Rheumatoid Arthritis

Module II

Management: Current concepts and synthetic disease modifying anti-rheumatic drugs

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CURRENT CONCEPTS

Introduction

Since the mid-1990s, there have been major changes in the treatment and management of rheumatoid arthritis (RA). Generally, approaches have been aimed at earlier identification of the disease, earlier intervention with disease-modifying antirheumatic drugs (DMARDs), aggressive dosing of existing medications, combination therapy, and the introduction of new classes of therapeutic agents such as protein-based biologic therapies. These changes have resulted in significant improvements for patients with RA, including a reduction in the symptoms and signs of disease, joint preservation and a reduction of structural progression, and an improvement in function and quality of life.

The initial approach to treatment of RA begins with a diagnosis, estimation of the patient's prognosis, and the implementation of a therapeutic plan. It is never too early or too late to initiate treatment. This philosophy epitomizes the importance of initiating therapy at any stage of this disease. When a patient has been diagnosed with RA, or at the very least has features of inflammatory arthritis unattributed to other causes, such as infection, malignancy, or metabolic disease, therapy with DMARDs should be initiated with the goals of preventing or controlling joint damage, preventing loss of function, and decreasing pain. DMARDs are the fundamental treatment for inflammatory arthritis, and all other therapeutic approaches should be considered adjuncts. Optimal therapeutic plans include more than just DMARD therapy, however. The treatment plan also should include patient education; possible consultation with physical therapists, social workers, and occupational therapists and adjunctive therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids orally (in low dosages), intramuscularly, or intra-articularly.

Disease modification therapy

Initiating DMARD therapy is paramount in the treatment of RA. The decision of which DMARD or DMARDs to start is less clear, however. In any given patient, any of the DMARDs can be efficacious and well tolerated, but no one DMARD is efficacious and safe in every patient. Few patients experience remission on any DMARDs, and most experience some sort of side effect from the medications prescribed to treat the disease if treated long enough. The American College of Rheumatology (ACR) and EULAR treatment guidelines for the management of RA provide an important frame of reference from which to guide
therapeutic decision making. The ACR treatment guidelines call for a comprehensive approach to the patient with involvement of the primary care provider and the rheumatologist, and provide a general guideline for starting, changing, or adding DMARDs to the treatment of a patient with active disease.

DMARD therapy generally begins with the initiation of therapy with the traditional small molecules, such as methotrexate (MTX), hydroxychloroquine (HCQ), or sulfasalazine (SSZ). These agents are of proven benefit, are generally well tolerated with well-known side-effect profiles, and can be prescribed at a reasonable cost. Of the three agents, MTX is the most commonly prescribed DMARD. After initiating a DMARD, patients need to be re-evaluated periodically with a goal of strict control of disease activity and monitored for potential side effects from the medications being used.

Although other small molecule treatments exist (e.g., azathioprine, gold salts, penicillamine, cyclosporine), these agents are used infrequently and usually reserved for patients refractory to other therapy or with idiosyncratic side effects with the other agents. After consideration has been given to the use of these traditional small molecule therapies, the practitioner must take stock of the growing efficacy and safety data in the support of the newer generation DMARDs such as leflunomide; the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept, and infliximab, the interleukin (IL)-1 receptor antagonist anakinra; the selective costimulation modulator abatacept; and the B cell–targeted approach using rituximab (RTX). These agents have been well studied in clinical trials showing efficacy alone or in combination with traditional therapies. The ability of these agents to slow radiographic progression of disease and restore function seems to be at least equal to, and in some cases greater than, that seen with traditional therapies.

**Treatment strategies**
The question of when to change or to add DMARD therapies in the treatment regimen is a difficult one, and in many cases it can be a matter of individual style. In some cases, it can be a socioeconomic decision, however, based on the costs of therapies. In some situations, use of newer DMARDs or biologic agents may be limited by third-party payers, and in most circumstances, they are allowed only after failure of one or more of the standard agents.
When initiating DMARD therapy, most patients are started on traditional small molecules, as outlined earlier, initially as monotherapy or used together in combinations. Data suggest that when given as monotherapy, these agents can be safe and effective. When an approach of careful monitoring and tight control is used, significant results can be obtained even with traditional compounds.

Over time, numerous different approaches to DMARD use have materialized, including sequential monotherapy, step-up combination approaches, initial combination therapy, and step-down combination approaches. Each approach has its own merits and is examined more fully subsequently. The ACR and the EULAR guidelines for the management of RA call for a comprehensive approach to the patient, but rely on DMARDs to result in disease modification. The traditional approach has called for sequential monotherapy, reassessment of disease, and change to an alternative DMARD if the patient has inadequate benefit or has adverse side effects. This type of approach was modified further into the “sawtooth” strategy. This approach advocated early DMARD initiation with continual serial use and careful quantitative monitoring of disability. When a patient's disability worsens, there is a sequential change in DMARD therapy in an attempt to decrease disability to prior levels if possible. This strategy has merit because it offers the potential for long-term disease modification, careful monitoring, and a reliance on DMARD approaches over that of analgesics and NSAIDs. This approach has been modified further to include combination approaches as increasing data continue to support the superiority of combinations over sequential monotherapy.

Another element in the evolving optimism about treatment of RA has been the use of multiple agents in combination therapy, many of which are aimed at a different segment of the pathophysiologic processes within the synovium. Beginning with uncontrolled, but encouraging, results using combination therapy in the early 1980s, it has been shown that a combination of disease-modifying drugs provides additive, perhaps synergistic, benefit to patients without increasing toxicity. Considerable data suggest that many therapies can be used in combination safely and efficaciously. In most cases, MTX has served as the building block on which combination therapy is based. Drugs that have shown benefit when combined with MTX include HCQ, SSZ, cyclosporine, leflunomide, anakinra, adalimumab, etanercept, infliximab, abatacept, and rituximab (RTX).
The traditional approach to the management of RA has evolved from a step-up treatment with sequential monotherapy to a step-up combination approach, where initial treatment with MTX is supplemented with a combination of DMARD interventions in patients with an inadequate response. This has become a favored approach among many rheumatologists. Other combination strategies have proved efficacious as well.

The initial use of combinations of DMARDs has significant merit and differs from the step-up approach in that combinations are used initially, rather than waiting for an inadequate response to one or more agents before adding additional agents to the regimen. Supporting this approach to combination therapy are data that “triple therapy”—MTX, SSZ, and HCQ—has been found to be more effective than MTX alone.

**Monitoring the effect of therapy**
Assessing the effectiveness of a therapeutic approach is crucial to the appropriate management of an individual patient. The ACR & EULAR guidelines for the management of RA call for periodic assessment of disease activity, and patients with inadequate response should have DMARDs changed or added. In most clinical practices, this assessment is done by physician gestalt or global assessment after a careful history, examination, laboratory studies, and radiographs. In most situations, this approach leads to quality care; however, when intensive monitoring is applied with a goal of tighter control, better outcomes can be achieved. More quantitative (but more time-consuming) approaches exist, such as the ACR response criteria, the DAS/DAS28, the HAQ, the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI).

The DAS is an effective tool to assess disease activity and measure change in activity. It is a composite score making use of tender joint count (53 or 28), swollen joint count (44 or 28), general health assessment, and a marker of inflammation (ESR or CRP). It is a continuous measure allowing for measurement of absolute change in disease burden and percentage improvement. The DAS also has thresholds or cut-offs for low disease activity and for remission. DAS calculators can be found online to simplify this process for clinicians wishing to use this tool.

The HAQ is a widely accepted and validated instrument for the assessment of function and disability. It is a patient self-reported questionnaire, and the HAQ disability index is
frequently used in trials, registries, and many practice settings. The HAQ measures eight subscales relating to physical disability and is scored between 0 and 3 (0 = no disability and 3 = completely disabled). Many variations have been made to the HAQ by other investigators, but in general they measure similar features of function and disability.

The SDAI and the CDAI are two relatively new composite scoring systems. The SDAI is calculated using the numerical sum of the tender joint count (28 joints), the swollen joint count (28 joints), the patient's global assessment, the physician's global assessment, and the CRP (mg/dL). The CDAI is similar to the SDAI, but does not use an acute-phase marker. The removal of the laboratory measure makes it feasible to perform this measure directly in the office with the patient and base decisions on it without having to wait. Regardless of which tool is used, it is increasingly important to incorporate validated outcomes tools into clinical practice to assess disease activity, and to guide decision making regarding change and addition of DMARDs and expensive biologic agents.

**The concept of early rheumatoid arthritis**

For patients with a symmetric polyarthritis in three or more joint areas involving the hands, feet, or both for at least 6 weeks, and a presumptive diagnosis of RA, aggressive treatment is warranted. Patients generally are apprehensive and concerned about developing a chronic, debilitating disease. Anxiety, depression, loss of self-esteem, inability to work, and an inability to develop new coping behaviors may evolve. This “learned helplessness” must be combated by education, reassurance, counseling, and the confident attitude of the physician. Most important is the initiation of a program to down regulate activity of the synovitis with the goal of inducing a remission, or at least marked improvement, in the disease. Disease-modifying therapy is indicated at this point, as are some adjunctive therapies. Early intervention may offer the greatest likelihood of preventing disability, and there may be a window of opportunity to have a significant impact on the trajectory of the disease over a lifetime.

The case for early intervention and for a window of opportunity has been made using several lines of evidence, as follows:

1. Functional health status declines early, with mild functional loss by 1 year and moderate-to-severe functional losses by 6 years. Subsequently, work disability also
occurs, especially early in disease, with work disability estimated to occur in 25% of RA patients at 6.4 years and 50% at 20.9 years after disease onset.

2. Mortality rates are increased in patients with RA. Mortality rate has been shown to increase over 5 to 20 years, with 35% mortality by 20 years. Morbidity and mortality rates in RA are predicted by, and are directly proportional to, clinical status. More severe and active disease has a poorer outcome.

3. Radiographic changes develop early in disease. Erosions of bone and narrowing of joint spaces develop within the first 2 years of disease in most patients and are progressive afterward over several decades. The rate of progression of radiographic scores is rapid early in disease and apparently continues along a similar trajectory for the duration of the disease if left untreated. When the proliferative synovium has begun to invade and destroy articular cartilage, joints are at risk for irreversible destruction, even when disease activity decreases.

4. In terms of economic impact, early disease activity predicts long-term costs. Data suggest that long-term medical costs and outcomes are significantly associated with early changes in disability. Further data would support the fact that patients with very poor function may experience direct medical costs 2.55 to 6.97 times as high as patients with good function, with most of those costs coming from hospitalization.

5. An interval of time may exist in which the introduction of DMARD therapy can result in a change in the natural course of disease—not just for a transient to short-lived time frame, but more fundamentally in the scope of the progression of the disease for a lifetime. Data supporting this view have come from numerous trials looking at intervention in early RA.

Given the growing body of evidence, it seems that the introduction of effective therapy (particularly combination therapies) early in the course of disease can result in a profound impact on the nature of the disease years later. An interval of time may exist for intervention whereupon the outcome is a long-term change in the nature of the disease, regardless of what type of therapy or intervention is used in the future. Estimation of a patient’s prognosis may assist further in choosing which patients may need the most aggressive approaches.
Markers of poor prognosis

The challenge for the physician is to form an appreciation for the severity of a patient's disease and formulate a treatment plan accordingly. As a general guideline, the rate of progression toward joint destruction and disability in RA is proportional to the intensity of inflammatory and proliferative reactions within the joints, the degree of disability, and the persistence of this disease over time. In other words, a patient who has low-grade attacks of synovitis that are separated in time from each other would be much less likely to advance to joint deformity than a patient who has continuous, highly active synovitis.

Progression of joint damage has been best predicted by ESR, IgM rheumatoid factor positivity, erosions at baseline, and the presence of HLA-DRB1*04 alleles. Other factors are the baseline HAQ scores, swollen and tender joint counts, elevated acute-phase proteins, and the presence of erosions on radiographs.

Some studies have suggested that the HLA-DRB1 shared epitope alleles may not be independent risk factors for the development of RA, but rather a risk factor for the development of anti–cyclic citrullinated peptide (anti-CCP) antibodies. Anti-CCP antibodies are believed to be sensitive and specific for the diagnosis of RA and may predate the development of the disease. Research has continued to suggest that the presence of anti-CCP antibodies is highly specific for RA, and that anti-CCP-positive patients have more active disease and more severe radiographic evidence of destruction, and that the presence of anti-CCP antibodies early in disease is a prognostic marker of erosive disease. Data also suggest that the presence of anti-CCP is strongly associated with severe extra-articular features of RA.

Refined imaging techniques can help in the staging of disease and in following effects of therapy. Magnetic resonance imaging (MRI) although not yet justified as a cost-effective measure of synovitis, nevertheless can provide a good estimate of synovial volume within joints. Ultrasound also is proving potentially useful for diagnosing active disease at an early stage. Radiographic studies have shown that MRI and ultrasound exhibit very high specificity and sensitivity much higher than traditional radiographs. As imaging modalities decrease in cost, increase in availability, and grow in sophistication, it is possible they will have increased utility in the future for diagnostic and prognostic purposes in patients with inflammatory arthritis.
Generally, the markers discussed previously, including severe or aggressive baseline disease, poor function, the presence of rheumatoid factor and anti-CCP antibodies, and elevation of acute-phase markers, all suggest a worse prognosis. Beyond this, the presence of erosions and joint space narrowing on imaging studies early in the disease also are predictive of more destructive disease.

SYNTHETIC DMARDs (Table 1)

**Hydroxychloroquine**

HCQ is a logical consideration as an agent in patients with mild disease, or as an adjunct to other DMARDs as part of a combination approach in patients with more aggressive disease. There are few side effects, and approximately 40% of patients receive measurable benefit. When employing dosing schedules not exceeding 400 mg of HCQ each day, few cases of true retinopathy causing visual loss have been reported in the past, providing a measure of reassurance to clinicians about its safety. It has been hypothesized that these antimalarial agents inhibit antigen processing and presentation, leading to downregulation of the CD4⁺ response in sites of immune damage. It also has been shown that HCQ increases apoptosis of rheumatoid synoviocytes.

To date, there are no convincing data on the ability of HCQ to slow radiographic progression, and for patients with active, progressing disease, HCQ would be inadequate as monotherapy. Generally, the mild benefits and the lack of toxicity make HCQ a reasonable agent in early or mild disease, or as an adjunct to other DMARDs in combination therapy.

**Sulphasalazine**

SSZ is another DMARD alternative in the treatment of RA. In 1942, Svartz reported, in uncontrolled studies, the benefits of SSZ, which she synthesized from salicylic acid and a sulfonamide. The drug was first used by gastroenterologists for treatment of inflammatory bowel disease. The drug is generally thought to be efficacious for the treatment of RA in doses of 2000 to 3000 mg/day. Although allergic reactions and rashes can occur, gastrointestinal complaints tend to be more common; these potentially can be lessened through the use of enteric-coated preparations.
Beyond its role early in disease, or in the treatment of mild-to-moderate disease, is the potential role of SSZ in combination therapy. This therapy seems to be efficacious and well tolerated in combination with MTX and HCQ.

**Methotrexate**
The question for rheumatologists generally is not whether to use MTX, but rather, in a given patient, whether there are any reasons not to use it. Many factors, now well documented, support the use of MTX in RA, as follows:

- MTX acts quickly after being started, often within several weeks of the once-weekly dosing schedule.
- Doses can be escalated over time, from the initial levels of approximately 15 mg once weekly to more than 25 mg weekly (often given subcutaneously), to achieve efficacy without parallel increases in toxicity.
- MTX is inexpensive, and the monitoring necessary for toxicity is less expensive than for gold, penicillamine, other immunosuppressive agents, or cytotoxic drugs.
- MTX can suppress disease activity in a significant proportion of patients with longstanding RA in whom other traditional therapies have failed.
- MTX is well tolerated with more patients likely to be taking MTX than any other non-biologic DMARD therapy 2 to 5 years after it is first prescribed.
- In addition to providing efficacy in clinical parameters, MTX slows structural damage.
- Using MTX as a building block or the cornerstone of combination therapy has resulted in enhanced efficacy over MTX alone, without added increases in side effects.
- There have been minimal unexpected side effects after more than 20 years of surveillance.

As a practical matter, the dose of MTX can be rapidly escalated. Rapid dose escalation from 7.5 mg/wk to 20 mg/wk orally over 8 weeks has become the standard regimen for initiating therapy in early RA trials. This rapid dose escalation is generally well tolerated and has been shown to lead to rapid and sustained benefits in patients receiving MTX. Patients on MTX with persistent disease should have their dose titrated higher (either rapidly or in the more traditional 2.5-mg increments) until they improve, develop side effects, or reach the 20-mg to 25-mg threshold.
For patients unable to tolerate oral MTX, it is reasonable to consider changing to a subcutaneous or intramuscular injection once per week to limit some of the gastrointestinal side effects. Another alternative would be to use folic acid daily or folinic acid weekly as a means to reduce some of the side effects of the medication. Folic acid and folinic acid reduce the nausea and mucous membrane ulcerations that are bothersome side effects of the drug; administration of 5 mg of folic acid once weekly seems to be sufficient, although many physicians prescribe 1 mg daily.

It is generally accepted that in patients with normal liver function, minimal use of alcohol, and negative serologies for hepatitis B and C, liver function tests are necessary only once every 4 to 8 weeks. Routine biopsies of the liver, even after many years of continuous therapy, are not required as long as patients are appropriately monitored. If liver function tests suggest hepatocellular inflammation and a decreasing serum albumin despite improvement in the clinical activity of disease, biopsies should be considered if the drug is to be continued.

The other organ threatened by MTX, more in an idiosyncratic or hypersensitivity pattern than liver toxicity, has been the lungs. The pathology shows interstitial pneumonitis and bronchiolitis. Initial symptoms are often vague and nonspecific—a cough, sometimes with fever and dyspnea. While anticipating such a complication, the physician also must be concerned about and rule out infection with opportunistic organisms. Patients started on MTX must be given guidance and reminded to report any upper respiratory symptoms to the physician.

**Leflunomide**

The role of leflunomide in the treatment of RA continues to evolve. It seems to be effective as a monotherapy and safe and effective as an addition to MTX in combination therapy. Leflunomide suppresses the de novo synthesis of pyrimidine (uridine and cytidine) nucleotides by inhibiting dihydroorotate dehydrogenase. T lymphocytes and B lymphocytes have low amounts of this enzyme and no salvage pathways for pyrimidine nucleotide synthesis. The action of leflunomide is specific for lymphocytes.
Regarding adverse events, diarrhea was more common in leflunomide-treated patients, but others were the same as for MTX, including sporadic elevations of parenchymal liver enzymes.

Leflunomide is effective as monotherapy and has the ability to slow the radiographic progression of RA. It is reasonable, however, to consider using leflunomide as an add-on to MTX for patients who have only a partial response to MTX. Starting with 10 mg of leflunomide daily after a loading dose smaller than usual (e.g., 100 mg for the first 2 days) is a reasonable strategy.

It has been recommended that if serum aspartate transaminase or alanine transaminase increases to twice the upper limits of normal, or if these values are repeatedly mildly abnormal, the leflunomide dose should be reduced and discontinued if these abnormalities persist.

Generally, it is prudent to consider following the same guidelines for monitoring leflunomide that are applied to MTX, including warnings for patients regarding alcohol intake and screening for preexisting hepatitis B and C. Leflunomide can be used anywhere in the treatment algorithm, but generally has been given most commonly to patients instead of MTX when the latter drug is poorly tolerated or contraindicated. It also can be used in combination with MTX in resistant active arthritis.

**Gold salts, Penicillamine and azathioprine**

Three other secondary choices, some of which can be used in combinations with primary choices in active synovitis, are gold salts, penicillamine, and azathioprine. These agents generally would not be favored in early disease and have now been relegated to a role as agents used when other therapies have failed for either lack of efficacy or side effects.

There is ample published evidence that intramuscular gold therapy is beneficial for RA. Early use of gold salt injections may retard progression of joint erosions. Despite the known benefits, there also is ample evidence that the two intramuscular compounds, gold sodium thiomolate and gold sodium thioglucose, are being used less by rheumatologists because of the need for meticulous monitoring for serious toxicity (e.g., cytopenias, proteinuria) and the costs of administration and monitoring.
Auranofin, the triethylphosphine gold compound taken by mouth, has been available since the mid-1980s and continues to search for its niche in treatment strategies. Several issues are clear. Auranofin has different and less severe toxicity than the intramuscular preparations. Cytopenia and proteinuria do not occur, but a bothersome mild enterocolitis that generates diarrhea leads to treatment failure in many cases. Auranofin is less efficacious than MTX, injectable gold, penicillamine, or SSZ. The efficacy of auranofin, although less than the more potent drugs, has been shown, and there is justification for combining it with HCQ, SSZ, or MTX in treating early stages of active synovitis.

Azathioprine, in doses of 1 to 2.5 mg/kg/day, has been used alone and in combination in RA, often as a “steroid-sparing agent.” Neutropenia is the most common complication. One factor that leads to early toxicity from azathioprine is heterozygosity for mutant thiopurine methyltransferase alleles. Patients who have this defect (perhaps 10% of the population is at risk) metabolize the drug poorly and are forced to discontinue azathioprine therapy within 1 month because of hematologic side effects.

Initially used with apparent success, penicillamine was found to cause a selective decrease in CD4⁺ helper T cells. Although the “go low, go slow” sequence of starting with 125 or 250 mg/day and keeping doses no higher than 750 mg/day resulted in diminished toxicity, there have been sufficient side effects in many patients to discourage the routine use of penicillamine. Perhaps because of genetic differences among patients, the drug has been used with more apparent success and definite enthusiasm in the United Kingdom and Europe.

**Cyclosporine**

Cyclosporine, used by transplantation immunologists for many years to reduce solid organ allograft rejection, inhibits the activation of CD4⁺ helper-inducer T lymphocytes by blocking IL-2 and other T helper type 1 cytokine production, and by inhibiting CD40 ligand expression in T lymphocytes. The latter effect prevents T cells from delivering CD40 ligand–dependent signals to B cells. Newer micro-emulsion forms of cyclosporine are absorbed better and more consistently than older oil-based formulations.

Cyclosporine was first used in Europe in doses (e.g., 10 mg/kg/day) that caused unacceptable declines in renal function. Adding lower doses (2.5 to 5 mg/kg/day) to a stable dose of MTX and decreasing the cyclosporine if the patient's creatinine level increases to more than 30% of
initial values have been shown to provide substantial additive benefit over MTX alone. There is little to be gained by using cyclosporine as monotherapy early in disease, but in patients with RA who have an insufficient response to MTX, cyclosporine is a reasonable alternative to be added.
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