patient’s hand involvement and difficulty with daily activities, referral to occupational and/or physical therapy also should be considered. Instruction in joint preservation techniques and range-of-motion exercises and modalities such as heat application will provide symptomatic relief and will hopefully maintain function. Adaptive aids such as rest bars for her computer and workstation analysis may improve her functioning at work.

Phone Follow-up and Rheumatology Consultation

The patient calls the internist 2 weeks later and says that although she improved while on the steroid dose-pack, her joints are again painful and swollen, although the celecoxib is helping somewhat. The internist consults with a rheumatologist, who suggests that the patient be started on low-dose prednisone at 7.5 mg each morning. The rheumatologist also recommends that she see the patient in 2 weeks as a new patient.

• When should a patient with RA be referred for rheumatologic consultation?

Indications for Referral

Current evidence is convincing that articular damage in RA occurs earlier in the disease (within 2 years) than previously appreciated [27]. This destruction is mediated by joint inflammation, which is clinically observable as synovitis. An understanding of these factors, combined with the realization of poor outcomes in patients with RA followed over many years, has led to support of earlier and more aggressive therapy. Thus, the goal of treatment of RA is not only to reduce pain and improve function but to suppress ongoing inflammation in the hope that long-term clinical outcomes will be improved. Therefore, the presence of persistent joint inflammation should lead to rheumatologic referral. This inflammation will most commonly be manifested by joint synovitis (swollen, boggy, or tender joints) but may also be reflected in persistent symptoms of pain, prolonged morning stiffness, excessive fatigue, or laboratory evidence of persistently elevated ESR or C-reactive protein level.

Almost all patients with RA should see a rheumatologist periodically, and those with poor prognostic factors should be seen more frequently, perhaps monthly, until disease control is optimal. Patients with large numbers of involved joints or extra-articular features or who are seropositive for RF should be referred early in the disease course (Figure). Patients with mild disease may be tried on the therapies discussed earlier and referred if articular pain and swelling persist or if other symptoms are of concern to the patient or physician. Other potential reasons for referral include confirmation of the diagnosis, need for intra-articular injection, inability to taper glucocorticoids, or need for consultation regarding osteoporosis or its prevention.

A patient’s principal physician and rheumatologist often collaborate on the required monitoring for adverse effects of combination therapy. Thus, the primary care physician needs to be aware of monitoring guidelines and toxicities of therapies employed.

Rheumatology Follow-up

The patient is seen by the rheumatologist 2 weeks after beginning low-dose steroid therapy. After beginning celecoxib, the patient noticed decreased pain in her hand and other joints. The symptoms of fatigue and prolonged morning stiffness improved markedly after beginning the corticosteroids. Her GI symptoms have resolved. Although she continues to experience hand pain late in the day if she uses her hands a great deal, her ability to type and perform the other duties of her job are much improved.

On evaluation, the rheumatologist finds that the distal interphalangial (DIP) joints are normal. Proximal interphalangial and MCP joints have boggy proliferative synovitis with tenderness. The synovitis of these joints results in decreased range of motion manifested by decreased ability to make a fist, as the internist noted. Examination of the wrists reveals dorsal tenosynovitis with decreased extension and flexion. Both elbows are mildly swollen and have a 5-degree flexion contracture. As noted, there are small bilateral knee effusions without warmth. Both ankles are swollen. There is synovitis of several metatarsophalangeal (MTP) joints manifested by soft tissue synovial swelling, tenderness, and splaying of the toes.

The rheumatologist institutes low-dose weekly methotrexate and hydroxychloroquine. Because the patient noted decreased pain, her celecoxib dose is decreased to 200 mg daily. A DEXA scan is performed and confirms normal bone mineral density.

• What is the role of combination therapy in optimizing outcomes in RA?

• How effective are the DMARDs in modifying disease?

Rheumatologists understand that speed is of the essence in controlling the inflammation of RA. Agents such as gold or
penicillamine, which may take 4 to 6 months to have an effect, are too slow; they have largely been replaced by agents such as methotrexate, hydroxychloroquine, and sulfasalazine, which typically start to work within 6 to 12 weeks. Lesser numbers of erosions are a “stalking horse” for good outcomes in RA, and drugs such as methotrexate, sulfasalazine, and cyclophosphamide as well as intramuscular gold have been associated with fewer radiographic erosions over the course of their use in RA. The goal is to control inflammation quickly so that synovitis does not become pannus, a locally invasive connective tissue that destroys cartilage and bone and has been likened to a locally invasive malignancy. The premise (but not promise) is that inflammation controlled early is easier to suppress. Certainly the converse is true: later treatment of inflammation often requires multiple second-line agents in combination and cannot reverse tissue destruction that has already occurred. Nor is it clear that drugs used to control synovitis will actually control pannus progression once it begins. Eighty percent of RA patients develop radiographic evidence of erosions, the hallmark of pannus formation, within the first 2 years of illness [27].

Combination Therapy
Rheumatologists often turn to combination therapy (Table 4) for patients who have a poor prognosis at onset or who fail to respond completely in 2 to 3 months to relatively simple measures such as NSAIDs, low-dose prednisone, tetracyclines, and hydroxychloroquine (Figure). Previous trials with combination therapies failed to show better outcomes than with single-agent treatment [28], but these trials looked at patients treated late, did not employ the current treatment mainstays methotrexate and sulfasalazine, and sometimes employed drugs like cyclophosphamide, which, while effective, is too toxic in the long run. Recent studies have been much more encouraging, particularly regarding the triple combination of methotrexate, sulfasalazine, and hydroxychloroquine studied by O’Dell’s consortium, the Rheumatoid Arthritis Investigative Network (RAIN) [29]. Published information from this group suggests that a sustained, significant decrease in disease activity (as manifested by patients achieving greater than 50% improvement in several measures of inflammation) can be maintained for 2 years in 80% of patients on triple therapy compared to only 40% of those on either methotrexate alone or hydroxychloroquine and sulfasalazine in combination. O’Dell presented new information at the 1998 national meeting of the American College of Rheumatology extending that data to 5 years for the triple therapy group and showing that more than 50% of those patients were still well-controlled [30]. This is the most encouraging information available in long-term RA treatment. Further, the improvement did not come at a risk of greater side effects or drug toxicity.

The helper T cell–selective agent cyclosporine is another agent best used in combination therapy, typically with methotrexate. Doses needed for cyclosporine monotherapy are too nephrotoxic, but results with low-dose cyclosporine and methotrexate together have been encouraging, although long-term renal damage remains a concern [31,32].

Newer Agents
Two newer agents are now available as part of the rheumatologist’s armamentarium of second-line–agent therapies. Sometimes patients cannot take methotrexate, the gold standard drug for RA. Hematologic toxicities, hypersensitivity pneumonitis, or stomatitis may prevent or limit its usefulness. Leflunomide, a DNA pyrimidine pathway inhibitor, works in a similar fashion to methotrexate, a purine pathway inhibitor; but the toxicities of methotrexate are less common; diarrhea, skin rashes, and alopecia are the most common side effects of leflunomide. Hepatic enzyme elevations are not uncommon, but it is not yet known whether leflunomide causes hepatic fibrosis, an uncommon outcome of methotrexate treatment. Leflunomide has been shown to retard disease progression over 12 months of treatment as measured by radiographic evidence of erosions and joint space narrowing [33]. The drug may even work well in combination with methotrexate [34].

Etanercept is a completely novel agent that works by “soaking up” tumor necrosis factor (TNF). TNF is a “switching yard” for the body’s responses to inflammation and infection and is important for malignancy screening. Etanercept is 2 soluble TNF receptors linked with the Fc portion of an immunoglobulin molecule designed to bind TNF to down-regulate inflammation. Results of etanercept use in patients with RA have been dramatic, both singly and in combination with methotrexate, in controlling inflammation and inducing disease remission [35,36]. Patients treated with etanercept should stop taking the drug if they develop potentially serious infection.

These newer agents are quite expensive: leflunomide costs about $300 per month and etanercept about $1000 per month. Studies will have to show significantly better long-term outcomes than the relatively inexpensive triple combination of methotrexate-hydroxychloroquine-sulfasalazine for these agents to gain widespread use. In addition to impressive efficacy, etanercept needs no routine laboratory
monitoring, so it might be less expensive than it initially appears.

1 Month Later

The rheumatologist sees the patient again in 1 month. She finds that the patient has no joint pain, tenderness, or swelling. The patient reports that her morning stiffness has resolved and that her energy has returned to normal. Her ESR is 10 mm/hr.

Occasional flare-ups are treated by varying the dose of celecoxib from 200 mg daily to 200 mg twice daily; occasionally, slow tapers of low-dose prednisone are required for more substantial flare-ups. The patient never requires the addition of another second-line agent such as sulfasalazine during follow-up over the next 3 years.

• How should patients with RA be followed?

Both PCPs and rheumatologists need to follow several simple parameters to determine how well their RA patients are doing: number of tender/swollen joints, excluding those with secondary osteoarthritic involvement; duration of morning stiffness (“How long does it take you to ‘loosen up’ as much as you’re going to?”); time to onset of fatigue in the afternoon; and changes in the ESR or C-reactive protein level. Ideally, patients would have no tender or swollen joints, no morning stiffness, and no fatigue; in addition, laboratory testing should show normalization of the ESR and C-reactive protein to count as a remission (Table 5). Patients who do poorly need higher doses or added numbers of second-line agents; certainly acute worsening could be helped by increasing the NSAID or prednisone doses or by administering corticosteroid joint injections. The basic premise is to do whatever is needed to suppress inflammation. Untreated or undertreated RA patients do poorly. To paraphrase a quotation by rheumatologist Verna Wright at the University of Leeds, “Rheumatologists write ‘doing well’ in the charts of their RA patients from week to week, while year to year their patients become progressively more crippled in front of their eyes.” It is time to try harder.

Table 5. Criteria for Clinical Remission in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1. Duration of morning stiffness not exceeding 15 minutes</td>
<td>15 minutes</td>
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<tr>
<td>2. No fatigue</td>
<td></td>
</tr>
<tr>
<td>3. No joint pain (by history)</td>
<td></td>
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<tr>
<td>4. No joint tenderness or pain on motion</td>
<td></td>
</tr>
<tr>
<td>5. No soft tissue swelling in joints or tendon sheaths</td>
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<tr>
<td>6. Erythrocyte sedimentation rate (Westergren method) less than 30 mm/hour</td>
<td>30 mm/hour for a female or 20 mm/hour for a male</td>
</tr>
</tbody>
</table>

NOTE: These criteria are intended to describe either spontaneous remission or a state of drug-induced disease suppression that simulates spontaneous remission. No alternative explanation may be invoked to account for the failure to meet a particular requirement. For instance, in the presence of knee pain, which might be related to degenerative arthritis, a point for “no joint pain” may not be awarded. Exclusions: Clinical manifestations of active vasculitis, pericarditis, pleuritis or myocarditis, and unexplained recent weight loss or fever attributable to rheumatoid arthritis will prohibit a designation of complete clinical remission. (Reprinted with permission from Pinals RS, Masi AT, Larsen RA, et al. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308-15.)

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1. Which of the following clinical features would NOT be helpful in differentiating an inflammatory from a non-inflammatory joint problem?
(A) Fatigue
(B) The presence of prolonged morning stiffness
(C) Joint pain
(D) Joint soft tissue swelling
(E) The presence of an anemia of chronic disease

2. Which of the following statements regarding selective COX-2 inhibitors is FALSE?
(A) They preserve prostaglandin production in the gastric mucosa
(B) They are effective in treating osteoarthritis pain
(C) They inhibit platelet function
(D) They may reduce risk of NSAID ulcers

3. Known risk factors for NSAID-induced peptic ulcer disease include all of the following EXCEPT:
(A) History of gastric ulcer
(B) Age greater than 65 years
(C) High doses of NSAIDs
(D) Concomitant use of methotrexate

4. Indications for referral of the RA patient to a rheumatologist might reasonably include all of the following EXCEPT:
(A) Persistently active synovitis
(B) Continuing need for corticosteroids
(C) Marginal joint erosions on radiography
(D) Gastrointestinal upset due to NSAIDs

5. Which of the following clinical features is NOT consistent with a diagnosis of RA?
(A) Tenderness and soft tissue swelling of 5 joints
(B) Bilateral involvement of PIP and MCP joints
(C) Progressive, additive arthritis
(D) Elevated ANA level
(E) Heberden’s nodes
EVALUATION FORM: Rheumatoid Arthritis: Diagnosis and New Therapeutic Options

To receive CME credit for this case study, read the case study and then answer the multiple-choice questions on page 76. Circle your answers below. Also, please respond to the four questions that follow. Then, detach the evaluation form and mail or FAX to:

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

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   Condition 2: ________________________________________
   Condition 3: ________________________________________
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