

Preventing the Progression From Undifferentiated Arthritis to Rheumatoid Arthritis: The Clinical and Economic Implications

Michael H. Schiff, MD

Introduction

Over the past few years, the management of rheumatoid arthritis (RA) has emphasized early, aggressive therapy with traditional disease-modifying antirheumatic drugs (DMARDs) and/or antirheumatic biologic agents. This has been the result of a greater understanding of the pathophysiology of undifferentiated arthritis (UA) and RA, along with the availability of several biologic agents that down-regulate aspects of the autoimmune response that contribute to RA.

Approximately 40% to 50% of patients with UA experience spontaneous remission while roughly 30% progress to RA, and the remainder develop other conditions.^{1,2} Researchers have investigated criteria that can help identify those patients with UA who have a high probability of progressing to persistent and/or erosive RA. Once reliable criteria have been defined, the next question is whether active therapy, with either traditional DMARDs or antirheumatic biologic agents, can be effective in slowing or preventing disease progression. Clinical trials demonstrate that early treatment can delay or stop disease progression.³⁻⁶ From a managed care perspective, limiting treatment to only those patients with UA who would most benefit from active intervention has significant implications.

This article reviews the latest research supporting efforts to identify patients with UA who are at high risk of progressing to persistent and/or erosive RA, and offers insights on therapeutic approaches for these patients.

Defining Undifferentiated Arthritis

The term “undifferentiated arthritis” was incorporated into studies performed by the Leiden Early Arthritis Clinic in the Netherlands to describe cases of inflammatory arthritis where a specific diagnosis could not be made (Table 1).^{1,7,8} The question that follows is, why is UA important?

UA to RA Progression

Disease progression in patients who initially present with UA is comparable to that in patients who are initially diagnosed with RA. A study by van Aken and colleagues compared disease progression in patients who initially presented with UA and progressed to RA within 1 year (UA-RA group; n = 92) with disease progression in those who initially presented with RA (RA-RA group; n = 62) based

Abstract

A significant percentage of patients presenting with undifferentiated arthritis (UA) will progress to rheumatoid arthritis (RA), while others will undergo spontaneous remission. Evidence supports the use of therapeutic intervention in patients with UA to delay or halt disease progression and its long-term consequences. However, there is first a need to screen patients with UA to identify those with a high probability of progressing to RA who would benefit from antirheumatic therapy. The 2010 American College of Rheumatology/European League Against Rheumatism RA classification criteria were designed for this purpose. These criteria can aid clinicians in deciding when it is appropriate to initiate therapy in patients at risk of progressing to RA. These criteria can also have important implications in reducing the inappropriate and unnecessary use of antirheumatic agents in patients less likely to develop RA, thus reducing healthcare costs and minimizing the risk of sequelae associated with these agents. Use of disease-modifying antirheumatic drugs and biologic agents in patients with UA has been associated with delays in disease progression. However, further clinical studies are needed to fully evaluate the long-term clinical and economic outcomes of these agents in patients with UA.

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Table 1. UA Criteria: Leiden Early Arthritis Clinic, the Netherlands¹

Patients who did not fulfill the American College of Rheumatology 1987 criteria ⁷ for the diagnosis of RA
Patients who did not have psoriatic arthritis or spondyloarthritis
Patients with probable RA according to the 1958 criteria ⁸
RA indicates rheumatoid arthritis; UA, undifferentiated arthritis.

on the 1987 American College of Rheumatology (ACR) criteria.¹ Outcome measures were followed for 4 years following initial presentation.

No significant differences between the 2 groups were observed during any follow-up period (years 1, 2, 3, and 4) for radiographic progression of joint damage (as measured by Sharp/van der Heijde score) or disease activity and functional capacity (as measured by Health Assessment Questionnaire [HAQ] or Disease Activity Score [DAS]). Similar disease progression was observed in both groups despite more patients in the RA-RA group initiated on a DMARD by 3 months after presentation (100% vs 46%). This study suggests that patients with UA who eventually progress to RA have the same outcomes as those initially diagnosed with RA.

Predicting UA to RA Progression

Prediction rules are important tools in determining which patients with UA will progress to RA. The first validated prediction rule was developed in Europe and published in 2008. It used patient information that is regularly gathered during the initial office visit^{9,10}—age, gender, number and types of joints involved, duration of morning stiffness, C-reactive protein level, and serologic assay results (presence of rheumatoid factor [RF] and anti-citrullinated protein antibody [ACPA]). When applied to 3 independent cohorts of patients with early-onset UA, this prediction rule accurately estimated the risk of developing RA in more than 75% of the patients with UA.¹⁰

ACR/EULAR RA Classification Criteria, 2010

In September 2010, the ACR, in collaboration with the European League Against Rheumatism (EULAR), released the updated RA classification criteria with the goal of distinguishing newly presenting patients with undifferentiated inflammatory arthritis who had a high probability of developing persistent or erosive RA (Table 2).¹¹ These represent a significant change from the 1987 ACR criteria, which were not designed to identify patients with early RA or those at high risk of progressing to RA.^{7,12} The authors emphasize that the

2010 scoring system requires testing in various patient cohorts to demonstrate its validity. It will be important to determine if these criteria perform better for some patient cohorts than others and allow accurate individualization of treatment decision-making.

The 2010 ACR/EULAR RA classification criteria can have a significant impact on the management of patients at the very early stages of disease. Although the authors clearly state that this classification system is not designed as a referral tool to help diagnose patients with RA, it is likely that the criteria will be incorporated into clinical practice as part of the overall diagnostic procedure. This can aid clinicians in identifying patients at early stages of RA who would benefit from therapeutic intervention and/or referral to a specialist. It is also possible that these criteria will be adopted by managed care organizations to determine the appropriateness of particular interventions for patients with early signs of RA. There are also economic benefits to limiting therapy to those who have a high probability of developing persistent RA while minimizing therapy for low-risk patients.

Screening Patients With UA at Risk for Progressing to RA

Screening patients who initially present with UA to identify those who are at a high probability of progressing to RA can be beneficial for the patient and the provider.

Serologic Factors

Serologic factors are a convenient and accurate measure to predict progression to RA. RF has been used for several decades and is the only serologic factor mentioned in the 1987 ACR criteria.^{7,13} More recently, several other biologic markers have been identified, including various ACPAs (tested as anti-cyclic citrullinated peptides [anti-CCPs]).^{14,15}

To test the predictive value of ACPAs for progression to RA, van Gaalen and colleagues compared serologic assay

Table 2. 2010 ACR/EULAR RA Classification Criteria: Scoring System¹¹

Joint involvement (0–5 points)
Serologic assay results (RF or ACPA) (0–3 points)
Acute-phase reactants (CRP level or erythrocyte sedimentation rate) (0–1 point)
Duration of symptoms (0–1 point)
Cut-off point of 6 (or 60% probability of progressing to persistent and/or erosive RA): indicative of the presence of definite RA
ACPA indicates anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor.

results and disease progression in patients with UA.¹⁶ Of the 318 patients with UA, 69 were anti-CCP positive and 249 were anti-CCP negative at study entry. After 3 years, 93% of anti-CCP positive patients met the ACR criteria for RA, compared with 25% of anti-CCP negative patients (odds ratio, 37.8; 95% confidence interval [CI], 13.8–111.9) (Figure 1). The authors concluded that the presence of anti-CCP antibodies helps differentiate those patients with UA who are at risk for developing RA. The predictive value of RF and ACPA was further supported by a 4-year follow-up study of patients with undifferentiated polyarthritis.¹⁷

Although several different serologic markers can be used to screen patients with UA, studies have not definitively determined whether there are differences in predictive values associated with them. One study compared the predictive value of several of these markers, including RF and anti-CCPs.¹⁸ The results suggested that there were no significant differences in the predictive value of these serologic markers in distinguishing patients with UA who would later progress to RA. Furthermore, using a combination of serologic tests did not improve the predictive value, indicating that 1 assay is sufficient to make a determination.

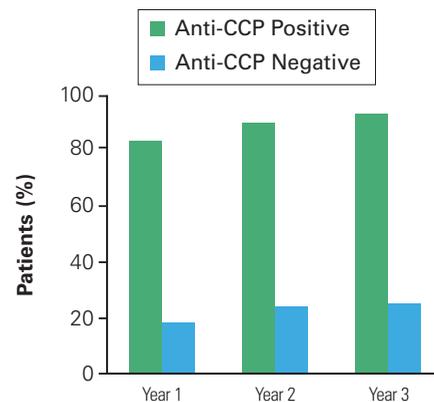
Radiographic Criteria

In addition to serologic markers, researchers have attempted to identify other measures to predict progression from UA to RA. These include radiologic evaluation of baseline erosions in joints of the hands and feet, magnetic resonance imaging (MRI) of joints, or a combination of radiologic evaluation, serologic assays, and symptoms.^{19–22} Although these methods may prove effective in predicting which patients with UA may progress to RA, the inclusion of radiographic criteria, particularly MRI scans, can be prohibitive in terms of cost and time as a screening tool, and because an experienced musculoskeletal radiologist would be needed.

2010 ACR/EULAR RA Classification Criteria

The 2010 ACR/EULAR RA classification criteria provide a standardized algorithm for assessing patients with UA. These criteria will be important when developing inclusion criteria for clinical trials with patients in the very early stages of disease. They will also allow a comparison of patient cohorts from different clinical trials that adopt these criteria. Because these criteria use information regularly gathered at initial presentation in the clinic, assessment will not add to the time and cost of evaluation. Although these criteria are not meant to be used as a reference tool for diagnosis, they can be incorporated as part of the screening and diagnostic process

■ **Figure 1.** Patients Fulfilling ACR Criteria for RA Based on Presence of Anti-CCP Antibodies¹⁶



ACR indicates American College of Rheumatology; CCP, cyclic citrullinated peptide; RA, rheumatoid arthritis.

for patients presenting with UA, and aid in the treatment decision-making process.

Benefits of Targeting Patients With UA for Active Treatment

When managing patients with UA, it is important to do a cost-versus-benefit analysis of initiating treatment immediately or delaying treatment until a definitive RA diagnosis is made. Delaying treatment can preserve resources and reduce the inappropriate or unnecessary use of antirheumatic agents in patients who may undergo spontaneous remission and do not eventually progress to RA. However, the cost-effectiveness of delaying treatment diminishes when long-term consequences are considered—more rapid progression of disease and disability and decreased likelihood of remission.

As mentioned earlier, the progression of disease in patients with UA who are eventually diagnosed with RA is similar to that in patients diagnosed with RA at initial presentation. Therefore, clinicians must focus on preventing or delaying disease progression through therapeutic intervention. Evidence suggests that treatment at earlier stages of disease is more effective than treating patients with long-standing disease and is associated with a greater probability of disease remission.^{6,23} This translates into long-term benefits such as improved quality of life, reduced disability, and decreased overall healthcare costs.

Clinical Implications of Treating Patients With UA

The PROMPT (PRObable RA: Methotrexate versus Placebo Treatment) study assessed the clinical consequences

of delaying therapy in patients with UA.⁴ It was a randomized, double-blind, placebo-controlled trial that evaluated the effectiveness of immediate methotrexate therapy for patients with UA versus delaying antirheumatic therapy until the 1987 ACR criteria were met for an RA diagnosis. A total of 110 patients who met the 1958 ACR criteria for *probable* RA were randomized to receive methotrexate weekly or placebo. The primary outcome measure was the percentage of patients meeting the 1987 criteria for RA.

PROMPT Study: Results

After 6 months, approximately 10% of patients in the methotrexate group met criteria for an RA diagnosis, compared with approximately 30% in the placebo group (Figure 2).

After 30 months, 40% of patients in the methotrexate group and 53% in the placebo group progressed to RA. All patients in the placebo group who progressed to RA did so during the first year, compared with only 50% of patients in the methotrexate group.

Most patients showed no change in radiographic progression, as determined by Sharp/van der Heijde score (73% in the placebo group and 88% in the methotrexate group). However, a greater percentage of patients in the placebo group showed some progression of disease above the smallest detectable change (27.5% vs 11.8%; $P = .046$).

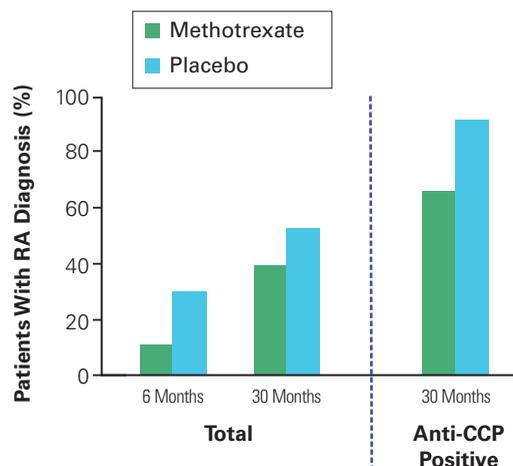
RESULTS BY PRESENCE OF ACPA

The benefits of methotrexate were more pronounced for ACPA-positive patients. A total of 14 of the 15 ACPA-positive patients who received placebo progressed to RA, compared with 8 of the 12 who received methotrexate (hazard ratio, 4.9; 95% CI, 1.88–12.79; $P < .001$). Only 2 of the 12 ACPA-positive patients receiving methotrexate achieved remission, suggesting that methotrexate did not induce remission but rather delayed the onset of RA. Despite the low rate of remission in patients who received methotrexate, the results show that early treatment can have an impact on disease progression of ACPA-positive patients.

Economic Implications of Treating Patients With UA

RA is associated with costs not only to the healthcare system but to the patient and society through lost productivity and reduced quality-adjusted life-years.²⁴ A recent European study estimated the overall mean annual costs of RA at €14,906—including costs to healthcare, patients and family, and productivity.²⁵ In the United States, excess healthcare costs associated with RA are estimated at \$8.4 billion while other costs attributable to RA are an additional \$10.9 billion (2005 US dol-

■ **Figure 2.** PROMPT Study Results: Patients With RA Diagnosis⁴



CCP indicates cyclic citrullinated peptide; PROMPT, PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment; RA, rheumatoid arthritis.

lars)—33% of these costs are allocated to employers, 28% to patients, 20% to the government, and 19% to caregivers.²⁶ Any effort to significantly reduce the burden of this condition must focus on decreasing the number of patients who progress to RA.

The cost difference between managing patients with UA versus those with RA can be significant. A French study using 2003 data determined that the direct and indirect costs of UA and RA were €2424 and €5928, respectively (Figure 3).²⁷ Two strong predictors of higher costs overall were increased pain and the presence of RF. Although differences in the annual costs of UA and RA have been observed, more research is needed to fully understand the cost-effectiveness of early intervention in patients with UA and of screening patients with UA (ie, use of serologic assays) to identify those who would benefit from early therapy.

Therapeutic Options to Prevent or Delay UA to RA Progression

Few clinical trials have evaluated the use of antirheumatic agents to prevent the progression of UA to RA.

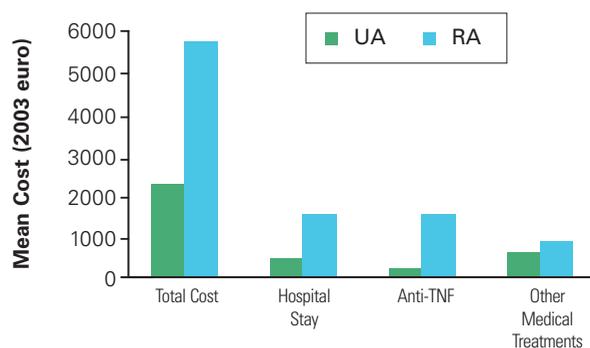
Methotrexate Versus Placebo

As described earlier, the pivotal PROMPT study demonstrated that for patients presenting with UA, methotrexate was effective in delaying the progression to RA and reducing radiographic progression, although it did not show any significant benefit in disease remission.⁴

Infliximab Versus Placebo

Infliximab was compared with placebo in patients with UA

■ **Figure 3.** Costs Associated With UA and RA²⁷



RA indicates rheumatoid arthritis; TNF, tumor necrosis factor; UA, undifferentiated arthritis.

of less than 12 months' duration who relapsed after a single corticosteroid injection.²⁸ This double-blind, placebo-controlled trial included 17 DMARD-naïve patients. Infliximab was administered to 10 patients at weeks 0, 2, 6, and 14 and methotrexate was added at week 14 in the event of no clinical response. At week 26, 1 of 7 patients (14%) in the placebo group and 2 of 10 (20%) in the infliximab group achieved clinical remission. There were no significant differences between the 2 groups with respect to any of the secondary outcomes—early morning stiffness, tender joint score, HAQ, or DAS in 28 joints. By week 52, all patients in the infliximab group and 5 of 7 patients in the placebo group had progressed to RA. The use of infliximab showed modest short-term relief in these patients but did not prevent the development of RA.

Abatacept Versus Placebo

Another study compared abatacept with placebo in patients with UA who also tested positive for ACPA.⁵ The patients received abatacept (n = 28) or placebo (n = 28) for 6 months and were assessed at months 12 and 24. At month 12, fewer patients in the abatacept group developed RA, although the difference was not significant (46% vs 67%; 95% CI, -47.4% to 7.8%). Abatacept was associated with a delay in progression to RA. Patients in the abatacept group showed greater radiographic and MRI inhibition of disease, which was maintained 6 months after the treatment stopped. The authors concluded that the progression of RA can be altered by modulating the T-cell response at very early stages of disease.

These 2 small studies suggest the possibility of some beneficial effect of biologic agents in patients with UA. Larger, randomized clinical trials are needed to answer the question of whether biologic therapy is warranted in this patient population.

Conclusion

Release of the 2010 ACR/EULAR RA classification criteria may encourage evaluation of the long-term clinical and economic outcomes associated with aggressive treatment with antirheumatic agents in UA. Screening patients for serologic markers of RA can be an accurate and cost-effective method to identify those who would benefit from pharmacotherapy, while minimizing the inappropriate use of antirheumatic agents in low-risk patients.

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Address correspondence to: Michael H. Schiff, MD, University of Colorado School of Medicine, 5400 South Monaco St, Greenwood Village, CO 80111. E-mail: lmschiff@aol.com.

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