# Perspectives on Rheumatoid Arthritis for the Orthopedic Surgeon: Overview of Early Diagnosis and the Tumor Necrosis Factor Antagonists

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## Abstract

**Rheumatoid arthritis (RA) is the most common inflammatory arthritis in the United States. As part of ongoing efforts to halt joint damage, preserve function, and reduce associated mortality, the current emphasis in RA management is on prompt diagnosis and the early use of disease modifying antirheumatic drug (DMARD) therapy. Improved serologic tests and updated classification criteria are now available to assist in making an earlier diagnosis of RA. As a therapeutic class, tumor necrosis factor antagonists are widely used by rheumatologists and provide significant benefits to patients who have an incomplete response to methotrexate or other DMARDs. With the reported low concordance between orthopedic surgeons and rheumatologists regarding the potential benefits of surgery to treat RA, there is an opportunity for improved collaboration between these specialties in the care of RA patients. Updates on diagnosis and medical therapy of RA may help orthopedic surgeons appreciate the rheumatologist's approach to this disease.**


Rheumatoid arthritis (RA) is the most common inflammatory arthritis; prevalence estimates range from 0.6% in the United States[1] to as much as 2% worldwide.[2] Rheumatoid arthritis is a systemic autoimmune disease associated with disability[3] and increased mortality.[4] As part of ongoing efforts to halt joint damage, preserve function, and reduce associated mortality, the current emphasis in RA management is on prompt diagnosis and the early use of disease modifying antirheumatic drug (DMARD) therapy.

Despite an increasingly aggressive medical approach to RA management, orthopedic surgeons will continue to play a role in the treatment of these patients. For RA patients unable to achieve remission with medical therapy, surgical options should be considered to reduce pain and improve function. The reported low concordance between orthopedic surgeons and rheumatologists regarding the potential benefits of surgery[5] suggests an opportunity for improved collaboration between these specialties in the care of RA patients. Updates on diagnosis and medical therapy of RA may help orthopedic surgeons appreciate the rheumatologist's approach to this disease.

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The diagnosis of RA is made by a combination of symptoms, physical examination findings, serologic tests, and radiographic abnormalities. Common sites of involvement in RA include the wrists, the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints of the fingers, the knees, and the metatarsophalangeal (MTP) joints of the feet. Although originally designed for research purposes, the 1987 classification criteria for RA developed by the American College of Rheumatology (formerly the American Rheumatism Association) have guided the approach to diagnosis.[6] The 1987 criteria have good sensitivity and specificity in established disease,[6] but a low ability to distinguish which patients with newly observed inflammatory polyarthritis will progress to persistent RA.[7] These criteria also predate the use of the highly specific cyclic citrullinated peptide (CCP) antibody, an important marker of disease, especially in patients who test negative

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*Am J Orthop.* 2011;40(9): E193-E195. 

for rheumatoid factor (RF).[1] These limitations of the 1987 criteria possibly contribute to delays in referral of patients with evolving RA to rheumatologists.

## Why Should Orthopedists Know About Diagnosing RA?

Efforts to enhance early referral of potential RA patients to rheumatologists largely have been directed at primary care providers. Clinical guidelines extracted from the approach of early arthritis clinics suggest patient features that should prompt referral to rheumatology.[8] As some patients with early RA are initially referred to orthopedists, elements of these guidelines may be useful for surgeons to facilitate early referrals of suspected RA patients to their rheumatology colleagues. In 2010, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published revised classification criteria for RA, providing an updated framework rheumatologists and orthopedic surgeons could use to make an earlier diagnosis of RA.[9]

## Why Should Orthopedists Know About Nonsurgical Management of RA?

The current medical management of RA is focused on early DMARD therapy. New therapeutic agents that target specific immunopathologic aspects of RA are increasingly used in combination with standard DMARDs, such as methotrexate. These biologic DMARDs or "biologics," entered clinical use in 1998; the first available agents were the tumor necrosis factor-alpha (TNF-α) antagonists, infliximab and etanercept. Additional drugs in this class have since been approved, including adalimumab, golimumab, and certolizumab. Other classes of biologic DMARDs are available for RA treatment and are typically used when patients have an inadequate response to TNF-α antagonists. These include rituximab, an antibody directed against B lymphocytes; abatacept, a selective T-cell costimulation inhibitor; and tocilizumab, an interleukin (IL)-6 receptor antagonist.

The increased use of biologic DMARDs by rheumatologists makes it highly likely that orthopedic surgeons will encounter RA patients treated with these agents. A familiarity of these agents will improve the collaboration of orthopedic surgeons with rheumatologists in the care of these patients. The remainder of this column will focus on the TNF-α] antagonists approved for use in RA.

Familiarity with outcome instruments used in rheumatology clinical trials is useful to interpret the performance of biologic DMARDs. The commonly used ACR scoring system incorporates changes in 7 laboratory and clinical domains (including tender and swollen joints counts) to quantify percentage improvement in individual patients.[10] For example, an ACR20 response, currently accepted as the minimum meaningful clinical difference, represents 20% improvement in 5 of the 7 criteria without worsening in the remaining 2 domains.

## TNF-α Antagonists

Five TNF-α antagonists are currently available: infliximab, etanercept, adalimumab, golimumab, and certolizumab. Each has unique immunologic properties, but all inhibit the proinflammatory action of TNF-α in RA. All 5 agents have demonstrated clinical efficacy and the ability to avert radiographic progression. These agents are typically used in combination with nonbiologic DMARDs, most often methotrexate. In the absence of data to suggest superiority of any of these medications, initial choice is largely determined by patient and physician preference.

### Infliximab

Infliximab, the first of this class, is a chimeric, human-mouse, monoclonal TNF-α antibody that binds to both receptor-bound and soluble TNF-α. Infliximab is administered by intravenous infusion. The usual dosing regimen is 3 mg/kg at baseline, 2 weeks, 6 weeks, and every 4 to 8 weeks thereafter, with a maximum dose of 10 mg/kg per infusion. In a study of 428 patients by Lipsky and colleagues,[11] patients with persistently active disease, despite methotrexate monotherapy, were randomly assigned to receive infliximab plus methotrexate, or placebo plus methotrexate. Approximately 52% of the infliximab plus methotrexate group achieved an ACR20 response, compared with 17% of the patients treated with placebo plus methotrexate.

### Etanercept

Etanercept is a soluble p75 TNF-α receptor that competes with the native receptor, blocking the proinflammatory effect of TNF-α. Initially, in studies and clinical use, etanercept was administered as a subcutaneous injection twice weekly. In the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO), combination treatment with etanercept and methotrexate produced an ACR20 response in 85% of patients, compared with 76% in the etanercept plus placebo group and 75% in the methotrexate plus placebo group.[12] Subsequently, in a study of 420 RA patients, Keystone and colleagues[13] compared the efficacy of 2 etanercept dosing schemes: 50 mg once weekly vs 25 mg twice weekly. No significant differences were observed in safety or efficacy between the 2 treatment groups. Based on these results, etanercept is typically prescribed at the dosing schedule of 50 mg subcutaneously administered once weekly.

### Adalimumab

Adalimumab is a fully humanized, monoclonal antibody directed against TNF-α. Its dose in RA is 40 mg injected subcutaneously every 2 weeks. In the PREMIER trial, researchers randomly assigned 799 patients with less than 3 years of disease, who were methotrexate naïve, to receive either oral methotrexate 20 mg per week plus placebo every other week, subcutaneous adalimumab 40 mg every other week plus placebo weekly, or oral methotrexate 20 mg per week plus subcutaneous adalimumab 40 mg every other week. At 2-year follow-up, 69% of patients assigned to combination therapy achieved an ACR20 response, compared with 49% of patients treated with adalimumab plus placebo and 56% of patients treated with methotrexate plus placebo.[14]

### Golimumab

Golimumab is a human monoclonal antibody to TNF-α. It is administered as a monthly subcutaneous injection, offering improved patient convenience compared to the other TNF-α antagonists. In a study of active RA patients despite methotrexate monotherapy, methotrexate plus placebo was compared to methotrexate plus golimumab 50 mg every 2 weeks or 4 weeks and methotrexate plus golimumab 100 mg every 2 weeks or 4 weeks.[15] At 16 weeks, an ACR20 response was achieved by 37% of the placebo group, 60% of patients receiving golimumab 50 mg monthly, 50% of patients receiving golimumab every 2 weeks, 56% of patients receiving golimumab 100 mg monthly, and 79% of patients receiving golimumab 100 mg every 2 weeks.[15] The U.S. Food and Drug Administration–approved dose for golimumab for RA is 50 mg once monthly.[16]

### Certolizumab

Certolizumab pegol is the final TNF-α inhibitor available for the treatment of RA. Its structure is unique in that is consists of a humanized Fab′ fragment attached to a 40-kd polyethylene glycol framework.[17] Certolizumab pegol was studied in RA patients with active disease despite methotrexate treatment: patients were assigned to receive placebo plus methotrexate; certolizumab pegol 200 mg every 2 weeks plus methotrexate after initial dosing with 400 mg every 2 weeks at 0, 2, and 4 weeks; or certolizumab pegol 400 mg every 2 weeks plus methotrexate. At 24 weeks, ACR20 response rates were 13.6% in the placebo group, 58.8% in the 200 mg certolizumab pegol group, and 60.8% in the 400 mg certolizumab group[17]. Approved dosing of certolizumab pegol is 400 mg injected subcutaneously at 0, 2, and 4 weeks, followed by 200 mg injected every 2 weeks with an optional maintenance dose of 400 mg injected every 4 weeks.[16]

## Conclusion

Rheumatoid arthritis is the most common inflammatory arthritis worldwide. Improved serologic tests and updated classification criteria are now available to assist in making an earlier diagnosis of RA. As a therapeutic class, tumor necrosis factor antagonists are widely used by rheumatologists and provide significant benefits to patients who have an incomplete response to methotrexate or other DMARDs.

Future topics of discussion include an overview of other classes of biologics and a rheumatology perspective on the perioperative management of DMARDs and biologics in RA patients who require orthopedic surgery.

## Authors' Disclosure Statement

The author reports no actual or potential conflict of interest in relation to this article.

## References


1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15–25.
2. Vallbracht I, Rieber J, Oppermann M, Förger F, Siebert U, Helmke K. Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis. *Ann Rheum Dis.* 2004;63(9):1079–1084.
3. Welsing PM, van Gestel AM, Swinkels HL, Kiemeny LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum.* 2001;44(9):2009–2017.
4. Pincus T, Sokka T, Wolfe F. Premature mortality in patients with rheumatoid arthritis: Evolving concepts. *Arthritis Rheum.* 2001;44(6):1234–1236.
5. Alderman AK, Chung KC, Kim M, Fox DA, Ubel PA. Effectiveness of rheumatoid hand surgery: contrasting perceptions of hand surgeons and rheumatologists. *J Hand Surg.* 2003;28A:3-11.
6. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31(3):315–324.
7. Harrison BJ, Symmons DP, Barrett EM, Silman AJ; American Rheumatism Association. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. *J Rheumatol.* 1998;25(12):2324–2330.
8. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis.* 2002;61(40):290–297.
9. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569-2581.
10. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum.* 2007;57:193-202.
11. Lipsky PE, van der Heijde DM, St Clair EW, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* 2000;343(22):1594–1602.
12. Klareskog L, van der Heijde D, de Jager JP, et al; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effects of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet.* 2004;363(9410):675–681.
13. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2004;50(2):353–363.
14. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54(1):26–37.
15. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum.* 2008;58(4):964-975.
16. Simponi [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2011.
17. Keystone E, van der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is signficiantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 2008;58:3319-3329.
18. Cimzia [package insert]. Smyrna, GA: UCB, Inc.; 2011.