Core Management Principles in Rheumatoid Arthritis to Help Guide Managed Care Professionals

Sandeep K. Agarwal, MD, PhD

ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that affects approximately 1% of the population. Initial symptoms include joint swelling, stiffness, and tenderness, which are all causes of disability. The diagnosis of RA is based on patient history of joint pain and stiffness, the documentation of symmetric polyarticular joint synovitis, and laboratory measures including radiographs, inflammatory markers, and autoantibodies. As the disease progresses, synovial inflammation leads to cartilage damage, bone erosions, and joint destruction, the major causes of long-term disability. RA is associated with many comorbidities and complications, including cardiovascular disease, which is responsible for higher rates of mortality among patients compared with the general population. Over the past 2 decades, advances in the development of synthetic disease-modifying antirheumatic drugs (DMARDs) and biologic agents for RA have markedly changed treatment goals and management strategies.

OBJECTIVES: To review recent updates in the diagnosis and treatment of RA, as well as the importance of early and aggressive treatment and management strategies.

SUMMARY: Borrowing from other medical fields, a paradigm of “tight control” of RA has been supported by evidence and is gaining wide acceptance in rheumatology. In 2010, the American College of Rheumatology and the European League Against Rheumatism (EULAR) published revised classification criteria for RA, which will assist in the diagnosis of early RA and facilitate appropriate treatment intervention. Over the last decade, many patients on biologic agents have demonstrated that early and aggressive treatment of RA is beneficial in treating synovial inflammation, delaying joint damage, and improving patient outcomes. Contemporary management strategies based on early diagnosis, aggressive treatment, and regular monitoring have helped a significant number of patients with RA achieve current treatment goals of low levels of disease activity and, in some cases, clinical remission.

J Manag Care Pharm. 2011;17(9-b):S3-S8

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Accordingly, a joint working group of ACR and the European League Against Rheumatism (EULAR) was formed to develop new classification criteria for RA (Table 1).\(^\text{11}\) The criteria incorporate 4 domains including the types of joints involved, presence of autoantibodies, laboratory markers of inflammation, and symptom duration. These criteria are intended for patients with at least 1 joint with definite clinical synovitis (swelling, not just tenderness), and in whom the synovitis is not explained by another disease such as psoriasis, systemic lupus erythematosus, or gout. Patients are considered to have RA if they have a score of at least 6. Since these criteria are targeting early RA diagnoses, patients with long-standing disease that has become inactive or less active who previously satisfied these criteria or have erosions on radiographs will still be classified as having RA.

The new criteria are an important step forward to assist in the diagnosis of RA early in the disease course, thereby facilitating early intervention. However, it should be noted that these criteria are not intended to be a primary care screening or referral tool. They are classification criteria and not diagnostic criteria. It remains to be determined if these newer classification criteria are able to be used as diagnostic criteria and if they are successful in identifying patients with early RA. Indeed several recent reports have demonstrated that the 2010 classification criteria are slightly more sensitive than the 1987 ACR criteria.\(^\text{12-14}\) Finally, as imaging techniques such as MRI and ultrasound improve and/or become more affordable, it will be important to adapt these criteria to include these modalities.

**Benefits of Aggressive Treatment in Early RA**

Treatment of RA has clearly been shown to be effective in not only minimizing short-term disability by treating inflammation, pain, and stiffness, but also in preventing long-term disability through the slowing of radiographic progression in RA patients with established disease. Treatment with synthetic DMARDs (sulfasalazine, methotrexate, or leflunomide) is not only effective in treating joint inflammation,\(^\text{15-20}\) but also in slowing radiographic progression.\(^\text{19,21}\) Furthermore, it has been shown that biologics are also effective in decreasing clinical symptoms of RA and reducing radiographic progression.\(^\text{22-25}\)

Current paradigms now support the early and aggressive treatment of RA compared with delayed treatment. The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study compared combination synthetic DMARD therapy with single DMARD therapy in a cohort of early RA patients.\(^\text{26}\) At 2 years, 71% of the combination DMARD group achieved a 50% clinical response (ACR 50) compared with 58% using single-drug therapy.\(^\text{26}\) Interestingly, at 5 years (years 3-5 treatment was per physician discretion), both groups had similar improvement in clinical activity scores, but the combination group had significantly better radiographic scores than the single DMARD group.\(^\text{27}\) In addition, a meta-analysis comparing early (less than 2 years of disease duration) with delayed use of synthetic DMARDs demonstrated a significant reduction in long-term radiographic progression for RA patients treated early with DMARDs.\(^\text{28}\)

With the introduction of biologics, it has become more evident that early and aggressive treatment of RA is beneficial for some patients. Clinical studies have demonstrated that treatment of early RA patients with a combination of a tumor necrosis (TNF) inhibitor and methotrexate results in better clinical outcomes.\(^\text{29,30}\) The Behandel Strategieen (BeSt) study was a single-blind clinical trial where RA patients with less than 2 years of disease duration were randomized to 1

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**TABLE 1 2010 Rheumatoid Arthritis Classification Criteria\(^a\)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td><strong>Joints</strong></td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (large joints excluded)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (large joints excluded)</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative anti-CCP</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA (≤ 3 times the upper limit of normal)</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA (&gt; 3 times the upper limit of normal)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
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<tr>
<td>≥ 6 weeks</td>
<td>1</td>
</tr>
<tr>
<td><strong>Acute phase reactants</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or ESR</td>
<td>1</td>
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ACPA = anti-citrullinated protein antibody; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.
of 4 arms: (1) sequential DMARD monotherapy substitution, (2) step-up combination DMARD therapy, (3) combination DMARD therapy plus corticosteroids, and (4) combination therapy with DMARD plus infliximab (TNF inhibitor). Patients treated with infliximab combination therapy had faster clinical improvement (Disease Activity Score [DAS] in 44 Joints, Health Assessment Questionnaire [HAQ]) and less radiographic progression using the Sharp/Van der Heijde radiographic joints score than the monotherapy or step-up combination DMARD therapy. A 5-year follow-up report of the BeSt trial demonstrated that all groups had good clinical outcomes, but the infliximab combination group had less joint damage as assessed by radiographs. In the PREMIER study, patients with less than 3 years of disease duration were randomized to methotrexate alone, adalimumab alone, or methotrexate/adalimumab combination therapy. Early treatment with combination therapy proved superior to methotrexate alone or adalimumab alone in clinical treatment responses as well as radiographic progression of joint damage. Interestingly, methotrexate alone and adalimumab alone had similar clinical responses in treatment-naive patients, but adalimumab alone had less radiographic progression. Finally, the Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis (COMET) trial tested methotrexate monotherapy versus methotrexate and etanercept in methotrexate-naive RA patients with early moderate-to-severe disease of 3-24 months duration. At 1 year, 50% of patients in the combination group achieved remission compared with 28% in the methotrexate alone group. Furthermore, 80% of patients in the combination group achieved radiographic nonprogression, compared with 50% in the methotrexate alone group. In total, these studies suggest an advantage of treating patients early in the disease course, emphasizing the importance of early diagnosis, referral, and intervention.

**Goal-Directed Therapy in RA**

In the past, many of the decisions made by physicians for initiation and changes in treatment relied on an informal assessment of disease activity and functional status of the patient and physician. Subsequently, many clinical assessment tools have been developed and validated to quantify disease activity and patient functional status. Borrowing from other medical fields such as type 1 diabetes, a paradigm of “tight control” of RA has emerged. Indeed several studies have provided important data showing improved clinical outcomes in RA patients who had treatment decisions partially based on quantitative measurements and goals. In the Tight Control of Rheumatoid Arthritis (TICORA) study, patients in the “tight control,” or intensive, group had treatment augmented if the disease activity was higher than a specific cut-off. The routine therapy group was seen every 3 months and treatment decisions were based on physician judgement, not a specific target or disease activity measure. The intensive group had lower disease activity scores and higher disease remission rates than the routine therapy group. In the Computer Assistant Management in Early Rheumatoid Arthritis (CAMERA) trial, patients in the intensive group came to the clinic monthly where the dose of methotrexate was tailored to a predefined quantitative response level using a computer decision program. The result was a significant improvement in clinical responses relative to the conventional group. Therefore, multiple studies have now confirmed that goal-directed therapy in RA using quantitative measurements of disease activity results in improved clinical outcomes.

**Medical Treatment of Rheumatoid Arthritis**

In 2008, the ACR updated the recommendations for the medical treatment of RA. The guidelines discuss use of synthetic DMARDs that are commonly used including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide, as well as biologic agents. Currently, in the United States, there are 9 biologics approved for the treatment of RA, including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab), anakinra (IL-1 receptor antagonist), abatacept (CTLA4-Ig fusion protein), rituximab (anti-CD20 antibody), and tocilizumab (anti-IL-6 receptor antibody). Rituximab and tocilizumab are currently approved for RA patients who have failed treatment with at least 1 TNF inhibitor. Use of nonsteroidal medications and corticosteroids can be considered in all RA patients as adjunctive therapy but are not primary forms of therapy due to their lack of disease-modifying effects or long-term side effects.

Three clinical factors are important to help in clinical decision making: disease duration, RA disease activity assessment, and prognostic factors of poor outcomes. Disease duration is divided into less than 6 months, 6-24 months, and greater

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**TABLE 2**

<table>
<thead>
<tr>
<th>Disease Activity Levels Using Various RA Disease Activity Instruments*</th>
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<tr>
<td><strong>Instrument</strong></td>
</tr>
<tr>
<td>DAS28</td>
</tr>
<tr>
<td>SDAI</td>
</tr>
<tr>
<td>CDAI</td>
</tr>
<tr>
<td>RADAI</td>
</tr>
<tr>
<td>PAS</td>
</tr>
<tr>
<td>RAPID</td>
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CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score using 28 joint counts; PAS = Patient Activity Scale; RA = rheumatoid arthritis, RADAI = Rheumatoid Arthritis Disease Activity Index; RAPID = Routine Assessment Patient Index Data.
than 24 months. RA disease activity could be assessed as high, medium, or low based on several validated instruments to measure RA disease activity (Table 2): Disease Activity Score in 28 joints (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), rheumatoid arthritis disease activity index (RADAI), patient activity scale (PAS) or routine assessment patient index data (RAPID). Finally, the prognostic factors that should be considered in the treatment decision are functional limitation (HAQ Disability Index), extra-articular disease, seropositivity for RA or anti-CCP, and/or bony erosions by plain film radiography.

According to these most recent guidelines, synthetic DMARDs should be considered for all patients with RA. In patients with low disease activity who do not have features of poor prognosis and have less than 2 years of disease duration, monotherapy may be appropriate. In patients with long-standing disease, moderate to high disease activity, and/or features of poor prognosis, combination synthetic DMARD therapy was suggested. Interestingly, based on the growing literature demonstrating benefits of early aggressive therapy for patients with less than 6 months of disease duration and with high disease activity, the combination of methotrexate and a TNF inhibitor should be strongly considered. Otherwise, use of biologics is reserved for patients who have persistent disease activity (moderate to high) despite methotrexate or similar synthetic DMARDs.

The guidelines do not sufficiently address whether patients who fail methotrexate or similar synthetic DMARDs should be given a second synthetic DMARD. The best path for the patient who fails a single TNF inhibitor also has not been sufficiently addressed. Should this patient switch to another TNF inhibitor or change classes of biologics? Indeed the literature is conflicting in this regard with some studies suggesting that patients can respond to a second TNF inhibitor. Other studies suggest that the response to the second TNF inhibitor is less, and 1 study even suggested that the response to another class of biologics may be better than a second TNF inhibitor. Furthermore, the guidelines do not address whether the dose of infliximab should be increased and/or the dosing interval decreased. Both have been commonly used by physicians and can increase the duration of treatment but may not alter the ultimate discontinuation of the medication. These issues need to be studied and clarified to help patients, physicians, and health care providers make the best treatment decisions.

Finally, a critical part of the medical management of the RA patient is screening patients for comorbidities that might contraindicate specific treatments prior to treatment initiation. Leflunomide, methotrexate, and biologic agents should not be used in patients with active bacterial infections, active herpes zoster infections, or life-threatening fungal infections. Leflunomide and methotrexate are contraindicated in patients with white blood cell counts less than 3,000 per cubic millimeter (mm³) or a history of a hematologic malignancy in the past 5 years. Patients with liver function abnormalities should not receive all 3 drugs (sulfasalazine, leflunomide, and methotrexate), and patients with renal insufficiency should not be prescribed methotrexate. Leflunomide and methotrexate should not be used in patients with active or chronic hepatitis B and C. Finally, methotrexate and leflunomide should not be used in pregnant or lactating women.

All patients being considered for a biologic agent should be screened before, and annually thereafter, for exposure to tuberculosis. This can be performed with a tuberculin skin test or the interferon serum tuberculosis assays. The TNF inhibitors are contraindicated in patients with hepatitis B. Furthermore, patients with a history of multiple sclerosis or demyelinating disorders or congestive heart failure (New York Heart Association class III-IV) should not be prescribed TNF inhibitors.

The treatment of RA with synthetic DMARDs and biologics is effective but carries potential risks. Therefore, all patients should be routinely monitored for side effects with regular physician visits and blood tests. Blood counts, serum transaminases, serum albumin, and serum creatinine should be monitored frequently in all patients taking methotrexate, leflunomide, and sulfasalazine. Initially, the testing should be done monthly, but once a stable dose has been achieved for over 6 months, every 8-12 weeks is considered sufficient, and it is reasonable to obtain a complete blood count and liver function tests in patients on TNF inhibitors every 6 months. Patients on hydroxychloroquine should receive routine ophthalmologic examinations as well. All patients being treated should receive annual influenza vaccinations (injections of killed virus, not inactivated live virus nasal spray), routine pneumococcal vaccination, and hepatitis B vaccination. Finally, in patients on biologics, all live vaccinations should be avoided in patients and household contacts.

**Conclusions**

The treatment of RA has undergone several paradigm shifts, resulting in vastly improved patient outcomes. The armamentarium of medications that is effective in treating inflammation as well as slowing joint damage and destruction has greatly expanded. Low disease activity, and occasionally remission, as well as the prevention of joint damage are realistic goals for all patients. All patients with RA should receive disease-modifying treatments including synthetic DMARDs and possibly biologics early in the disease course. With aggressive but judicious use of medications and careful monitoring of disease activity and side effects, the health and quality of life in patients with RA will be vastly improved.
DISCLOSURES

This supplement was sponsored by PRIME Education, Inc. and Purdue University through an independent educational grant from Genentech, Biogen Idec, and Centocor Ortho Biotech Services LLC. Sandeep Agarwal received compensation from PRIME Education, Inc. for participating in the live continuing education activity on which this article is based and for writing the article. Agarwal reports payment for lectures and service on speaker bureaus from Genentech for programs on vasculitis.

REFERENCES


