

SPECIAL SUPPLEMENT TO

**M A N A G E D**

# Care

## New Options In the Treatment of Rheumatoid Arthritis

### HIGHLIGHTS

- Available Therapeutic Options

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- Important Breakthroughs in Patient Care

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- Economic Implications for Health Plans

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- Discussion: Step-Care Algorithm To Optimize Patient Benefits and Economic Impact

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## About this publication

This *MANAGED CARE* special supplement, "New Options in the Treatment of Rheumatoid Arthritis," is supported by an unrestricted educational grant from Aventis Pharmaceuticals. The material in this publication stems from a meeting that took place April 17–18, 2001, in Tampa, Fla. The program brought together leading experts in the field of rheumatology to discuss new and exciting treatment options for rheumatoid arthritis.

The goal of the meeting was to create a new step-care algorithm for treating patients affected by this debilitating illness that is associated with substantial morbidity and mortality. Thomas E. Scott, M.D., Joel M. Kremer, M.D., and Joseph J. Doyle, R.Ph., M.B.A., described recent developments in combination treatment, using new agents that are radically improving patient care, bringing a significant reduction in disease-related disability, measurable improvements in quality of life, and a substantial decrease in economic losses. The clinical measures for rheumatoid arthritis, which are based on the standard instruments recommended by the FDA in all clinical trials, demonstrate that leflunomide is superior to older agents in combination with methotrexate, the previous gold standard for rheumatoid arthritis treatment.

The material in this special supplement has been independently peer reviewed. The sponsor played no role in reviewer selection.

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SPECIAL SUPPLEMENT

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## New Options In the Treatment Of Rheumatoid Arthritis

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# Pharmaceutical Agents For the Treatment Of Rheumatoid Arthritis

THOMAS E. SCOTT, M.D.

**M**isconceptions about rheumatoid arthritis (RA) abound, even among physicians. Generally viewed as a benign disease with manageable symptoms, RA has been approached as a condition that the patient can learn to live with. Many primary care physicians do not fully recognize how devastating RA really is, and that it is a systemic disorder affecting multiple organs.

Rather than being a disease characterized by tender and swollen joints, RA is a progressive and systemic inflammatory disorder of unknown etiology to which multi-system extra-articular manifestations are linked. The criteria for studies of RA define it as a symmetrical inflammatory polyarthritis (meaning it affects both sides of the body equally), with prolonged morning stiffness; these symptoms almost always involve the hands and wrists. An astute clinician who sees a patient with ankle and knee inflammation and no involvement of the hands and wrists would question a diagnosis of RA.

Patients generally report pain and fatigue in their initial office visits. The fatigue is attributable to the systemic inflammation, which diminishes their energy. Patients often have organ inflammation, the so-called extra-articular manifestations of RA, which can include the potential for pericarditis and pleurisy to develop. Additionally, there are problems with vasculitis — inflammation of the small blood vessels that can lead to stroke, neuritis, and vasculitic skin lesions. Patients with RA often have abnormalities in blood counts, with elevated platelets and low serum iron, and may be anemic.

Joint erosions are characteristic of RA. Because other conditions are characterized by symptoms similar to those associated with RA, it is important to discern whether the condition is symmetric, to look carefully at the lab studies to determine if the patient has a positive serum rheumatoid factor, and to ascertain whether there is radiographic evidence of erosion. The available diagnostic tools can help the physician differentiate this disease from others sharing similar symptoms, such as lupus, which presents as a symmetric arthritis but shows no erosion on radiograph.

The common estimate is that 1 percent of the adult population is affected by RA.<sup>1</sup> A high percentage of these

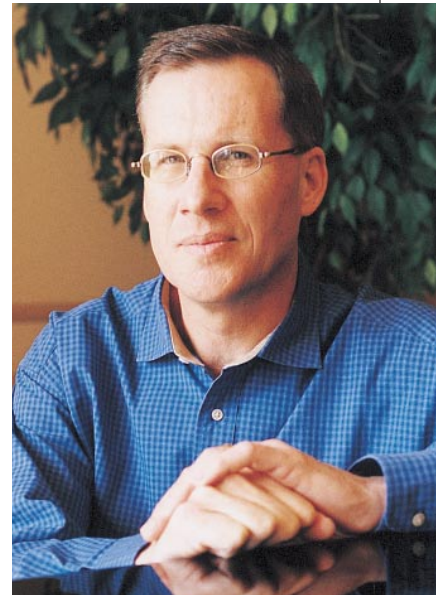
patients are within Class IV, the most advanced stage of rheumatoid arthritis as described by the American College of Rheumatology (ACR), using the patient's functional status (Table 1). Forty to sixty percent of these patients typically survive five years or less following diagnosis.

RA is expensive to treat. The total per-patient costs are not quite as high as those for coronary artery disease, yet costs rise substantially when joint replacement, disability, and the losses associated with quality of life are considered. If new agents, such as leflunomide and the tumor necrosis factor (TNF) inhibitors, can prevent disability and joint damage, as well as total joint replacement, then significant dollars will be saved — given that a total hip or knee arthroplasty costs upwards of \$16,000 exclusive of postoperative care and rehabilitation.<sup>2</sup>

## Defining severity and progression

Assessing a patient's prognosis is important for determining the treatment program. Certain indicators are useful in identifying patients whose disease is likely to become severe.

Serum rheumatoid factor is positive in approximately 75 percent of RA patients, and a higher titer serum



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rheumatoid factor tends to predict severity. For patients presenting with extremely high elevations of C-reactive protein and erythrocyte sedimentation rate, which are inflammation indicators, more aggressive treatment and close patient monitoring are needed.

Extra-articular manifestations are clinically apparent physical factors in patients with the systemic disease; such patients may be found to have pleurisy or pericarditis, rheumatoid nodules, neurological symptoms, or vasculitic skin rashes. An inflammatory disease involving the eye (the “sicca” syndrome) also is common in patients with RA. Such extra-articular manifestations indicate a worse prognosis.<sup>3</sup>

Functional status is highly predictive of severity and outcome, and the criteria for this assessment can be effectively used to measure improvement in the effort to avoid more severe stages of this disease. With the introduction of the newer agents, therapy aims to prevent the advanced disease state associated with Class IV status.

### Early, aggressive treatment

Because RA is not a benign disorder, early diagnosis and aggressive treatment are important. Structural damage and disability can occur within the first two to three years of the disease, and slower progression of this disease has been linked to early treatment. Radical changes in treatment approaches to RA have recently developed as a result of new pharmacotherapeutic options that make early treatment possible and the avoidance of disability a realistic goal. The medical profession now recognizes the overriding importance of controlling inflammation early to avert irreversible joint damage and disability. Early diagnosis is thus essential, as is aggressive treatment.

### Changing pharmacologic goals

Historically, RA treatment was aimed at decreasing swelling and tenderness and increasing range of motion, to reduce pain and morning stiffness. These goals have been expanded to include the maintenance of functional status through the use of extremely safe agents that control disease activity in a large proportion of patients. Patients should be able to perform their activities of daily life, their work, and even play sports. Rheumatologists want to maximize the patient’s quality of life and to see radiographic demonstration of slowed progression. These needs are being met more often with the newer agents — leflunomide and the anti-TNF agents — which have produced measurable improvements along these lines. The following discussion places the newer agents in the context of the traditional agents (non-

**TABLE 1 ACR criteria for assessing functional status in RA**

Classification	Specifications
<b>Class I</b>	Complete ability to perform usual activities (e.g., self-care, vocational/avocational)
<b>Class II</b>	Ability to perform usual self-care and vocational activities; limited avocational activities
<b>Class III</b>	Ability to perform usual self-care activities; limited vocational/avocational activities
<b>Class IV</b>	Limited ability to perform usual self-care and vocational/avocational activities

steroidals, corticosteroids, and the older DMARDs).

**Nonsteroidal agents.** The various nonsteroidal anti-inflammatory drugs (NSAIDs) have long been a mainstay of RA treatment because they control inflammation and pain to some degree. Yet they reduce swelling and improve mobility and quality of life in only a low percentage of patients with RA. These agents do not reduce disease progression or deformities and erosions.

Nonsteroidal agents function by inhibiting an enzyme, cyclooxygenase, which produces prostaglandins. Prostaglandins mediate pain as well as inflammation. Cyclooxygenase exists as two isoforms, COX-1 and COX-2. The COX-1 enzyme is responsible for producing the “housekeeping” prostaglandins, which maintain mucosal integrity in the gastrointestinal tract — and to some degree, renal blood flow — and also allow platelets to adhere to one another. The COX-2 enzyme produces proinflammatory prostaglandins. Traditional NSAIDs such as naproxen and ibuprofen inhibit the proinflammatory prostaglandins as well as the “good” prostaglandins, which is problematic.

New nonsteroidal agents such as celecoxib and rofecoxib, which selectively inhibit COX-2 to a greater extent than COX-1, have generated substantial misunderstanding among patients, as a result of direct-to-consumer advertising. They are not disease-modifying agents, and they have not been shown to be superior to traditional NSAIDs with respect to relieving signs and symptoms of RA<sup>4,5</sup> or osteoarthritis (OA).<sup>6,7</sup> Their benefits lie in their relatively rapid onset of action and reduced toxicity, compared with agents that inhibit both COX-1 and COX-2. The COX-2 inhibitors are associated with fewer ulcers, fewer gastrointestinal bleeds, and fewer problems with platelet inhibition and anemia.<sup>8</sup> Also, patients on COX-2 drugs can take warfarin and not be at an increased risk of bleeding.

**Corticosteroids.** Like NSAIDs, corticosteroids are not disease-modifying drugs. Corticosteroids also are overused in RA treatment, because they offer quick relief. Steroids have been used to bridge gaps during treatment while waiting for other medications to become ef-

**TABLE 2 Selection of an initial DMARD**

Drug	Approximate time to benefit	Usual maintenance dose	Toxicity	Toxicities to monitor
<b>Azathioprine</b>	2–3 months	50–150 mg, daily	Moderate	Myelosuppression, hepatotoxicity, lymphoproliferative
<b>Cyclosporine</b>	2–4 months	1.0–2.5 mg/kg/d	High	Renal, hyperuricemia
<b>Gold, oral</b>	4–6 months	3 mg, daily or twice daily	Low	Myelosuppression, rash, proteinuria, gastrointestinal
<b>Gold, parenteral</b>	3–6 months	25–50 mg IM, every 2–4 weeks	Moderate	Myelosuppression, rash, proteinuria
<b>Hydroxychloroquine</b>	2–4 months	200 mg, twice daily	Low	Macular damage
<b>Leflunomide</b>	2–4 months	20 mg, daily	Low	Hepatotoxicity, gastrointestinal
<b>Methotrexate</b>	1–2 months	7.5–15 mg, per week	Moderate	Hepatotoxicity, pulmonary, myelosuppression
<b>D-penicillamine</b>	3–6 months	250–750 mg, daily	High	Myelosuppression, proteinuria
<b>Sulfasalazine</b>	1–2 months	1,000 mg, 2 or 3 times daily	Low	Myelosuppression, gastrointestinal

Sources: Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum.* 1996;39:713–722; Arava prescribing information, 2000.

fective. Even low doses ( $\leq 10$  mg daily) of long-term oral prednisone can lead to osteoporosis,<sup>9</sup> and it can be challenging to taper the dose of these drugs without a recurrence of symptoms. The osteoporosis can be prevented with bisphosphonates, however. Steroid injections are highly effective for targeting a specific joint, an option that most primary care physicians cannot offer. Steroids may be beneficial in the long term and are inexpensive.

### DMARDs

Disease-modifying antirheumatic drugs (DMARDs) interfere with the inflammatory process by a variety of mostly unclear mechanisms. The older DMARDs are characterized above all by their relatively slow onset of action — anywhere from one to six months is needed before a clinical benefit can be discerned (Table 2). In addition, many are noted for their toxicity, which mandates frequent monitoring.

The older DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and injectable gold salts. Although oral gold, penicillamine, cyclosporine, and azathioprine also have generally been referred to as DMARDs, even by the American College of Rheumatology, they are not true disease-modifying agents be-

cause they do not reduce erosions and disability.

A small percentage of patients would do well on *hydroxychloroquine* alone, a drug that originated as a treatment for malaria. In the past, this treatment choice was more common in combination therapy, used with sulfasalazine and methotrexate. Hydroxychloroquine is generally perceived as a drug for mild disease, and it is now used more in the treatment of lupus than RA. Hydroxychloroquine raises concerns about macular damage.

Rheumatologists no longer use *penicillamine*, a metabolite of penicillin, to treat RA, although it is used as an off-label treatment for scleroderma. Like most of the older agents, it does not halt disease progression. Penicillamine is highly toxic and can lead to drug-induced lupus, thrombocytopenia, proteinuria, loss of taste, and rash.

*Sulfasalazine* seems to work better in combination therapy and for patients with inflammatory bowel disease who get arthritis, although in some patients diarrhea is exacerbated by this drug.

*Parenteral gold* is now recognized to have limited effectiveness, and approximately 35 percent of patients on gold therapy experience side effects that often lead to discontinuation of the drug.

*Cyclosporine* is an immunosuppressive agent associ-

ated with increased risk of infection and renal insufficiency. The myelosuppressive drug *azathioprine* can control RA for 10 years but the risk of lymphoma and liver toxicity is heightened. Toxicity concerns are high in the patient population, because RA often affects women in their childbearing years, and many RA patients will be on long-term medication.

### **Methotrexate: the treatment standard**

After more than 15 years of extensive clinical experience, methotrexate remains an effective tool in the armamentarium against RA. Although its mechanism of action relative to its anti-inflammatory effects remains unclear, it has immunosuppressive and cytotoxic effects that are due to the inhibition of dihydrofolate reductase. Methotrexate is a proven agent in reducing painful and swollen joints, and does well in the overall clinical parameters, including X-ray data.

Patients on methotrexate must be diligent about having their liver function monitored every four to eight weeks to avoid serious toxicities that can lead to cirrhosis in rare cases. Routine toxicity monitoring should include a complete blood cell count (CBC), liver profile, serum albumin, and serum creatinine. Complications commonly occur with compliance and follow-up when monitoring is done outside the physician practice. Moreover, treatment challenges increase with patients who continue to ingest alcohol. Significant myelosuppression may develop in RA patients, particularly the elderly, whose treatment may be high doses of methotrexate ( $\geq 20$  mg/week). A fair number of patients also develop lung toxicity from this drug. Toxicity can generally be prevented with daily folic acid supplementation.

Methotrexate is not as effective as the TNF inhibitors and leflunomide in reducing the incidence of erosions. Combination therapy, using methotrexate with infliximab, etanercept, or leflunomide, offers the added advantage of using methotrexate at lower doses that are better tolerated due to the reduction in toxicity.

### **Anti-TNF therapies**

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) appears to be an extremely important mediator of RA. Produced by macrophages and T-cells, it affects various cellular pathways that lead to inflammation. It also increases permeability through its effects on the endothelium of blood vessels, enabling cells to infiltrate joints. TNF- $\alpha$  affects the lining of the synovium, as well as bone and cartilage. If left unchecked, TNF- $\alpha$  production rises sharply, leading to pain, swelling, and even joint destruction. TNF- $\alpha$  has two types of receptors, p55 and p75, both of which occur as cell-surface receptors and in soluble forms. If a drug can prevent TNF- $\alpha$  from binding with its receptors, it can block these negative effects downstream.

Two anti-TNF agents are available, etanercept and infliximab. Etanercept consists of two recombinant p75 soluble receptors attached to the Fc portion of human IgG1. Infliximab is a chimeric IgG1 monoclonal antibody, composed of human constant and murine variable regions. Essentially, both agents act as sponges to soak up circulating TNF- $\alpha$  before it can bind with its cell-surface receptors and deliver its signal.

The chimeric nature of infliximab is important clinically because human antibodies to infliximab can develop, which can result in a diminished therapeutic response over time. There is increasing recognition that the dose of infliximab must continue to be increased to maintain efficacy throughout the treatment of RA, which leads to sharp rises in cost.

In addition, antibodies against infliximab have been associated with drug-induced lupus, which was reported in two RA patients receiving infliximab in clinical trials (and which resolved following the cessation of therapy and appropriate medical treatment). In three-year follow-up safety studies, acute infusion reactions (headache, fever, chills, urticaria, chest pain) have been seen in 17 percent of patients receiving infliximab, versus 7 percent of those receiving placebo.

**Combination studies.** With drugs such as infliximab, effectiveness decreases after six weeks if not used with methotrexate, thus necessitating an infusion or a dose increase that may lead to greater adverse effects. Used in combination with methotrexate, both infliximab and etanercept are effective at lower doses, and negative effects are considerably reduced. Concomitant treatment with methotrexate can reduce the incidence of the formation of antibodies against infliximab.

In a study using methotrexate and infliximab at 3 mg/kg every eight weeks and 10 mg/kg every eight weeks, improvement in some patients was observed after the first infusion.<sup>10</sup> There was an upward curve in improvement, with no drop-off at 54 weeks. For the small subset of patients who do not achieve as good a response with time, the options are to either increase the dose or reduce the dosage interval. As a practical issue, because the infusion takes two to three hours, the dose can be increased to 5 mg/kg, rather than have the patient come to the office every four weeks for treatment.

Etanercept has been shown in clinical trials to be efficacious when used alone or in combination with methotrexate. In a 12-month study of patients with early RA, intravenous etanercept acted more rapidly than oral methotrexate to decrease symptoms and slow joint damage.<sup>11</sup> The combination of subcutaneous etanercept and methotrexate provided greater clinical benefit than methotrexate alone in patients with persistent RA.<sup>12</sup> After 24 weeks, 71 percent of patients receiving the etanercept-methotrexate combination met the ACR-20 criteria, vs 27 percent of patients receiving methotrexate plus placebo.

The anti-TNF therapies are inaccurately viewed by some as a cure for RA. Approximately 25 percent of patients may not respond to etanercept; a similar percentage may not respond to infliximab. There is still no single agent, or combination therapy, that takes care of all patients. Questions remain about the long-term use of these drugs. Serious infections have been reported in patients receiving TNF inhibitors.

### Leflunomide: a breakthrough agent

Less costly than either of these new biological agents, leflunomide is a viable alternative in the treatment of RA. It is the first of the new agents to have been designed specifically for RA, and it has been shown to halt progression of disability.

Compared with some of the older DMARDs, leflunomide has a relatively rapid onset of action of four to eight weeks. Some evidence indicates its onset of action may be sooner than that of methotrexate. Significantly, the data on leflunomide demonstrate that the drug works as well at two years as it does initially.

Leflunomide is well tolerated by most patients, and many studies with leflunomide have shown safety and efficacy over two years. Also, unlike some of the other RA therapies, such as methotrexate, leflunomide is directed toward a specific part of the immune response: T-cells that proliferate and turn on the immune response in the joints. Importantly, leflunomide is more selective than the

agents used in the past. Because leflunomide selectively targets autoimmune lymphocytes, the probability of adverse events is reduced.

Some patients receiving leflunomide may experience mild gastrointestinal reactions. To avoid hepatic toxicity, careful blood monitoring is necessary during treatment with leflunomide. Treatment with the combination of leflunomide and methotrexate also necessitates monitoring the liver. Adding an NSAID to the mix could affect liver function. In some patients, leflunomide will have to be discontinued due to persistent liver function test abnormalities. Some patients cannot tolerate the diarrhea, and an extremely small percentage of patients with alopecia drop off the drug.

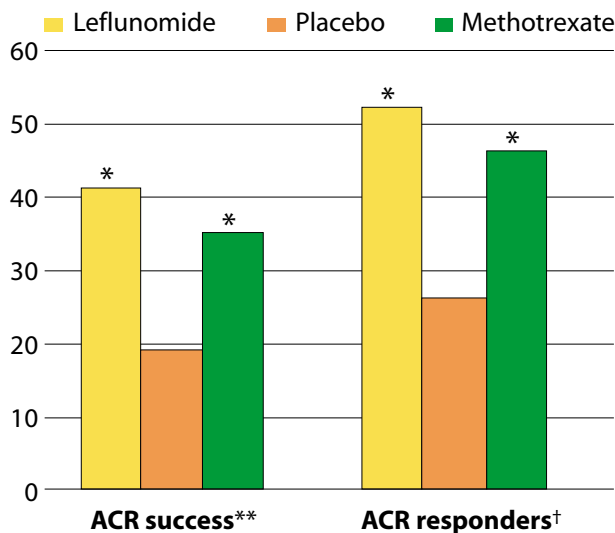
**Disease progression.** Early studies compared disease progression with leflunomide, placebo, and methotrexate, using ACR-20 responder criteria (defined as a patient who shows  $\geq 20$  percent improvement) in a combination of responses. Leflunomide performed much better than placebo<sup>13</sup> (Figure 1) and was superior to methotrexate<sup>14</sup> in these early studies. This was particularly exciting news. The release of these data came at a time when methotrexate was considered the gold standard; demonstrating that leflunomide was as good or better than methotrexate was an extremely important finding.

A primary goal in RA therapy is to reduce the progression of disease to an extent that is visible on radiographic examination. Randomized controlled trials of leflunomide have revealed that it definitely slows radiographic progression of RA.<sup>15</sup> Methotrexate reduces disease progression as well, but a two-year radiographic comparison clearly shows fewer erosions with leflunomide. Some patients who cannot tolerate methotrexate do well on leflunomide alone, yet for most patients, treatment with both of these drugs together may be synergistic, maximizing the beneficial effects. In my practice, I have more patients on a combination of methotrexate and leflunomide than on either agent alone.

**Quality of life.** Increasingly, patients are focusing on improvements in their quality of life and ability to function, rather than on the treatment of isolated symptoms. Using the Health Assessment Questionnaire (HAQ) or the modified HAQ as an outcome measure, a recent study shows patients on leflunomide did better than placebo, an improvement with time that was even greater than that seen with methotrexate.

Patient quality of life and work productivity show improvement with leflunomide (Figures 2 and 3).<sup>16</sup> (On the HAQ, an improvement is represented by a larger negative

**FIGURE 1 Efficacy of leflunomide, placebo, and methotrexate based on ACR-responder index**



\* $P \leq .0001$  vs placebo. \*\*ACR "success" is defined as a patient who completed 12 months' treatment and is classified as an ACR responder at endpoint; †ACR responder is defined as a patient who shows  $\geq 20$  percent improvement in disease progression.

number, in contrast to Short Form 36, where improved work productivity is indicated by a positive number.) In all three of these outcome measures — work productivity, SF-36, and problem elicitation technique — leflunomide was better than placebo, and in one, better than methotrexate.

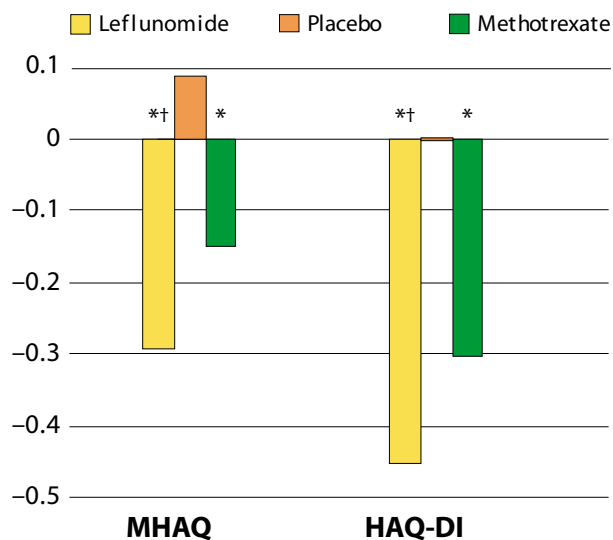
### Selecting a treatment option

In evaluating the available treatment options, it is important to seek data showing decreased progression of joint erosions and the resulting reduction in deformity and disability. DMARDs such as methotrexate and leflunomide actually slow disease progression and improve functional status. This slowing is clinically apparent, as radiographic examination reveals that inflammatory changes in the joints resolve. Once erosions are present in a Class III or IV patient, a positive change is much harder to achieve. Increased disability is averted, however, with early and aggressive combination therapy.

In the old paradigm, treatment began with anti-inflammatory agents — low-dose prednisone, possibly gold or hydroxychloroquine — and then progressed to the more powerful agents. With the advent of leflunomide, etanercept, and infliximab, the old pyramid has been inverted. The new treatment paradigm is shown in Figure 4. Today, when patients fail NSAIDs, have persistent swelling and erosions, and begin to get deformities, rheumatologists generally choose methotrexate.

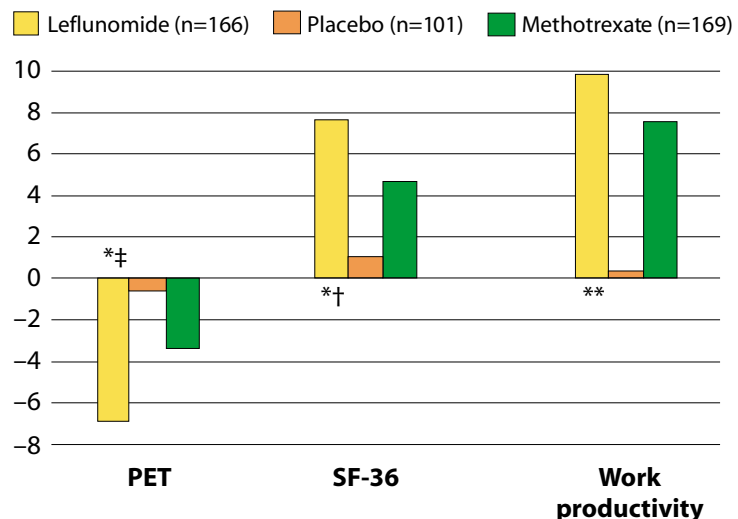
The introduction of the newer agents initially led many rheumatologists to switch patients away from methotrexate, yet increasingly they are realizing that patients do better on methotrexate in combination with leflunomide or one of the anti-TNF agents, perhaps a benefit of synergistic effects. [See Dr. Kremer's discussion on the synergistic potential of the leflunomide-methotrexate combination, page 10.] More and more, rheumatologists are using methotrexate in combination as first-line therapy. For patients with refractory disease, methotrexate and leflunomide may be the combination of choice.

**FIGURE 2 Functional activities and health-related quality-of-life parameters in active RA**



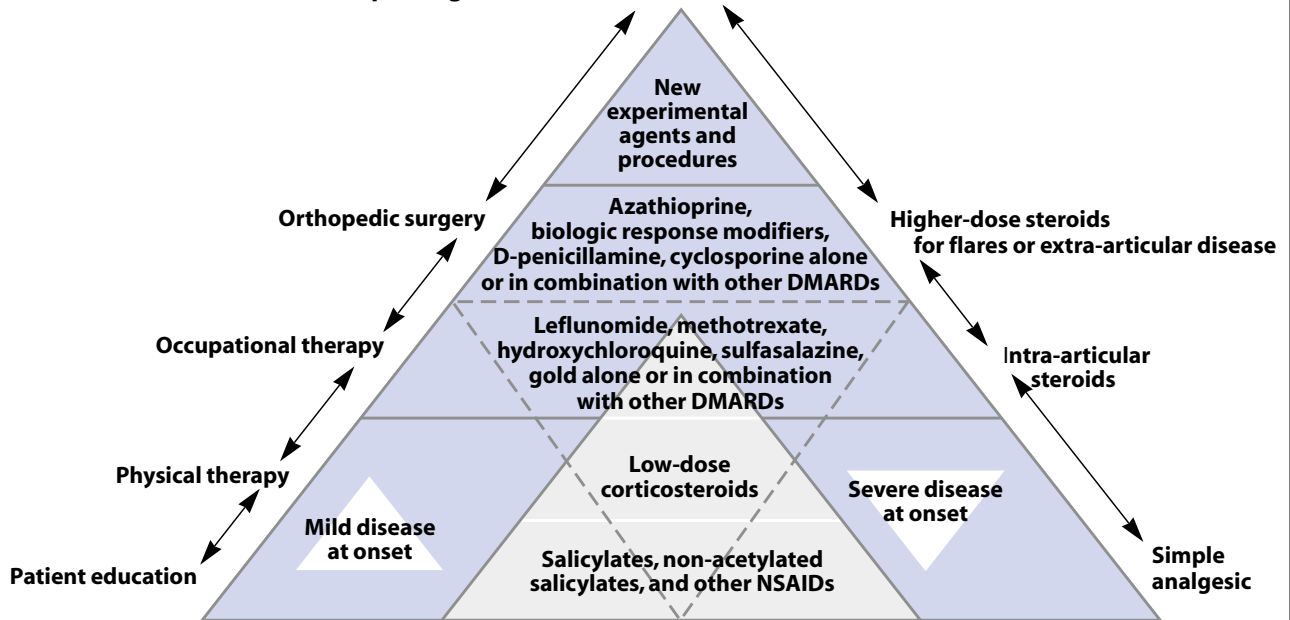
\* $P \leq .0001$  vs placebo; † $P \leq .01$  leflunomide vs methotrexate. Negative values indicate improvement. MHAQ = Modified Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire (disability index).

**FIGURE 3 Functional activities and health-related quality-of-life parameters in active RA (continued)**



\* $P \leq .0001$  leflunomide vs placebo; † $P \leq .01$  leflunomide vs methotrexate; ‡ $P \leq .001$  leflunomide vs methotrexate; \*\* $P \leq .01$  leflunomide vs placebo. Negative values for PET indicate improvement; positive values for SF-36 and work productivity indicate improvement. PET = Problem Elicitation Technique (weighted top 5 scores); SF-36 = Medical Outcomes Survey Short Form 36 (physical component).

**FIGURE 4 The new treatment paradigm**



SOURCE: WEAVER AL, 1998.

There has yet to be a comparative study of methotrexate and leflunomide vs methotrexate plus either infliximab or etanercept, and there are no clear data on which combination is better. From a strict cost perspective, the difference between leflunomide and the anti-TNF therapies argues for using leflunomide in combination with methotrexate first. Leflunomide costs approximately \$300 a month and methotrexate about \$75 per month, as opposed to etanercept, which is over \$1,000 per month, and infliximab, with a monthly cost that can range from \$1,000 to \$2,000 or more (infliximab is dosed by weight). Infliximab is often prescribed for Medicare patients, however, because they generally do not have secondary insurance that covers medications; 80 percent of the cost of infliximab is covered by Medicare, and these patients often have additional coverage for the other 20 percent. The patient's insurance coverage makes a difference in private practice.

For many patients, leflunomide and the anti-TNF agents offer improved gastrointestinal tolerability and reduced renal insufficiency compared to the older agents. The TNF inhibitors also provide a fast response that is gratifying for both patient and physician. Nevertheless, it is important to look at the long term, what happens at two years with respect to costs, which can be exacerbated by the potential need to increase dosages. Partly due to cost considerations, for many patients the leflunomide-methotrexate combination is an excellent choice.

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# Combination DMARD Therapy For Rheumatoid Arthritis

JOEL M. KREMER, M.D.

**T**o understand the place of the new agents in our armamentarium against rheumatoid arthritis (RA), we first must examine the recent history of therapy for patients with this disease. During the 1980s, the treatment of RA was traditionally depicted



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(DMARDs) available then. Early fears about the side effects of methotrexate were overcome, and the ability to monitor and recognize liver and lung toxicity was developed.

In addition, RA has been identified as a source of increased mortality. Patients die prematurely, because the burden of inflammation/immunologic activity is associated with comorbidities, including atherosclerosis, premature coronary disease, premature death from malignancies, and infections.

To measure disease activity, rheumatologists count swollen joints and arrange them in composite scores. The focus, however, should be on damage, disability, and death, along with quality-of-life issues.

## Rebuilding the therapeutic pyramid

Using the traditional therapeutic pyramid — which was first described more than 40 years ago — and subjecting patients to sequential monotherapy means that by the time an effective drug is used, radiographic erosion, deformity, and disability may be present. With growing recognition of the rapid progression of this disease, the traditional pyramid is no longer seen to be sufficient.

During the 1980s, the side effects of drugs were regarded as more severe than the so-called side effects of RA. At that time, early RA was thought to progress slowly. In fact, the 1985 edition of William N. Kelly's *Textbook of Rheumatology*,<sup>1</sup> a highly regarded book, described RA as primarily a benign disease with which most patients do well. Sixteen years later, those beliefs have been abandoned.

Today, the effects of RA are recognized to be more severe than the adverse effects associated with the pharmacological agents being used to treat patients. Moreover, because disease progression is rapid in the first few years, if treatment is delayed, the need for aggressive therapy becomes obvious, but only after damage begins. Clearly, this is too late. RA is not a benign disease, and no single agent is capable of halting its progression.

The new treatment paradigm is combination therapy. The idea has been around for a long time, but unlike 1990, when only two or three of 336 combination studies demonstrated efficacy of the agents then available,<sup>2</sup> the new agents offer different possibilities and expanded pharmacotherapeutic potential when used in combination with methotrexate.

The ideal combination would provide complementary biologic effects: accessible, nonadditive toxicity; maximally effective dosage; an acceptable dosing schedule and rate of administration; rapid onset of action; and cost-effectiveness.

The combination of cyclosporine and methotrexate

serves as an example of therapy that falls short of the ideal. Cyclosporine affects the renal clearance of methotrexate to the extent that when these drugs are used together, methotrexate's area under the curve increases by 29 percent. This creates the potential for increased toxicity. This is not to say that these two drugs should not be combined, but that practitioners using these two agents need to use extreme care in monitoring their patients on this therapeutic regimen. Additionally, cyclosporine cannot be used at its maximally effective dose. For suppression of immunity in transplant patients, it is used at the rate of 10 mg/kg, whereas for the treatment of RA, only 2 mg/kg or 3 mg/kg is used.

### Cornerstone of combination therapy

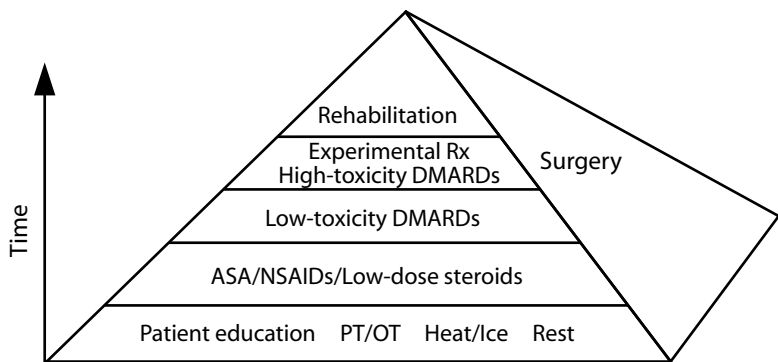
Methotrexate is the cornerstone of modern combination therapy — and it probably will be for at least the next five years — but it presents certain challenges, which fall into three groups, that are addressed in the following questions.

- How much improvement will result from adding a new agent to methotrexate?
- What are the risks from combining a new agent with methotrexate?
- Why is the combination of this new agent and methotrexate being used, as opposed to another combination?

The combination of leflunomide and methotrexate is among the new combinations being used to treat RA. Leflunomide — the only one of the new drugs that is administered orally — is a prodrug that is converted to an active metabolite, A77 1726, which inhibits the clonal expansion of T-cells. This is accomplished by inhibiting the enzyme dihydroorotate dehydrogenase (DHODH), which is a key enzyme in the de novo synthesis of uridine monophosphate (UMP). An eightfold increase in the precursor of this pyrimidine nucleotide\* is necessary for the clonal expansion of lymphocytes, but leflunomide limits the increase to only twofold, by salvage pathways within the cell. Leflunomide's primary mechanism of action is shown in Figure 2.

In vitro studies have shown that methotrexate inhibits the most proximal step in the metabolic pathway for purine nucleotide biosynthesis, the conversion of phosphoribosylpyrophosphate (PRPP). When that happens, the PRPP is shunted into pyrimidine pathways, with the net result being the upregulation of UMP — the synthesis

**FIGURE 1 The outmoded therapeutic pyramid for RA**



ASA = Acetylsalicylic Acid; PT = Physical Therapy; OT = Occupational Therapy

SOURCE: Gardner GC. Rheumatoid arthritis: past, present, and future.

of which is specifically inhibited by leflunomide.

In other words, a biochemical effect of methotrexate is to increase UMP, but that increase can be blocked by the addition of leflunomide. This would clearly be a synergistic interaction of the two drugs. This in vitro observation needs to be expanded to prove true biochemical synergy. If that can be demonstrated, it would be the first case of true biochemical synergy ever reported in RA treatment.

### Combination therapy with methotrexate and leflunomide

Leflunomide has the potential for hepatotoxicity, which initially raised the question of whether it could be used successfully with methotrexate. Leflunomide undergoes continuous enterohepatic recirculation. It is virtually 100 percent protein-bound, which means that if a patient experiences toxicity, the oral resin binder cholestyramine can be administered to clear it from the system within 7 to 10 days.

In an open study of 30 patients receiving leflunomide and methotrexate, significant improvement was observed in five clinical parameters. This study served as the basis of a double-blind, placebo-controlled trial of 24 weeks in which 263 patients with active RA and an inadequate long-term response to methotrexate received, after a loading dose of leflunomide or placebo, either leflunomide 10 mg q.d. plus methotrexate (n = 130) or placebo plus methotrexate (n = 133) for eight weeks, at which point investigators had the option of doubling the dose

\* In addition to serving as the building blocks of the nucleic acids RNA and DNA, nucleotides are involved in regulatory and signaling mechanisms. Nucleotides consist of a sugar (ribose [found in RNA] or deoxyribose [found in DNA]), one or more phosphate groups, and a base. There are two kinds of nucleotide bases: pyrimidines and purines. The purine bases are adenine and guanine; the pyrimidines are cytosine, thymine (found in DNA but not RNA), and uracil (found in RNA but not DNA).

to 20 mg daily. By the end of the study, two-thirds of the patients had gone to 20 mg, whereas one-third had achieved an adequate clinical response while remaining on 10 mg. The ACR-20 response rate for patients receiving leflunomide plus methotrexate was 51.5 percent, versus 23.3 percent among patients receiving methotrexate plus placebo. The Health Assessment Questionnaire showed a significant improvement in the ability of patients receiving leflunomide plus methotrexate to perform daily activities, and the Short Form 36 showed that these patients improved in the physical component.

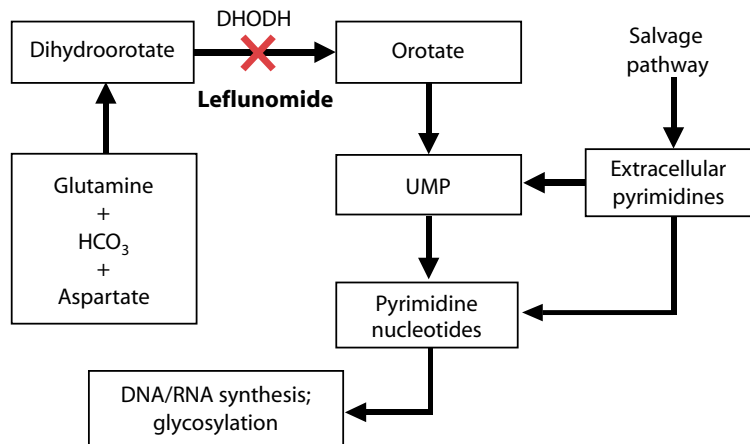
Diarrhea was experienced by 25 percent of the patients receiving leflunomide plus methotrexate, the same rate seen in leflunomide monotherapy. This side effect is fairly easily treated with antidiarrheal agents and usually is not a reason to discontinue therapy. Infectious complications necessitating withdrawal from the study were no more common in the combination group than in the placebo group.

In this study, the algorithm for liver function tests (LFTs) was elaborate and fairly rigid. If transaminase enzymes were elevated to two to five times the upper limit of normal, the results could be confirmed within 72 hours. If they were confirmed, the medication was decreased. Only one dosage lowering was allowed during this study. The tests were then repeated in one or two weeks. If they remained elevated (greater than three times normal), the medication had to be discontinued. If they were not elevated at this range, the tests were repeated at the next visit, and if they then were greater than twice normal, the patient was removed from the study. Increases in LFTs of >3 times upper limits of normal during the 24-week treatment period of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for leflunomide and methotrexate were 3.8 percent and 1.5 percent respectively, compared to 0.89 on both ALT and AST for placebo and methotrexate.<sup>3</sup>

In the open phase of a combination study, I adjust the dosage of either methotrexate or leflunomide to maintain the liver function tests in the normal range, in accordance with the guidelines for methotrexate that we published in 1994. If you maintain LFTs and serum albumin in the normal range over a period of years, a biopsy of the liver demonstrates improvement, because baseline is often abnormal in these patients due to the use of steroids and NSAIDs. Provided the transaminases stay in the normal range, the combination of these two drugs does not appear to adversely affect the liver.

The guidelines recommend monitoring liver enzymes every four to eight weeks. For the combination of

**FIGURE 2 Leflunomide primary mechanism of action**



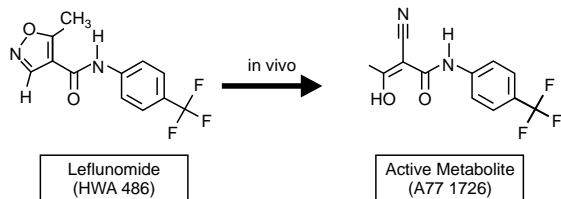
methotrexate and leflunomide, I have recommended monthly LFTs for about six months — and that an elevation in transaminases is not to be ignored. If transaminases are elevated at one to two months, it becomes necessary to adjust the dosage of either methotrexate or leflunomide.

### Anti-TNF therapy

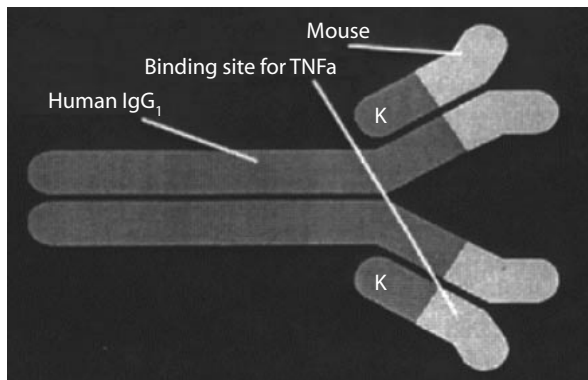
Tumor necrosis factor (TNF) inhibitors such as etanercept and infliximab are also effective for treating RA. Produced primarily by macrophages and monocytes, TNF is a so-called proximal cytokine that drives many of the other more distal disease processes that can contribute to the severity of RA. Ordinarily, TNF interacts with two types of receptors, p55 and p75, which are found on the cell surface but also exist as soluble forms. A fusion protein, etanercept, had been created by attaching two recombinant p75 receptors to the Fc portion of human IgG1. Patients inject etanercept subcutaneously twice weekly. (See Figure 3.)

A six-month, double-blind, placebo-controlled trial recently showed that adding etanercept to methotrexate results in significantly greater clinical benefit than methotrexate alone in patients with persistently active RA, despite long-term treatment with methotrexate.<sup>4</sup> After 24 weeks, patients receiving the combination showed improvement in ACR criteria versus patients receiving methotrexate plus placebo. (See Table 1.)

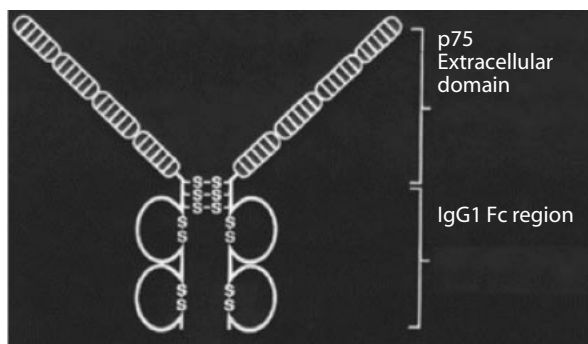
These results indicate that, as with leflunomide, patients who are incapable of further improvement on methotrexate alone are nevertheless able to receive additional therapeutic benefit with combination therapy. Two-year follow-up data show that the results are sustained. In addition, the mean dose of prednisone decreases, which is associated with less morbidity and mortality. The mean weekly dosage of methotrexate also diminishes but does not disappear. Although 28 percent



**FIGURE 3a Structure of leflunomide and its active metabolite**



**FIGURE 3b Depiction of the structure of infliximab, a chimeric monoclonal antibody to TNF (darker areas represent human component, lighter areas represent mouse component)**



**FIGURE 3c Depiction of the structure of etanercept, two recombinant p75 TNF receptors linked to the Fc portion of the human IgG molecule**

of patients were able to stop methotrexate, 72 percent could not discontinue it. As an attempt is made to taper and discontinue methotrexate, at some point the patient reports not feeling as well, hence the need for combination therapy.

The chimeric (mouse and human) antibody against TNF, infliximab, has been used in combination with methotrexate to treat RA. Infliximab is given intravenously in the office. In a 54-week, double-blind study,

two different doses of infliximab were studied: 3 mg/kg and 10 mg/kg, administered every four weeks or every eight weeks.<sup>5</sup> Using a higher dose at the greater frequency did not produce a significantly different effect than did the lower dose at the less-frequent interval. This led the FDA to initially recommend using 3 mg/kg every eight weeks. In January, however, the FDA approved using the higher dosage more frequently.

This decision has important implications with respect to cost. A 100-mg vial of infliximab costs approximately \$500 wholesale and \$620 retail. If a patient requires three vials for dosing at the 3 mg/kg rate, the cost will be about \$1,800 retail per treatment. If that level of intervention is insufficient, increasing the dose to 6 mg/kg or 10 mg/kg will cause costs to double or triple. Thus, the cost of one year of infliximab therapy can be between \$8,000 and \$22,000. By comparison, one year of etanercept therapy can cost between \$14,500 and \$20,000; leflunomide (10 or 20 mg/day), about \$3,400; and methotrexate (15 mg/wk), about \$650 to \$900 (prices for all products vary from region to region).

Regional prices of the leading DMARDs and recommendations for their rational use are presented in a recent article in *Annals of Internal Medicine*.<sup>6</sup> Most patients with RA should receive methotrexate unless it is contraindicated. On the basis of the clinical response rate and overall toxicity reported so far, neither leflunomide, infliximab, nor etanercept is better than the others when used in combination with methotrexate. This argues for using the least-expensive drug, leflunomide, first. If the combination of methotrexate and leflunomide fails, moving to etanercept or infliximab will depend on the patient's insurance coverage or preference.

Currently, I am treating about 40 patients with the methotrexate-leflunomide combination and another 40 with the methotrexate-etanercept combination. I have used each combination for four years, and I cannot distinguish between them in terms of their effects. The availability of different combinations is necessary because some patients do not respond to methotrexate-leflunomide and others do not respond to methotrexate-etanercept. Thus far, no randomized studies have compared these particular combinations.

**TABLE 1 Percentage of patients meeting ACR criteria after 24 weeks**

	Etanercept + methotrexate (n = 59)	Placebo + methotrexate (n = 30)
ACR 20	71%	27%
ACR 50	39%	3%
ACR 70	15%	0%

Some rheumatologists perceive the TNF antagonists as providing a larger initial effect than the other DMARDs. Although the TNF antagonists produce an almost-euphoric early effect, it tends to diminish over time. In terms of actual outcomes, the TNF agents appear to be the equivalent of the methotrexate-leflunomide combination, although there are no studies to demonstrate that they are — or are not — equivalent.

In the near future, clinicians will be able to consider other novel agents for treating RA. Another TNF inhibitor being developed is D2E7, a so-called fully humanized monoclonal antibody that is in Phase III studies. Additionally, FDA approval is expected within the next year for anakinra, an interleukin-1 receptor antagonist (IL-1ra) given subcutaneously on a daily basis.

### PCP or rheumatologist?

The question of who should manage patients with RA is critical. The complexity of the issues associated not only with methotrexate but also with adding other agents makes it clear that perhaps 80 percent of patients with RA should not be managed by primary care physicians. Most primary care physicians lack the experience and expertise needed to use these drugs, make appropriate treatment decisions, and be familiar with the complexities of management, which is unfair to the patient. Just as the management of a solid tumor, leukemia, or severe, refractory, poorly controlled hypertension is unlikely to be entrusted to a primary care doctor, so should the management of most cases of RA be reserved for specialists.

Perhaps 25 percent of patients have RA that is sufficiently benign not to necessitate the intervention of a rheumatologist. These patients can be maintained with NSAIDs and hydroxychloroquine, or NSAIDs and sulfasalazine. Such patients are easily monitored by a primary care physician, possibly with periodic visits to a rheumatologist. Once methotrexate has become part of the regimen, however, — and at least three fourths of patients will require methotrexate — then a level of sophistication is needed that is unlikely to be found in a primary care physician.

There is a shortage of rheumatologists, and it can take two or three months for a patient to get an appointment. Nevertheless, rheumatologists are highly likely to respond to a request from a primary care physician to see a patient with RA, which rheumatologists regard as being different from back pain or fibromyalgia. Rheumatologists are motivated to see RA patients early. The onus is on the primary care physician. If the primary care physician calls the rheumatologist, the patient will be seen.

### Conclusion

Until recently, no effective treatment was available for patients with persistent synovitis. Now, however, evidence-based medicine demonstrates that combination therapy enables negative outcomes to be avoided. The argument that it is not cost-effective to add extra agents to avoid lifelong disability and deformity is suspect on ethical, as well as moral, grounds. It is not ethical or moral to withhold effective therapies that provide significantly enhanced therapeutic value. No physician should accept mere improvement or stability in the face of a clinically meaningful persistent disease state. Combination therapy can be used successfully to avoid the long-term morbidities and mortalities that accompany RA.

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# Economic and Quality-of-Life Impact Of Rheumatoid Arthritis

JOSEPH J. DOYLE, R.PH., M.B.A.

**R**heumatoid arthritis (RA) is a chronic, systemic inflammatory disorder of the joints that is associated with progressive decline in physical function and disability. RA affects approximately 0.5 to 1 percent of the worldwide population, with the highest incidence occurring in females between ages 30 and 50.<sup>1,2</sup> The prevalence of this debilitating disease increases with age, and life expectancy is severely affected by RA, with survival shortened by 3 to 18 years.<sup>3</sup>



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relative to improvements in physical function, as measured by the Health Assessment Questionnaire (HAQ), and relative to health-related quality of life (HRQoL), as measured by Short Form 36 (SF-36). Important data are emerging from clinical trials with the newer disease-modifying antirheumatic drugs (DMARDs) signifying the potential to radically enhance millions of affected lives. In evaluating these data, goals of treatment and patient-reported outcomes can be clearly identified using these two measuring tools. These instruments have been adopted by both the Outcomes Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the U.S. Food

The data further reveal that male life expectancy is shortened by seven years, and female life expectancy is shortened by three years.<sup>4</sup> In spite of such sobering statistics, new treatment options are yielding measurable improvements with respect to physical function and quality of life, and further, substantial economic improvements are associated with these changes.

Recent advances in pharmacotherapeutic approaches to treatment of RA can be clearly demonstrated

and Drug Administration to determine the extent of patient improvement in clinical trials. The HAQ was administered in all three pivotal trials of leflunomide, while SF-36 was administered in one of the three trials (US301). Leflunomide has been found to provide significant improvements in physical function and HRQoL.

## Costs of RA

In 1998, the total national cost of RA was estimated at \$14 billion.<sup>5</sup> The treatment of RA patients thus has major economic consequences within the health care system. Moreover, the above-cited figure may well be an underestimate due to the challenges associated with measuring the cost of disability, especially with the use of claims data. Additionally, the prevalence of this disease continually grows as America ages.

The data presented by the American College of Rheumatology (ACR) Ad Hoc Committee on Clinician Guidelines (1996) in "Guidelines for the Management of Rheumatoid Arthritis" reveal that more than 9 million physician visits per year are traceable to RA, with over 250,000 hospitalizations annually.<sup>6</sup> The direct costs of treating an RA patient are three times more than those costs associated with treating a patient who does not have this disease.<sup>2</sup>

A comparison of the lifetime direct and indirect costs of RA with those associated with other diseases clearly demonstrates the high cost of this disease. RA has lifetime costs that are approximately 82 percent of those of coronary artery disease, 68 percent of the cost of strokes, and 49 percent of the cost of cancer. Further, RA costs are five times greater than the lifetime costs associated with motor vehicle accidents.<sup>2</sup>

## Social impact of RA

Among RA patients, the rate of depression has been estimated to be between 14 and 43 percent, significantly higher than that seen in the general population. The divorce rate of 70 percent among patients with RA is also significantly higher, and substantial income losses are associated with this disease, estimated at 50 percent for men and 63 percent for women. Nearly one-third to two-thirds of these patients have a reduced work capacity.<sup>2</sup>

Disability has a major effect on day-to-day activities, and on HRQoL. Moreover, serious disability can occur early in the disease, and joint destruction can actually be more pronounced in the first years of this illness, making it crucial to initiate patient treatment as quickly as possible.<sup>7</sup> It has been estimated that 50 percent of these patients cannot function in their job within 10 years of disease onset.<sup>8</sup>

### Goals of therapy

A major goal in the treatment of RA is to improve signs and symptoms. The reduction of these symptoms can be clinically measured using the ACR response criteria. An ACR-20 response is defined as a 20 percent or greater improvement from baseline in 5 of the following 7 criteria: tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HAQ, patient global assessment, physician global assessment, and pain-intensity assessment.

Another goal is to reduce radiographic progression, which is slowing the rate of joint damage visible on X-ray. Additionally, treatment aims include the prevention of disability and the maintenance of physical function, to maximize patient HRQoL (Table 1).

The traditional drug therapy hierarchy, i.e., the old pyramid (page 11), is no longer seen as adequate in RA treatment, because RA is an extremely progressive and debilitating disease. According to the ACR Guidelines for Management of RA, initiation of DMARD therapy should not be delayed beyond three months for any patient who has active disease in spite of adequate treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>6</sup> In addition, use of DMARDs has been associated with lower long-term disability.<sup>7</sup>

### Clinical trial assessments: patient-reported outcomes

**Health Assessment Questionnaire.** The HAQ is a valid and widely accepted instrument that allows physicians and caregivers to track disease progression and monitor the effects of drug therapy. When using DMARDs, changes in the disease process over time can be readily seen using the HAQ. Though often perceived as a disease-specific questionnaire because of its use in RA trials, it has been used in many trials in which physical function is measured.

**TABLE 1 Treatment goals of RA therapy**

- Improvement in signs and symptoms
- Reduction in radiographic progression
- Prevention of disability
  - Maintain physical function
  - Maximize HRQoL

OMERACT, a working group that provides recommendations to the FDA and to the pharmaceutical industry on the design of clinical trials, recommends the use of both the HAQ and SF-36 in clinical trials. In addition, the FDA recommends that all RA clinical trials contain the HAQ as a component of the ACR response criteria. The HAQ is self-administered and consists of 20 questions, comprising eight domains measuring physical function on the following subscales: dressing, arising, eating, reaching, gripping, walking, activities, and hygiene. The HAQ is scored on a 0 to 3 basis, with 3 being the worst possible score and 0 being the best possible score.

In addition, the HAQ is a highly useful tool for correlating level of disability to cost, by measuring costs per unit of increase in HAQ score. As to its clinical importance, the HAQ allows the physician to determine for patients the level of improvement in physical function and the impact of drug therapy on physical function. The HAQ can also be summarized as one score, the Disability Index, commonly referred to as the HAQ DI. These domain scores are adjusted by the patient's use of aids and devices.

It has been proven that the HAQ is more predictive of RA disease progression than any other measurement of the ACR response criteria.<sup>9</sup> HAQ is the best measure to predict work disability, costs, functional disability, joint replacement, and premature mortality.<sup>9,10</sup> It has been estimated that an increase of one unit in the HAQ DI, over the first two years of disease, results in a 90 percent greater disability over the next three years.<sup>11</sup> This estimation reconfirms that the HAQ is a good predictor of future disability for patients with RA.

Literature from 1993 to 1998 states that standard care with NSAIDs and DMARDs still results in progression of RA. Yet the DMARD trials show that disease progression can be slowed or stabilized. Overall, looking at the progression of disability with standard care, there is an increase in the number of points per year, demonstrating that the patient's disability was getting worse. Whereas in 2000, a comparison reveals that HAQ DI scores are stabilizing,<sup>12,13</sup> which may be attributable to the emergence of the newer agents — leflunomide, and the biologics (Table 2).

In a review by Scott et al, disease progression and disability increase with disease duration.<sup>14</sup> The ARAMIS data on the effect of individual agents demonstrates, in a population of 2,888 patients, that the use of DMARDs improves physical functioning, but with the use of corticosteroids and NSAIDs, disability increases as measured by the HAQ DI scores.<sup>7</sup>

### Economic impact

A cost comparison of RA and osteoarthritis (OA) conducted by Lanes et al (1997) revealed that the total cost

for RA was much less than it was for OA.<sup>15</sup> With RA, the major cost driver was prescriptions, whereas the major cost driver with OA was hospitalizations. Interestingly, the cost in the managed care setting was relatively low for RA, owing to the rarity of this disease. The cost of OA was higher due to its greater prevalence in the population. Costs of hospital care and ambulatory care decrease after initiation of DMARD therapy. (See Table 3.) These results may be different since the introduction and use of the COX-2 inhibitors in OA and the use of biologics in RA.

**Health-related quality of life: Short Form-36.** SF-36 is one of the most commonly used measures of HRQoL. This questionnaire is self-administered and contains eight domains: physical function, mental health, role emotional, social function, vitality, general health, bodily pain, and role physical. These domains are scored on a scale of 0 to 100 — 100 being the best possible score, 0 being the worst possible score. There are two summary scores for the SF-36, the physical component summary (PCS) score and the mental component summary (MCS) score.

There is some overlap between the two questionnaires, that is, to some extent they measure the same aspect of the patient's HRQoL. To a patient with RA, physical function is central to quality of life (Figure 1).

When calculating the score for these questionnaires, it is important to determine the minimum clinically important difference (MCID). This difference reflects the

degree of improvement in the various outcomes measures that are important and meaningful to the patient. An individual score can be derived on the HAQ and on the SF-36, but such tabulations do not hold meaning for the patient unless one calculates the change in these scores over time.

The literature cited in Table 4 states that the MCID is -0.22.<sup>16,17</sup> This change in score is used to measure how well patients are doing. For the SF-36, the literature states that the MCID is a 5- to 10-point change. For the PCS and MCS scores, the MCID is 2.5 to 5.0, based on the literature. OMERACT uses a change of 33 to 36 percent across all assessments as the MCID.

### Leflunomide in RA

In large, Phase III, randomized, controlled trials, leflunomide provided significantly higher ACR-20 responder rates when compared to placebo (52 percent vs 26 percent;  $P < .001$ ).<sup>18-21</sup>

The efficacy of leflunomide has been shown to be equivalent to methotrexate and sulfasalazine.<sup>18-21</sup> Leflunomide has also been shown to provide significant improvements in physical function and HRQoL when compared to placebo and active comparators (metho-

**TABLE 2 Progression of HAQ DI index with standard care**

1993	Gardiner	0.03 points/year <sup>1</sup>
1996	Fries	0.017 points/year <sup>2</sup>
1998	Munro	0.119 points/year <sup>3</sup>
2000	Uhlig	Stabilized <sup>4</sup>
2000	Young	Stabilized <sup>5</sup>

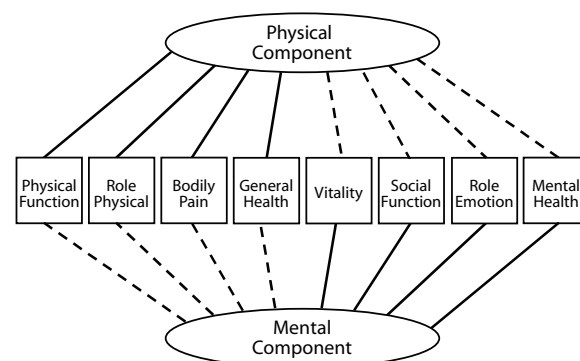
1. Gardiner, et al. *Br J Rheumatol*. 1993;32:724-728.
2. Fries, et al. *Arthritis Rheum*. 1996;39:616-622.
3. Munro, et al. *Ann Rheum Dis*. 1998;57:88-89.
4. Uhlig, et al. *Rheumatology [Oxford]*. 2000;39:732-741.
5. Young, et al. *Rheumatology [Oxford]*. 2000;39:603-611.

**TABLE 3 Cost of care in managed care setting<sup>1</sup>**

	RA		OA	
	\$	%	\$	%
Cost, \$ per patient/year	2,162		543	
Total cost	703,053	100	4,728,425	100
Rx	436,400	62	1,509,637	32
Physician visits	150,938	21	1,047,898	22
Hospital visits	115,674	16	2,170,890	46

1. Lanes SF et al. *Arthritis Rheum*. 1997;40:1475-1481

**FIGURE 1 SF-36 Two-component model**



**TABLE 4 Minimum clinically important differences (MCID)**

	Score range	Direction of scoring	MCID	
			Literature	OMERACT
HAQ DI <sup>1-4</sup>	0-3	-	0.22	33-36%
SF-36 <sup>2,5-7</sup>	0-100	+	5-10 points	33-36%
PCS/MCS	Mean 50±10	+	2.5-5 points	33-36%

1. Guzman, et al. *Arthritis Rheum*. 1996;39:5208.
2. Kosinski, et al. *Arthritis Rheum*. 2000;43:1478-1487.
3. Redelmeier, et al. *Arch Intern Med*. 1993;153:1337-1342.
4. Wells, et al. *J Rheumatol*. 1993;20:557-560.
5. Kosinski, et al. *Arthritis Rheum*. 2000;43:5140.
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7. Thumboo, et al. *J Rheumatol*. 1999;26:97-102.

trexate and sulfasalazine), as measured by HAQ DI and SF-36.<sup>18–21</sup> Furthermore, the efficacy of leflunomide, as seen at 6 and 12 months, is maintained throughout two years of treatment with no long-term safety issues.<sup>21–23</sup>

**Summary.** Although RA is a disabling disease with increased mortality and an unknown cure, early treatment with DMARD therapy improves patient outcomes. The economic and humanistic effects of this disease are substantial, with patients becoming increasingly disabled from RA. It is extremely encouraging to the rheumatology community that leflunomide provides significant and sustained improvements in clinical signs and symptoms, and offers practicing physicians an additional option in the treatment of RA. It improves and maintains physical function and HRQoL. Leflunomide's effects were consistent across three studies over two years of treatment. It has been demonstrated to improve physical function as measured by the HAQ DI, and HRQoL as indicated by the SF-36 data, two instruments held up as the gold standard for the assessment of patient outcomes in RA clinical trials.

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## DISCUSSION

# Treatment Algorithm: Managing Rheumatoid Arthritis

### Attendees

David C. Calabrese, R.Ph., M.P.H.

Eric Cannon, Pharm.D.

Jeffrey J. Casberg, R.Ph., M.S.

Imelda C. Coleman, Pharm.D.

Mauro J. Florentine, R.Ph.

Mark R. Harris

Robert Konop, Pharm.D.

Terry K. Maves, R.Ph.

Libby Meske, R.Ph.

Burton I. Orland, R.Ph.

Yvonne Southwell, R.Ph.

David M. Yoder, Pharm.D., M.B.A.

*After hearing the experts' presentations, the participants engaged in a wide-ranging discussion in which they talked about how to apply the information about new agents for the treatment of rheumatoid arthritis to their health plans. Mark Harris moderated the discussion.*

**BURTON ORLAND, R.Ph.:** How do you influence or change physicians' prescribing patterns? The number of prescriptions for etanercept versus leflunomide is currently two to one. The pharmacoeconomic data were good and so were the speakers, but how do we bring it back home to change prescribing patterns?

**JEFFREY CASBERG, R.Ph., M.S.:** I was seeking confirmation from these specialists that leflunomide is a good choice as first-line therapy. Both specialists confirmed that. I'll have to run it by some of the rheumatologists in my area to see if they agree. Hopefully they do.

**TERRY MAVES, R.Ph.:** It is interesting that some of the thought leaders are making clinical decisions based on what insurance somebody has, or the supply of a drug.

**MARK HARRIS:** Have you found SF-36 measures helpful in trying to differentiate product efficacy?

**DAVID CALABRESE, R.Ph., M.P.H.:** They are important to a degree in differentiating one product from another. In this particular instance, however, do we need to know that the SF-36 indicates that leflunomide improves quality of life, when we know there is a clinical improvement when leflunomide is added? It seems to me that we can make the leap of faith that if there's a clinical improvement, particularly in a disease that's

as symptomatic as rheumatoid arthritis, then the patient is going to get the benefit of improved quality of life. So my point is, when we're making formulary decisions, I don't know how much additional value SF-36 data would add. The fact is, we've already accepted that there is a definite clinical role for drugs like leflunomide and the injectable tumor necrosis factor inhibitors.

**HARRIS:** When you're making comparisons for P&T, is it important to know measures other than clinical measures, where all the products may show improvement in clinical efficacy?

**CALABRESE:** When you can show that leflunomide is better outside the clinical parameters, versus etanercept or infliximab, that may be useful.

**IMELDA COLEMAN, Pharm.D.:** What may seem not as important at two years, might make a big difference if you follow it through for 10 or 15 years. You're not going to have 15-year data, if you're not collecting two- and three-year data. We may not be seeing differences at this point, but if we don't take a look at this now, we won't know what the differences are down the road.

**YVONNE SOUTHWELL, R.Ph.:** Quality-of-life data certainly is instrumental in some of the formulary decisions we make. One component is quality of life, but that will not be the only consideration in the decision process.

**CALABRESE:** The biggest obstacle with physicians and the combination of methotrexate and leflunomide is the LFT issues. They're scared to be using these drugs in combination. They don't have enough experience with it. In many instances, our RA patients are those with multiple comorbidities, who may be on a statin, who may be on glitazone, where there are already LFT con-

cerns, and now we're talking about compounding those concerns by adding two drugs, both of which have added potential for liver toxicity. That's going to be the biggest challenge, compared to a combination of methotrexate and etanercept. That's a hurdle that you're going to have to overcome.

**ERIC CANNON, Pharm.D.:** An issue for me is that we've looked at the new TNF products and tried to place them in appropriate areas. We do have guidelines, asking that patients be tried on other DMARDs and leflunomide. Part of the problem, though, is we have many patients who already have failed four or five DMARDs. To me, to go back to that physician where I've got somebody who has failed sulfasalazine, hydroxychloroquine, and methotrexate, and to say, "I want you to use methotrexate in combination with something else, before you go to the injectable TNF inhibitors," is almost pushing against the next logical step. So it's difficult going forward. With newly diagnosed RA patients, it definitely makes sense to use the methotrexate-leflunomide combination, before moving to an injectable TNF inhibitor, but we also have many RA patients who've been on five or six DMARDs.

**HARRIS:** Virtually all of you said that you anticipated that you were going to have to get involved in more pharmacy management of injectable products.

**ORLAND:** I just think the cost of injectables is getting out of hand, and managed care pays the bill.



IMELDA COLEMAN, PHARM.D., LEFT; LIBBY MESKE, R.PH., RIGHT.

**MAVES:** Oncology has a huge influence on this.

**HARRIS:** In my past experience of working with injectable products, the physicians were upset with having to include the injectables in their global capitation rate. Have any of you gotten pushback from your physicians, as you're trying to get them to include these

higher priced products in their reimbursement rate?

**HARRIS:** And that's increasing, right?

**LIBBY MESKE, R.Ph.:** Many physicians get upset with having to include the injectables in their global capitation rate, due to the higher prices of these products. Some of our physicians are actually carving it out of their contracts and make it the plan's risk, instead of their own risk. In looking at the 2002 medical group and physician contracts, we're seeing that increase to a great extent.

**CALABRESE:** It varies from health plan to health plan, as to whether they include this in the capitation rate or carve it out. Our goal has been to strive for carve-outs, because unfortunately, when we're negotiating a capitation rate, it's not always adjusted for case mix and severity. Moreover, because we're considered a center of excellence in the management of certain patient populations, such as those being treated for infertility, multiple sclerosis, or cancer, we would be placed at a major disadvantage if we did not carve it out, in trying to manage that risk. So we strive to carve these particular categories out of our risk.

**HARRIS:** As was mentioned, there's now a lot of these carve-outs for injectables management. How many of you are looking at those types of companies to work with you on managing physicians' injectables?

**COLEMAN:** These newer, very expensive products affect our doctors' capitation tremendously. Proposals to develop an injectable program were met with mixed feelings. As a business, our clinics have been able to profit from lower-cost injectables. They want to keep those profitable injections within their control and return the most costly ones to the plan.

**MESKE:** We are starting to look at that as well. Beginning July 1, PacifiCare of Colorado is moving all the injectable prior authorizations, and even the distribution of the injectables, to Injectable Solutions, of California. So not only will the members be able to get their injectables through this company, but the physicians will contact Injectable Solutions for prior authorization and also to get the injectables delivered to their office for administration in the office.

**CANNON:** A question arises with respect to the plans that have leflunomide on third tier and whether that is due to its price compared to that of methotrexate. Why wouldn't leflunomide be

a brand on the second tier, if methotrexate is the generic choice and leflunomide is the second? For us, the answer is cost. It was a \$300 per month medication, and our third-tier copay is either \$20 or \$25, so \$25 for a \$300 medication probably is not a bad deal. We're moving toward some higher copays on that third tier, and even some 50 or 60 percent coinsurances. Actu-

ally, this is one of those drugs I would expect to see moved into the second-tier position, probably within the year.

**CASBERG:** I agree. One of the things we look at, besides where to put a drug, is the cost of the product. One of my goals is to maintain a particular amount of member cost-share across the pharmacy benefit.

**COLEMAN:** One reason we put leflunomide on third tier is that we have a Medicare population, and they have a limit to their drug benefit. If they go on leflunomide, it eats up their benefit within several months, and then they suffer because they stop all their medications. They stop their leflunomide, and they stop everything else. So we felt that by putting it on third tier, they'd be more likely to stay on their medication throughout the year.

**MAVES:** When these products came out, weren't they marketed as a replacement for methotrexate? At that point, we all said, "Try methotrexate first, and if that doesn't work for you, you can try leflunomide." I think that this is a good idea, to use both of these drugs. After looking at the data that were discussed today, this seems to make more sense; leflunomide shouldn't be viewed as a replacement for methotrexate but as an additive therapy.

**CALABRESE:** In this morning's program, both presenters concurred that methotrexate is the initial step. No one is suggesting that a patient should be started on a combination of the two. Where methotrexate does not appear to be managing the progression of the disease is the point at which you would consider adding leflunomide. The current clinical data do not support a major disruption of this step protocol.

*At the conclusion of the meeting, the participants devised a treatment algorithm for RA (see page 22). They agreed that patients diagnosed with RA should be started on methotrexate and then have leflunomide or another DMARD added to their drug regimen before a TNF injectable agent is used. They also agreed that liver function testing should be encouraged — if not required — for patients receiving leflunomide. This is an edited portion of their discussion:*

**ORLAND:** If there are comorbidities with the disease, maybe it should be managed by a subspecialist.

**MAVES:** If you're serious enough to use this medication, you're going through the rheumatologist. We follow the same idea with our AIDS drugs. We prior-authorize all our AIDS drugs, and basically, the prior authorization says it has to come through an infectious disease specialist. It's hard enough for them to keep up with what's going on. That same idea holds true here.

**ORLAND:** Let's say that if patients have RA, with or with-

out comorbidities, they must go through a rheumatologist. Let the rheumatologists make the decision whether they go back to primary care.

**ROBERT KONOP, Pharm.D.:** So if they're just on nonsteroidals, they go through a rheumatologist.

**ORLAND:** Yes, they do, if they fit the criteria for a person with RA.

**SOUTHWELL:** In our environment, PCPs can prescribe methotrexate, and then when they're going to add the next agent, their patients should be encouraged to see a rheumatologist. The patient may not have to stay



YVONNE SOUTHWELL, R.PH., LEFT; DAVID CALABRESE, R.PH., M.P.H., RIGHT.

with the rheumatologist. Some PCPs can maintain patients on those agents, but for initial prescription, the patients should be referred to a rheumatologist, if possible.

**DAVID M. YODER, Pharm.D., M.B.A.:** So any time they want to go past NSAIDs and methotrexate, they have to go to a rheumatologist. Correct?

**SOUTHWELL:** That's what I would do.

**MAURO J. FLORENTINE, R.Ph.:** But I would consider methotrexate as getting active therapy.

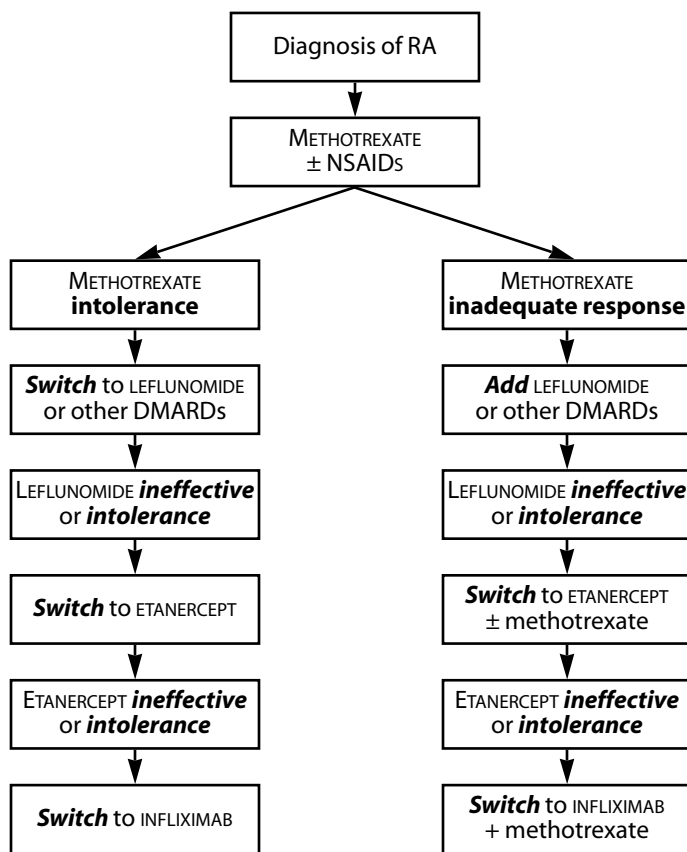
**YODER:** Different GPs are comfortable with different things.

**SOUTHWELL:** Depending on the environment, though, you're going to see PCPs prescribing NSAIDs for RA. Methotrexate could be the trigger for referral.

**FLORENTINE:** What if they're on sulfasalazine? You left out a whole population that still should probably be evaluated by a rheumatologist. They may not get methotrexate.

**YODER:** Is it our job to motivate physicians to manage costs or to manage patients? That's the key here. If we're motivating physicians to manage patients, I agree; if we're motivating physicians to manage costs, sulfasalazine is less expensive.

**COLEMAN:** Would you say if they tolerate the NSAIDs, and



**Rheumatoid arthritis treatment algorithm**

if they're doing well on methotrexate, they can continue to be seen by their primary care physicians?

**FLORENTINE:** Yes. If we're looking at a rheumatologist shortage to begin with, we don't want to refer everybody to rheumatology.

**ORLAND:** Is there a point after which a patient who has been taking methotrexate is eventually referred to a rheumatologist if there's no improvement in his condition?

**FLORENTINE:** Yes. Our primary care physicians are the gatekeepers. No one goes anywhere unless they send them there. You're going to come up with guidelines, and these guys are going to be calling the shots anyway. The second point is, no primary care physician will want to prescribe drugs other than NSAIDs — even sulfasalazine or methotrexate — without a rheumatology consult. I don't know many physicians who would start methotrexate in a patient who isn't responding to NSAIDs and physical therapy. Yes, they could, but do they want to, given the fact that they don't have the tools to do an appropriate diagnosis? I think they would send the patient to a rheumatologist, if for nothing other than an evaluation and a possible

treatment plan, and then the primary care physician can manage that treatment plan.

**SOUTHWELL:** The reality is, all our patients will not be able to see rheumatologists. A lot of rural people are lucky to be able to see a PCP.

**FLORENTINE:** I agree. Who is going to make that diagnosis? Who is going to do all the radiography?

**YODER:** You may have the rheumatologist doing the radiography, and the PCP prescribing the methotrexate. I agree that there aren't many PCPs who are going to prescribe methotrexate. They're going to want that rheumatology consult. They want the rheumatologist to say to our health plan member, "Your doctor is right: you need methotrexate. If you get worse, come see me again."

**MAVES:** If leflunomide costs \$10, \$15, or \$20, would you send the patient to a rheumatologist? Take cost out. That's what I did. When you take cost out, where does the rheumatologist come in? Do you need the rheumatologist to do the methotrexate, or do you need it after that? In the end, methotrexate would be in the domain of the primary care physician. The reason we're here, and the reason we all sit in rooms with rheumatologists and medical directors, is because of cost. But if you took cost out, we can proceed on safety and correct medication.

**SOUTHWELL:** PCPs may not have experience with the leflunomide. Eventually they may, though, and they might be quite familiar with

what they need to monitor, and so on.

**FLORENTINE:** Would you want your primary care physician to give you methotrexate?

**SOUTHWELL:** If that's all I was able to see, yes.

**FLORENTINE:** Would you?

**SOUTHWELL:** If there are PCPs who see a lot of these patients....

**FLORENTINE:** I don't think you'd know the difference.

**SOUTHWELL:** Yes. I don't think you would.

**COLEMAN:** If I were in a major metropolitan area, I'd go to a rheumatologist as soon as I had the diagnosis. But if I live out in Kettle, Mississippi, where I grew up, and there is no rheumatologist, then yes, I'd let my PCP take care of everything.

**YODER:** I'm in Baltimore/Washington, where you can find rheumatologists. But then I go out to West Virginia, where there are few rheumatologists.

**COLEMAN:** We have patients who live in the bayou and who will not drive an hour into New Orleans to see a rheumatologist.

**MAVES:** This all gets back to the idea that guidelines are local. Health care is a local phenomenon. It's not a national phenomenon. Obviously we don't have a one-

size-fits-all here, so we need to develop them locally.

**FLORENTINE:** I don't think most people, given the disease, are going to refuse to drive a half hour or an hour.

**MAVES:** The reality is, though, if you said that everybody who is going to get methotrexate has to have it through a rheumatologist, a lot less people are going to get methotrexate.

**YODER:** How many rheumatologists do you have in your network?

**FLORENTINE:** Twenty.

**MAVES:** We have two.

**SOUTHWELL:** If PCPs don't feel comfortable with the methotrexate, by all means they should be referring that patient.

**YODER:** But if anything beyond methotrexate is prescribed, they have to go to a rheumatologist.

**FLORENTINE:** I wouldn't want my PCP to give me methotrexate. And I understand that in a rural area, it may be the only thing, and I think the guidelines would be helpful in that situation.

**COLEMAN:** That's the way I feel about guidelines. You don't develop a guideline for rheumatologists. You just don't do it. But you do develop a guideline for primary care physicians, with your rheumatologist, so that everyone is on the same page. Our goal is to make sure that every patient gets the same level of care, not that they get one level of care if they're in the city and another level of care if they're in the bayou. Guidelines help just to say, "We should be doing this for our patients." To me, that's what a guideline is for.

**FLORENTINE:** Our Medicare members have a \$400 a year max pharmacy benefit. They've blown leflunomide in a month and a half. Self-injectables are 30 percent coinsurance. So infliximab is the only thing they can do, and have the member get something rather than nothing, which is unfortunate. That's a benefit design.

**HARRIS:** While, for the most part, managed care is not concerned with Medicare, it's also true that one drug may be a better choice for these patients based on Medicare's benefit design. Also, other issues arise within this patient group. For instance, some patients are simply unable to self-inject.

**YODER:** In our algorithm, why don't we work our way back from infliximab as last line? Before using infliximab, you should try etanercept, and you should try leflunomide before that.

**COLEMAN:** So we're saying to use leflunomide, etanercept, infliximab, in that order.

**YODER:** Infliximab is a step up in complexity from etanercept. Infliximab gets expensive very quickly, because of infusion centers and everything else. I would much rather see our patients try etanercept first.

**KONOP:** But you might have an issue of patient compliance with etanercept.

**SOUTHWELL:** I don't know if patient compliance is really an issue with this patient population.

**YODER:** Yes, I'm betting they're highly motivated. It basically comes down to a convenience issue. Do we want to pay three times what we would for etanercept, for the same clinical benefit, because some health plan members don't want to give themselves a shot? I think they should be encouraged to try etanercept first.

**CANNON:** In summary, based on diagnostic criteria set forth by ACR, the treatment algorithm for RA is pretty straightforward. With a positive diagnosis of RA, the initial therapy is methotrexate because these patients need aggressive, early treatment. There's no reason to hold back on the methotrexate, plus or minus NSAIDs for symptomatic relief.

If methotrexate does not provide adequate response or relief, leflunomide should be added. Patients who cannot tolerate methotrexate can be switched to leflunomide or an additional DMARD. A lot of the data right now would lead us to say that leflunomide is probably the next logical choice, but many patients probably would respond to sulfasalazine and hydrox-



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ychloroquine, too. At the point when the desired response isn't achieved with methotrexate, leflunomide, or additional DMARDs, then the TNF products would be appropriate, plus or minus methotrexate.\*

**COLEMAN:** Who will prescribe this, the PCP or the rheumatologist?

**SOUTHWELL:** In an ideal world, it would be wonderful for every patient who goes on methotrexate to automatically be referred to a rheumatologist. From both a cost

\* Note that the prescribing information for infliximab indicates that it should be used in combination with methotrexate to minimize antibody formation. With repeated dosing of infliximab in clinical trials, serum concentrations of infliximab were higher in RA patients who received concomitant methotrexate.

standpoint and the availability of rheumatologists, the reality is that not everybody is going to be able to get to a rheumatologist.

**CANNON:** The reality is, right now initial diagnosis and initial treatment probably is being made by internal medicine. Knowing that aggressive early treatment is probably the direction we want to go, I'm not willing, from a plan standpoint, to say, "You're internal medicine, so you can't diagnosis and treat RA." For one thing, I don't have enough rheumatologists. I think that for the physicians who are comfortable using the ACR criteria to make a diagnosis, there is really no reason they cannot start a patient on methotrexate or leflunomide.

When companies say they're going to market their products to rheumatologists and specialists only,

they've probably overlooked a large segment of the population that could be helping to make early diagnosis. They're overlooking part of the prescribing community that might be driving the utilization of a product that's going to benefit all our patients.

We go to rheumatologists when we need input for guidelines, when we need input into our P&T. They're the clinical advisers for our P&T committees. Rheumatologists need to understand more about the benefits of combination therapy, because the rheumatologists in my area aren't using a lot of combination therapy.

We've already endorsed leflunomide in our plans, and we believe that, before going to the TNF products, a logical step approach is to use methotrexate followed by leflunomide.