ABSTRACT

Permanent joint damage occurs early in rheumatoid arthritis (RA) pathogenesis, thus early aggressive treatment is recommended. Treatment goals include prevention of joint destruction and maintenance of function. Disease-modifying antirheumatic drugs (DMARDs) are important in the medication approach because these agents can lessen the destructive capability of RA. Traditional DMARDs continue to be effective at slowing disease progression, whereas recently available biologic DMARDs offer improved choices for disease control. Effective disease control requires the coordinated care of healthcare professionals, in addition to comprehensive patient education concerning disease management.


Rheumatoid arthritis (RA) has no known cure, but early detection and effective treatment can improve patient outcomes dramatically. As per the American College of Rheumatology (ACR) guidelines, "the ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function, and decrease pain... Treatment begins with educating patients about the disease and the risks of joint damage and loss of function, as well as reviewing the risks and benefits of existing treatment modalities."

TREATMENT STRATEGIES

Even though inflammation associated with RA may wax and wane over the course of the disease, joint destruction and functional loss will continue to progress. Since the mid 1990s, treatment strategies have shifted from a pyramid approach of controlling symptoms in advanced disease to early aggressive interventions that minimize joint destruction and slow disease progression. Successful treatment of RA will limit joint damage and functional loss. This requires early diagnosis and timely initiation of disease-modifying agents.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids are effective for symptomatic relief of pain and swelling; however, they are unlikely to prevent further joint damage. To control disease and possibly achieve remission, newly diagnosed patients should be started on disease-modifying antirheumatic drug (DMARD) therapy within 3 months of diagnosis. DMARDs have been shown to preserve joint integrity and function, but require appropriate monitoring by the physician for possible side effects. Pharmacotherapy for RA will often consist of combination therapy with NSAIDs, glucocorticosteroids, and DMARDs. The ACR treatment algorithm for RA is represented in Figure 1.

Through the years, DMARDs have evolved from gold, used in the 1930s, to biologics, first used for RA in the 1990s. DMARDs are still used for RA and remain the first choice for treatment of early disease. The Table summarizes toxicities, monitoring requirements, and dosing of various DMARDs.
Figure 1. ACR Guidelines for Rheumatoid Arthritis
Medical Management

Traditional DMARD Therapy

Traditional DMARDs consist of methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide, cyclosporine, gold, azathioprine (AZA), D-penicillamine, and minocycline. Whereas AZA, SSZ, and MTX will generally demonstrate treatment benefit within 1 to 3 months, gold, D-penicillamine, and HCQ may not show treatment benefit until 3 to 6 months of therapy.1

Methotrexate

Methotrexate is often selected as the initial DMARD for patients with early RA with active disease or for those who fail other agents.1 The agent has a rapid time to benefit (1–2 months) and a favorable efficacy/toxicity profile, can be titrated, and slows joint damage. MTX is usually well tolerated by patients, and patients continue therapy beyond 3 years, which is longer than treatment durations associated with other DMARDs.1

Although MTX is considered to have a favorable efficacy-to-toxicity ratio, folic acid or folinic acid supplementation may alleviate some adverse events (AEs) associated with MTX (ie, hematologic changes and oral ulcers).1 For a suboptimal response to MTX, the dose may be increased up to 25 mg weekly, either orally or intramuscularly, and is usually well tolerated. The combination of MTX with other DMARDs is also beneficial.1,15 The bioavailability of subcutaneous and intramuscular MTX does not differ significantly, and oral and parental doses of up to 25 mg demonstrate comparable bioavailability (85%–100%).16,17 Consequently, an appropriate dosage form should be selected to maximize compliance, cost, and preference.16

Hydroxychloroquine

The antimalarial drug HCQ is US Food and Drug Administration (FDA) approved for the treatment of RA and systemic lupus erythematosus.18 Its mechanism of action, although not fully understood, may involve inhibition of membrane traffic, impact on lysosomal fusion, and interference with antigen presentation. HCQ is well absorbed, with relatively mild toxicities, including gastrointestinal (GI) upset, abnormal retinal or skin pigmentation, long-term neuropathy, or myopathy. HCQ is typically used for mild disease or in combination therapy.

Sulfasalazine

Sulfasalazine, a combination of the anti-inflammatory 5-aminosalicylic acid and the antibacterial sulfapyridine, was developed in the 1930s based on the infectious etiology theory of RA causation.19 Although its mechanism of action is not fully known, SSZ slows radiographic RA progression more rapidly than HCQ.1 SSZ is widely used in Europe, perhaps because of its favorable effectiveness, cost, and tolerability.18 Toxicities may include GI upset, myelosuppression, and rare, potentially fatal autoimmune reactions possibly related to the sulfonamide moiety.1,19

Other Agents

Similar to MTX, leflunomide is an effective agent...
and a viable alternate for MTX as monotherapy or in combination. Although gold is associated with toxic effects and stringent monitoring, intramuscular gold is generally more effective than oral gold if therapy is justified. AZA, cyclosporine, D-penicillamine, and minocycline are less commonly used today for RA.

In summary:
- Conventional treatment with a single DMARD often fails to adequately control clinical symptoms or to prevent disease progression over time.
- Clinicians are now using traditional DMARDs in combinations of 2 or 3 drugs to improve efficacy.

### Table. Toxicities and Monitoring Requirements of DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicities</th>
<th>Monitoring Requirements</th>
<th>Usual Maintenance Dose</th>
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<tbody>
<tr>
<td><strong>Traditional DMARDs</strong></td>
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<tr>
<td>MTX</td>
<td>Cirrhosis, pulmonary toxicity, stomatitis,</td>
<td>Chest X ray (baseline), CBC, creatinine, and LFTs</td>
<td>Oral or injectable: 7.5–20 mg/wk</td>
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<tr>
<td></td>
<td>leukopenia, renal insufficiency, anemia,</td>
<td>every 1–2 mos</td>
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<td></td>
<td>opportunistic infections, and thrombocytopenia</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>Retinal toxicity</td>
<td>Eye examination annually if age &gt;40 years or history</td>
<td>200 mg oral twice daily</td>
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<tr>
<td></td>
<td></td>
<td>of eye disease</td>
<td></td>
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<tr>
<td>Sulfasalazine</td>
<td>CNS and GI toxicity, leukopenia, and</td>
<td>CBC and LFTs every 3 mos</td>
<td>1000 mg 2–3 times/day</td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Intramuscular gold</td>
<td>Dermatitis, stomatitis, proteinuria,</td>
<td>CBC and UA before each dose</td>
<td>25–50 mg every 2–4 wks</td>
</tr>
<tr>
<td></td>
<td>enterocolitis, and thrombocytopenia</td>
<td></td>
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<tr>
<td><strong>Biologic DMARDs</strong></td>
<td></td>
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<tr>
<td>Infliximab</td>
<td>Serious infections</td>
<td>See MTX</td>
<td>3 mg/kg IV every 4–8 wks (with MTX)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Serious infections</td>
<td>S/S infection</td>
<td>25 mg SC twice/wk; 50 mg SC weekly</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Serious infections</td>
<td>S/S infection</td>
<td>40 mg SC once every other wk; may increase to weekly</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Serious infections, neutropenia*</td>
<td>CBC every 1–3 months, S/S infection</td>
<td>100 mg SC daily</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Serious infections†</td>
<td>S/S infection</td>
<td>500–1000 mg IV every 4 wks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Serious infusion-related reactions</td>
<td>CBC during therapy</td>
<td>1000 mg IV on day 1 and day 15 (with MTX)</td>
</tr>
</tbody>
</table>

*Particularly if used with TNF-α blockers; concomitant use not recommended.
† Particularly if used with TNF-α blockers and anakinra; concomitant use not recommended.
CBC = complete blood count; CNS = central nervous system; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IV = intravenous; LFT = liver function test; MTX = methotrexate; SC = subcutaneous; S/S = signs or symptoms; TNF-α = tumor necrosis factor-α; UA = urinalysis.

Data from American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines; American College of Rheumatology Ad Hoc Committee on Clinical Guidelines; Infliximab [prescribing information]; Etanercept [prescribing information]; Adalimumab [prescribing information]; Anakinra [prescribing information]; Abatacept [prescribing information]; and Rituximab [prescribing information].
Various approaches to therapy with DMARDs:
- Traditional: Try one/Stop/Try the next
- Step Up: Add one after another—HCQ + MTX + SSZ
- Combination Therapy: From the start MTX/HCQ/SSZ
- Step Down: Start with all 3, and taper as you go.

**Biologic DMARD Therapy**

In response to pathogens and autoimmune stimulation, activated cells start a cascade of events that result in inflammation. Inflammation causes joint destruction, joint pain, and swelling in addition to cytokine release (i.e., interleukin [IL] molecules and tumor necrosis factor-α [TNF-α]) that bind to specific receptors to induce the local and systemic inflammatory responses that account for several other symptoms associated with RA. The inflammatory process is usually tightly controlled by the body. In a patient with RA this inflammatory process is a continuum. Biologic agents target different cells involved in this inflammatory cascade to break the cycle of inflammation, reducing pain, swelling, and joint damage. Biologic agents can target cytokines, T cells, or B cells involved in the RA inflammatory cascade.

Biologics are used in inadequate MTX responders in early and late disease. All biologics can trigger an immune response of varying magnitude in humans that may result in hypersensitivity reactions or loss of treatment response. Comparing immunogenicity among agents is difficult because patient populations, treatment regimens, and detection assays generally differ.

**Infliximab**

Infliximab is a murine-human chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to TNF-α, with high affinity and avidity. Although it prevents TNF-α from binding to its receptors, infliximab does not neutralize TNF-β (lymphotoxin-α), a related cytokine. Inhibition of TNF-α is shown to prevent proinflammatory cytokine induction, including IL-1 and IL-6. Antibodies to infliximab (also called human antichimeric antibodies or HACAs) may develop in some patients.

**Etanercept**

Etanercept is a chimeric fully human fusion protein of the ligand-binding portion of the TNF receptor linked to the Fc portion of human IgG1. It binds to TNF-α and TNF-β to block cell surface interactions. It is associated with the formation of human antihuman antibodies (HAMAs) in some patients.

**Adalimumab**

Adalimumab is a recombinant fully humanized IgG1 mAb that is produced in Chinese Hamster ovary cells transfected with expression vectors. It inhibits TNF-α but not TNF-β, and it also may be associated with the formation of HAMAs.

**Anakinra**

Anakinra is a recombinant nonglycosylated form of human IL-1 receptor antagonist. It blocks the activity of IL-1 through competitive inhibition of IL-1 type 1 receptor. Antibody development to anakinra also has been observed.

**Abatacept**

Abatacept is a recombinant soluble fusion protein of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 linked to the modified Fc portion of human IgG1. It acts as a selective costimulation modulator that inhibits T-cell activation by binding to CD80 and CD86 on the antigen-presenting cell, thereby blocking interaction with CD28 on the T cell. This unique upstream inhibition of the
inflammatory cascade interferes with macrophage, T-cell, and B-cell proinflammatory functions (Figure 2). Abatacept is indicated in patients with moderately to severely active RA who have an inadequate response to MTX and/or TNF blockers. Antibody development does occur but appears to be low.

**Rituximab**

Rituximab is a murine-human chimeric IgG1 mAb directed against the CD20 antigen, a transmembrane protein located on B cells. It is indicated in patients with moderately to severely active RA who have an inadequate response to TNF blockers. Depletion of peripheral B cells by rituximab appears clinically effective for RA. However, this benefit may not reflect synovial B-cell levels and may be offset by an increase in B lymphocyte stimulator protein, which is capable of triggering clinical relapse.

**Conclusions**

Rheumatoid arthritis is a dynamic disease that requires early diagnosis with aggressive treatment. Optimal therapy with DMARDs may include dosage adjustments, medication changes, and combination therapy. Biologics offer new treatment options to reduce disease severity by limiting joint damage and functional loss. Reported AEs associated with biologics have increased over the past decade due primarily to increased usage. Over 1 million patients have received these agents worldwide. Research in various stages of development continues to investigate safer, more effective biologics.

Patients need comprehensive coordinated care and the expertise of several healthcare providers. Nonpharmacologic interventions may include physical therapy, occupational therapy, social work, psychological support, and possibly surgical intervention. Education to improve patient perceptions should focus on therapy compliance to control disease and improve quality of life.

**Discussion**

**Ms Neuberger:** Is there an authoritative resource for reporting AEs associated with biologics, a resource that shares this information with healthcare professionals?

**Ms Grace:** The US FDA Web site has this information reported under individual agents.
standing is that even though bioavailability is similar, patients may be switched to the injectable form because the area under the curve (AUC), rate of absorption, and time-to-peak concentration may differ between the 2 dosage forms.

**Ms Grace:** Rate of absorption and time-to-peak serum concentration are faster with the injectable form whereas bioavailability remains similar between both forms for doses up to 25 mg weekly. However, AUC, which is directly related to bioavailability, can become more erratic at higher oral doses. Changing to the injectable form should be considered for doses of 25 mg or greater.

**Ms Dexter:** Another important concept is combination therapy of MTX and TNF-α blockers. MTX reduces the immunogenicity to TNF-α blockers, therefore physicians often will not discontinue MTX upon starting TNF-α blockers. The importance of concomitant therapy should be explained to patients.

**Ms Dolan:** Although MTX is used as monotherapy for some inflammatory diseases, it may reduce the immunogenicity of biologics as required for more severe RA cases. Combination therapy is supported by clinical studies, some of which are described in PI.28

**Ms Grace:** Because efficacy data for some biologics are based on combination therapy with MTX, their PI may not discuss monotherapy for RA treatment.

**Dr Saleh:** TNF-α blockers plus MTX is shown to be more effective for the treatment of RA as compared to monotherapy with either agent alone. In inflammatory joint conditions, such as spondyloarthropathy, MTX is shown to not be effective and patients will respond to monotherapy with TNF-α blockers.29

In a recent article in *Arthritis & Rheumatism*, the efficacy of subcutaneous MTX was shown to be superior to oral MTX despite similar tolerability.30 This superiority has been observed clinically at my facility, and failure to MTX is not declared until patients failed on both oral and subcutaneous MTX. At this point, therapy would be changed to an alternate DMARD. Intramuscular MTX is efficacious with a rapid onset of action. However, intramuscular MTX is more commonly used in places outside of the United States, such as Europe.

**Ms Dilliard:** Another rationale for switching to injectable MTX could be GI intolerance to the oral form. If GI symptoms persist or worsen despite pharmacologic interventions, changing to injectable MTX may be warranted.

Although not routinely measured, HACA scores may be a reason for dose escalation of mAb therapy or changes to alternate agents.

**Ms Ruffing:** Nurses should stress that medication compliance is vital and that medication synergy is involved with combination therapy. Patients often equate the number of medications prescribed to the severity of disease. Patients may assume that one medication may be stopped when another medication is prescribed. Accordingly, patients should know that new therapies may require up to 12 weeks before onset of action becomes symptomatically evident. Without explaining complicated mechanisms of action, nurses should describe why symptom relief may not occur immediately. Conversely, patients may experience immediate symptom relief because of corticosteroid premedications, and this effect should be explained. In the case of rituximab, retreatment is often necessary in order to effectively target B cells in the synovial joints versus serology B cells alone. In summary, nurses need to anticipate patients’ perceptions and help set realistic goals that involve both pharmacologic and nonpharmacologic interventions.

**Ms Grace:** Nurses should consider that age and educational levels can affect patients’ perceptions and compliance to therapy. All patients require appropriate integration and education about their care.

**Ms Neuberger:** Patients should become involved in monitoring therapy response and managing side effects. Patient education must include infection precautions, particularly in light of US FDA warnings about rituximab and rare progressive multifocal leukoencephalopathy, a fatal disease caused by a viral reactivation.31 Despite obscure details and uncommon occurrence of serious AEs as per PI descriptions, these events can occur and should be understood by nurses.

### REFERENCES