PHARMACOLOGIC MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

Victoria Ruffing, RN*

ABSTRACT

Early, aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) is now the standard of care for patients with rheumatoid arthritis. As combination therapy becomes more common and DMARDs are started earlier in the course of disease, it can be expected that an increasing number of patients will rely on nurses to help them understand their drug therapy choices. There are 2 types of DMARDs: synthetic DMARDs, which suppress the autoimmune response in RA in a generalized way; and biologic DMARDs, also called biologic response modifiers, which target particular components of the inflammatory cascade. The most frequently used synthetic DMARD is methotrexate; others commonly used are sulphasalazine, hydroxychloroquine, and leflunomide. Biologic DMARDs target tumor necrosis factor (etanercept, infliximab, and adalimumab), interleukin-1 (anakinra), B cells (rituximab), and T-cell activation (abatacept). Nonsteroidal anti-inflammatory drugs and corticosteroids also have important uses in the treatment of rheumatoid arthritis. Unsettled issues include whether DMARD therapy is cost effective, whether the drugs proven efficacious in clinical trials are effective in the “real world,” and how patient response should be evaluated in clinical practice. Nurses are often the first people patients tell about persistent symptoms, and they should ensure patients’ comments reach the physicians, especially now that newer biologics are available to treat refractory disease.


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INTRODUCTION

One of the greatest advances in the management of rheumatoid arthritis (RA) was the recognition that permanent joint destruction can often be prevented if aggressive treatment starts early. Historically, concerns about the toxicities of disease-modifying antirheumatic drugs (DMARDs) caused physicians to avoid using them unless patients had persistent severe symptoms or joint damage was seen on radiographs. Now, it is known that RA progresses most quickly in the first years of the disease. A recent meta-analysis showed that the long-term risk of joint damage is reduced in patients who start DMARD therapy early (within an average of 9 months after symptom onset).

Because of the potential for serious joint damage without proper drug therapy, the American College of Rheumatology (ACR) recommends that RA treatment be directed by a rheumatologist. Most rheumatologists are happy to collaborate with primary care physicians in caring for patients with RA. Most patients with RA should consult a rheumatologist within 3 months after symptom onset, so that DMARD therapy can be started early if warranted.

Medications used to treat RA are divided into 4 main categories: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, synthetic DMARDs, and biologic DMARDs, also called biologic response modifiers or biologics. Currently, all biologics for RA are administered intravenously, most commonly in an office-based setting, or subcutaneously, which most patients can self-administer at home. This article explains what nurses need to know about commonly used agents, in addition to unsettled issues in the treatment of RA. Potential adverse events and appropriate monitoring are discussed in the article by Vickie Ensor Bands, BSN, MSA.
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

In addition to their anti-inflammatory effects, NSAIDs are analgesics. They are frequently used by patients with RA for pain relief, especially in the weeks or months before the diagnosis is established. NSAIDs do not prevent joint destruction or slow the progression of the disease, so they should rarely, if ever, be used as the sole medication for patients with RA. The choice of NSAID should be based on considerations of efficacy, safety, convenience, and cost. According to a recent statement from the American Heart Association (AHA), the risk of cardiovascular effects from selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib or valdecoxib, is greatest in patients who have a prior history of cardiovascular disease or are at high risk of cardiovascular disease. The AHA recommends that such individuals should use selective COX-2 inhibitors for pain relief only when there are no appropriate alternatives, and in the lowest dose and for the shortest duration possible. Patients’ responses to NSAIDs are highly individual, and if there is no response after 2 to 3 weeks, it is worthwhile to try another NSAID.

CORTICOSTEROIDS

Low-dose oral corticosteroid therapy (5–10 mg of prednisone daily, or the equivalent) is highly effective in suppressing inflammation and relieving symptoms. Corticosteroids are generally given to provide relief until a DMARD becomes effective, or when rapid control of inflammation is desired. Injections directly into a joint can treat a localized disease flare.

Whether corticosteroids decrease the progression of RA has been controversial. A recent systematic review found that low-dose therapy given along with conventional DMARDs reduces the progression of early RA for at least 2 years. However, this finding will probably not lead to more routine use of corticosteroids because increased risk of osteoporosis and infection, in addition to possible cardiovascular risks, would contraindicate them. Most prudent rheumatologists do whatever possible to wean patients from corticosteroids and reserve them only for flares.

SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

By definition, a DMARD (synthetic or biologic) slows or stops the progression of RA. Table 1 compares the characteristics of the synthetic DMARDs most commonly used to treat RA.

METHOTREXATE

Methotrexate is an antineoplastic agent that at low doses is anti-inflammatory and has immunomodulatory effects (ie, it modifies or regulates 1 or more immune functions). Methotrexate is often the first-choice DMARD because it is the synthetic DMARD most likely to induce a long-term response, and it has a favorable toxicity profile, low cost, and a long track record in the treatment of RA. One observational study showed that mortality is significantly lower in patients with RA who have been treated with methotrexate than in those who have not. If response is suboptimal with oral methotrexate, a trial of subcutaneous or intramuscular injection may be warranted.

SULFASALAZINE

Sulfasalazine is an anti-inflammatory that also appears to have immunomodulatory effects. It is usually used in combination with methotrexate or another synthetic DMARD, especially in mild disease.

HYDROXYCHLOROQUINE

Hydroxychloroquine, an antimalarial, is the best tolerated of all the synthetic DMARDs. However,

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**Table 1. Synthetic DMARDs Commonly Used in the Treatment of Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route(s) of Administration</th>
<th>Approximate Time to Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Oral, subcutaneous injection, intramuscular injection</td>
<td>1–2 months</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Oral</td>
<td>1–3 months</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Oral</td>
<td>2–6 months</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Oral</td>
<td>1–3 months</td>
</tr>
</tbody>
</table>

according to a meta-analysis of blinded clinical trials, hydroxychloroquine is less effective than methotrexate or sulfasalazine.\textsuperscript{14} Hydroxychloroquine is sometimes used when the diagnosis of RA is uncertain and the physician does not want to expose a patient unnecessarily to the potential side effects of methotrexate.\textsuperscript{15}

**LEFLUNOMIDE**

Leflunomide is a newer DMARD that reduces inflammation by interfering with the proliferation of activated T cells. Randomized, controlled clinical trials have established leflunomide as an alternative to methotrexate, especially for patients who cannot tolerate methotrexate or who have an inadequate response.\textsuperscript{16-22} The combination of leflunomide and methotrexate appears to be more effective than methotrexate alone.\textsuperscript{23,24}

**OTHER SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS**

Azathioprine, D-penicillamine, and oral and intra-muscular gold are no longer commonly used for RA because of limited efficacy compared with the newer agents, inconvenient administration, and/or toxicity.\textsuperscript{4} Cyclosporine, an immunosuppressant agent, is beneficial because it inhibits the production of certain cytokines (proteins that act as messengers between immune system cells and can stimulate inflammation), however, because of the risk of renal toxicity, the use of cyclosporine is primarily confined to patients with refractory RA.\textsuperscript{3} Clinical trials performed in the 1990s showed that minocycline, a tetracycline antibiotic, is effective in treating RA, but it has not become commonly used, perhaps because of the introduction of the biologics.\textsuperscript{7}

**BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS**

Synthetic DMARDs suppress the autoimmune response in RA in a generalized way. In contrast, biologic DMARDs are genetically engineered to target particular components of the inflammatory cascade. Improvement in response to biologics is typically rapid, often occurring within a few weeks. The current trend is for biologics to be used for an increasingly large number of patients with RA and to be used earlier in the course of the disease.\textsuperscript{3,15,16,27}

**TUMOR NECROSIS FACTOR INHIBITORS**

Three of the biologic DMARDs that are commercially available for RA treatment suppress the inflammatory action of the cytokine known as tumor necrosis factor (TNF). Table 2 compares the characteristics of the biologics currently approved for RA treatment.\textsuperscript{15,16,27}

### Table 2. Biologic DMARDs Used in the Treatment of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Administration</th>
<th>Preinfusion Medication*</th>
<th>Approximate Time to Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>TNF-α</td>
<td>SC injection weekly or twice weekly</td>
<td>N/A</td>
<td>A few days to 3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF-α</td>
<td>IV infusion at weeks 0, 2, and 6, then every 8 weeks</td>
<td>Anti-inflammatories, corticosteroids, and/or antihistamines, if needed based on response to prior infusions</td>
<td>A few days to 3 months</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF-α</td>
<td>SC injection every 2 weeks</td>
<td>N/A</td>
<td>A few days to 3 months</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Interleukin-1</td>
<td>SC injection daily</td>
<td>N/A</td>
<td>2–16 weeks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20 antigen on B cells</td>
<td>IV infusion at weeks 0 and 2</td>
<td>Corticosteroids routinely recommended</td>
<td>8–16 weeks</td>
</tr>
<tr>
<td>Abatacept</td>
<td>T-cell co-stimulation</td>
<td>IV infusion at weeks 0, 2, and 4, then every 4 weeks</td>
<td>None needed</td>
<td>Within 4 months</td>
</tr>
</tbody>
</table>

*To reduce the risk of infusion-related events.

\textsuperscript{1}IV = intravenous; N/A = not applicable; SC = subcutaneous; TNF = tumor necrosis factor.

Data from Rindfleisch et al.\textsuperscript{1}; Leff\textsuperscript{5}; Furst et al.\textsuperscript{27}
The first of these, etanercept, was approved in 1998, and there is longer experience with TNF inhibitors than with other biologic DMARDs. No clinical trials have compared one TNF inhibitor with another, so the choice depends on factors such as patient preferences and access to treatment.27

**ETANERCEPT**

Reflecting the early cautiousness about using TNF inhibitors, the first large, placebo-controlled study that demonstrated the efficacy of etanercept included only patients who had discontinued synthetic DMARD therapy because of an inadequate response.28 A small trial then showed that in patients who had long-standing refractory RA with inadequate response to methotrexate, the addition of etanercept provided additional benefit, with no increase in the risk of adverse events.29 Since then, long-term follow-up research has demonstrated that, whether given alone or in combination with methotrexate, etanercept provides sustained response for at least several years, with no new or increased toxicities.30

In patients with early RA, etanercept is more beneficial than methotrexate, particularly with regard to radiographic outcomes.31,32 In patients with early RA33 and those with poor response to methotrexate,34 the combination of etanercept and methotrexate is superior to methotrexate alone or etanercept alone.

**INFlixIMAB**

The US Food and Drug Administration (FDA) approval of infliximab specifies that it must be used in combination with methotrexate.35 Patients can develop antibodies to infliximab that increase the likelihood of infusion reactions and accelerate infliximab clearance.36 Methotrexate and infliximab have a synergistic effect, possibly because methotrexate reduces the body’s anti-infliximab response.35,37

Like etanercept, infliximab has been studied in patients with early RA. In these patients, the combination of infliximab plus methotrexate is more effective than methotrexate alone.37

The standard schedule is to administer infliximab at 0, 2, and 6 weeks, then every 8 weeks. However, patients vary markedly as to how they metabolize the drug. For patients who do not have an adequate response, or who have an initial response followed by a relapse, it may be helpful to increase the dose or decrease the interval between infusions to every 4 to 6 weeks.38

**ADALIMUMAB**

Adalimumab is the newest of the TNF inhibitors and the least well studied. It is known to be safe and effective when given alone39,40 and when added to other antirheumatic therapy, including one or more synthetic DMARDs, corticosteroids, NSAIDs, and analgesics.41 Adalimumab appears to have additive effects when used with methotrexate,42,43 and combination therapy is now generally recommended, unless there are contraindications.44

**ANAKINRA**

Anakinra inhibits interleukin-1, a cytokine similar to TNF that contributes to joint damage in RA (Figure). It is effective alone or in combination with methotrexate, with responses shown to persist for at least a year.45-48 However, anakinra has not been particularly well accepted in clinical practice. Daily injections are required, and patient response seems to be limited. A recent meta-analysis showed that, overall,

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**Figure. Points at which Biologic Therapies for Rheumatoid Arthritis Target the Inflammatory Cascade**

IL = interleukin; RF = rheumatoid factor; TNF = tumor necrosis factor.

Reprinted from Leff J Infus Nurs. 2006;29:326-337,44
the efficacy of anakinra is less than that of TNF inhibitors. Anakinra may be useful for patients who have no response to, or cannot tolerate, methotrexate, leflunomide, or TNF inhibitors.

Concurrent use of anakinra and a TNF inhibitor should be avoided because it increases the incidence of serious infections, injection-site reactions, and neutropenia. Anakinra is not recommended as a first-choice DMARD because no trials have been performed in early RA.

**Biologics for Refractory Rheumatoid Arthritis**

Rituximab, a genetically engineered antibody, targets a subset of B cells that carry a particular antigen, a surface protein called CD20 (Figure). This drug has been used for a decade to treat CD20-positive, B-cell non-Hodgkin’s lymphoma. Two infusions, 2 weeks apart, is the schedule approved for RA. A recent phase III trial showed that a single 2-infusion course of rituximab, along with methotrexate therapy, provided significant improvements in patients with active, long-standing RA who had an inadequate response to 1 or more TNF inhibitors. In patients with RA, rituximab is approved for use only in combination with methotrexate, and only for patients with moderately to severely active disease who have had an inadequate response to 1 or more TNF inhibitors.

Abatacept belongs to a new class of drugs called selective co-stimulation blockers. Compared with other biologics, it works earlier in the inflammatory cascade (upstream), blocking one of the signals that causes T cells to become activated (Figure). Abatacept has been demonstrated to benefit patients with inadequate response to methotrexate, in addition to those with inadequate response to TNF inhibitors. It is approved for patients with moderately to severely active RA who have had an inadequate response to any type of DMARD. The US FDA labeling allows abatacept to be used alone or concurrently with DMARDs other than TNF inhibitors. However, use of abatacept concurrently with anakinra is not recommended.

**Investigational Biologics**

Three biologics are currently in late-stage clinical testing for RA. Preliminary results from a multinational phase III study suggest that tocilizumab, which targets interleukin, is safe and efficacious in patients with RA who have not responded to methotrexate. The 2 other drugs are in phase III trials that are still under way: golimumab, a TNF inhibitor being studied as a subcutaneous injection and an intravenous infusion; and ocrelizumab, an antibody similar to rituximab.

**Unsettled Issues in the Treatment of Rheumatoid Arthritis**

**Evaluation of Response**

No treatment cures RA. The therapeutic goals set out by the ACR are to prevent or control joint damage, prevent loss of function, and decrease pain. However, no clinically oriented guidelines exist on how to evaluate whether a patient has responded to an RA drug. In 1995, the ACR published criteria for use in clinical trials, in which the target is 20% improvement in a range of measures (Table 3). Now that better treatments are available, 50% or 70% improvement are common targets in research studies. In clinical practice, most physicians simply make a subjective judgment about whether a patient is responding.

Evaluation of improvement is important for deciding whether a patient on methotrexate or another synthetic DMARD should be started on a biologic, and whether a patient on a biologic should be switched to another agent or have the dose increased. Approximately 60% of patients treated with TNF inhibitors have not responded to methotrexate. The other drugs are in phase III trials that are still under way: golimumab, a TNF inhibitor being studied as a subcutaneous injection and an intravenous infusion; and ocrelizumab, an antibody similar to rituximab.

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**Table 3. American College of Rheumatology Definition of 20% Improvement in Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Disease Activity Measure</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tender joints</td>
<td>20% improvement</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>20% improvement</td>
</tr>
<tr>
<td>Patient’s assessment of pain</td>
<td></td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity</td>
<td></td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity</td>
<td></td>
</tr>
<tr>
<td>Patient’s assessment of physical function</td>
<td></td>
</tr>
<tr>
<td>Markers of inflammation (erythrocyte sedimentation rate and C-reactive protein)</td>
<td>20% improvement in 3 of these 5 measures</td>
</tr>
</tbody>
</table>

inhibitors continue to have joint inflammation or show minimal improvement, and some patients lose their response to TNF inhibitors over time.60,61 Nurses are often the first people who patients tell about persistent symptoms, and they should make sure that patients’ comments reach the physicians, especially now that newer biologics are available to treat refractory disease.

“REAL-WORLD” EFFECTIVENESS

Patients in routine practice typically have a wider range of demographic characteristics, disease severities, and comorbid conditions than patients in clinical trials. For most of the newer drugs used to treat RA, it remains to be seen whether effectiveness in the “real world” will match the results in controlled studies. However, a recent study is encouraging in this regard.62 The researchers reviewed 2 databases containing information on more than 4600 adults with RA who had been treated in rheumatology practices across the United States. They found that, as in clinical trials, methotrexate was highly effective, leflunomide and methotrexate had comparable effectiveness, and etanercept or etanercept plus methotrexate was more effective than methotrexate alone.

COST EFFECTIVENESS

Because of the introduction of newer DMARDs, including biologic agents, and increasing use of combination therapy, RA therapy can be quite expensive. The annual cost of biologics is $10,000 to $25,000 or more per patient, depending on the circumstances.64 Insurance company reimbursement for biologic therapy varies, often requiring detailed documentation of need. Medicare is more likely to pay for infusible therapy than for injectables.

High up-front expense might be justified in the long term if there are overall cost savings from improved quality of life and enhanced productivity.64 Only 2 studies have evaluated the cost effectiveness of RA therapy in the United States.65,66 Both concluded that TNF inhibitors could be considered a good value, depending on how cost effectiveness is defined. These were computer modeling studies in which a limited number of treatment options were considered, for relatively short time periods (6 months–1 year). Further cost-effectiveness research on TNF inhibitors and the other biologics used in RA is needed.

Conclusions

Pharmacologic therapy for RA has changed dramatically in the past decade. It is now understood that all patients, not just an unfortunate minority, are at risk of significant joint damage and disability. It has also been established that rapid suppression of mild disease can reduce or eliminate joint damage. Thus, early, aggressive therapy with DMARDs has become the standard of care. At the same time, several new therapeutic options have become available, carefully designed to target specific components of the inflammatory cascade.

Nurses need to understand each of these agents and know what alternatives are available if initial treatment fails. By educating themselves, they will be best equipped to help patients communicate with physicians and make informed decisions about their care.

REFERENCES


40. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with


