Perspectives on Rheumatoid Arthritis for the Orthopedic Surgeon: Overview of Non–Tumor Necrosis Factor Biologic Drugs and Perioperative Management

Michael P. Keith, MD

Abstract

Early use of disease modifying antirheumatic drug (DMARD) therapy has become the standard of care in the treatment of rheumatoid arthritis (RA). Methotrexate remains the DMARD of choice in patients without contraindications for its use. The addition of a tumor necrosis factor-α antagonist to methotrexate makes clinical remission more likely. Despite the effectiveness of this approach, some patients continue to have active disease. In these patients, the use of rituximab, abatacept, or tocilizumab provides additional options when first-line therapies inadequately control RA. For orthopedic surgeons and rheumatologists, additional therapeutic options increase the complexity of perioperative medical management. No consensus has been reached by rheumatology societies as to the optimal approach for the use of biologic and traditional DMARDs around the time of surgery. Therefore, perioperative medication management should be individualized and based on a discussion of potential risks and benefits involving patients, surgeons, and rheumatologists.

Early use of disease modifying antirheumatic drug (DMARD) therapy has become the standard of care in the medical management of rheumatoid arthritis (RA). Conventional DMARDs continue to play an important role in the treatment of RA. Methotrexate remains the first DMARD of choice in patients without contraindications for its use.[1,2] As reviewed recently,[3] the tumor necrosis factor–α (TNF-α) antagonists increase the likelihood of clinical remission for patients who have an incomplete response to methotrexate or other nonbiologic DMARDs. Available anti-TNF-α medications include etanercept, infliximab, adalimumab, golimumab, and certolizumab. Though each of these agents has unique immunologic properties, all of them oppose the proinflammatory effect of TNF-α in RA. Direct comparisons of one anti-TNF-α medication to another have not been performed, so initial choice is largely based on patient and physician preference.

Despite the effectiveness of the combination of methotrexate and TNF-α antagonists, 20%-40% of patients treated with this combination will experience an inadequate response to therapy.[4] For some patients, changing the anti-TNF-α agent will provide a clinical response.[5] However, when this approach is unsuccessful, several additional classes of biologic DMARDs are available.

Building on the discussion from the previous column,[3] the non-TNF-α antagonist biologic DMARDs rituximab, abatacept, and tocilizumab will be reviewed to familiarize orthopedic surgeons with the full spectrum of therapies they may encounter in caring for patients with RA. As the availability of additional therapies increases the complexity of medical management for RA, collaboration between rheumatologists and orthopedic surgeons is needed to ensure optimal perioperative management. Of particular importance to surgeons, data from the medical literature and the recommendations from rheumatology organizations pertaining to perioperative care of RA patients will be presented.

RITUXIMAB

Rituximab is a monoclonal antibody directed against CD20+ B lymphocytes. CD20 is a surface antigen expressed on pre–B and mature B lymphocytes, but not on stem cells or differentiated plasma cells.[6] Rituximab temporarily depletes the CD20+ B cell population, down regulating inflammatory processes involved in the pathogenesis of RA.[6] Edwards and colleagues initially described the efficacy of B cell depletion in RA in a randomized, double-blind, controlled study in 2004.[6]

Subsequent studies defined rituximab dosing in RA and demonstrated its utility in TNF-α antagonist treat-

CDR Keith is Chief of Rheumatology, Walter Reed National Military Medical Center, and Associate Professor of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Address correspondence to: Michael P. Keith, MD, FACP, FACR, Rheumatology Service, WRNMMC, 8901 Wisconsin Ave, Bethesda, MD 20889 (tel, 301-295-4517; fax, 301-295-5218; e-mail, michael.keith@med.navy.mil).

***Am J Orthop.* 2011;40(12):E272-E275.**

ment failures. The Dose-ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) study reported that rituximab, given as either a 500-mg or 1000-mg infusion, 2 weeks apart, combined with methotrexate was effective for treating RA. In the DANCER trial, ACR 20 responses of 55% and 54% were obtained in the 500-mg and 1000-mg rituximab arms respectively, compared with 28% for methotrexate plus placebo.[7] The Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial enrolled 520 patients who had an inadequate response to 1 or more TNF-α antagonists. In the REFLEX study, the combination of methotrexate and rituximab, given as two 1000-mg intravenous infusions on days 1 and 15, was highly effective for the treatment of RA in patients who experienced treatment failure with TNF-α antagonists.[8]

Rituximab is currently approved for the treatment of RA refractory to TNF-α inhibitors. Repeated rituximab infusions are generally well tolerated and intravenous corticosteroids given immediately prior to administration have been shown to reduce the risk of infusion reaction.[7] In a meta-analysis of RA patients treated with rituximab, no increased risk of infection was observed compared with placebo.[9]

Abatacept

In RA, T-lymphocyte activation plays an active role in immunopathogenesis. T-cell activation requires a secondary signal in addition to the primary signal accomplished through T-cell receptor interactions with the antigen-presenting cell. The immune system regulates this process through the action of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitor of the CD 28 and CD80/86 co-stimulatory pathway.[10] Abatacept is a fusion protein of CTLA-4 and immunoglobulin that inhibits the CD28 and CD80/86 costimulatory pathway, decreasing T-cell activation in RA.

Abatacept is approved by the US Food and Drug Administration for RA, in combination with methotrexate, as the initial biologic DMARD or in TNF-α antagonist failures. The Abatacept Trial in Treatment of Anti-TNF INadequate responders (ATTAIN) trial reported superior clinical outcomes at 6 months in TNF-α failures treated with abatacept plus a DMARD (usually methotrexate) versus a DMARD plus placebo; 50.4% of patients in the abatacept arm achieved ACR20 response compared with 19.5% in the placebo arm.[11] An additional study by Kremer and colleagues showed ACR 20 responses at 1 year of 67.9% for patients with an inadequate response to methotrexate monotherapy treated with abatacept plus methotrexate compared with 39.7% for patients who received methotrexate plus placebo.[12] Abatacept is administered by intravenous infusion at a dose of 10 mg/kg at baseline, 2 weeks, 4 weeks, and every 4 weeks thereafter.

Tocilizumab

Tocilizumab is the most recently approved biologic DMARD for the treatment of RA. It is an anti-interleukin-6 (IL-6) receptor antibody that prevents IL-6 from binding to its receptor.[2] IL-6 is highly active in RA: it induces activated B-cells to produce immunoglobulins; it generates autoreactive T-cells by causing an imbalance between Th17 lymphocytes and regulatory T-cells; it acts on hepatocytes to produce acute phase reactants including c-reactive protein; and it activates endothelial cells to produce cytokines to recruit leukocytes to inflamed joints.[13] Inhibition of IL-6 with tocilizumab has been studied in 2 groups of patients with RA: those with an incomplete response to methotrexate and those who experienced treatment failure with 1 or more TNF-α antagonists.

The Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) study examined the safety and efficacy of tocilizumab in RA patients with an inadequate response to methotrexate. The investigators randomly assigned 359 patients to 1 of 7 treatment arms: tocilizumab at 2 mg/kg, 4 mg/kg, or 8 mg/kg given as monotherapy or combined with methotrexate or methotrexate plus placebo.[14] An ACR20 response was obtained in 31% (II doses of mg/kg), 61% (4 mg/kg), and 63% (8 mg/kg) of the tocilizumab monotherapy arms, compared with 41% in patients treated with methotrexate plus placebo.[14] Similarly, an ACR20 response occurred in 64% (2 mg/kg), 63% (4 mg/kg), and 74% (8 mg/kg) of the tocilizumab plus methotrexate treated patients.[14]

The Research on Actemra Determining Efficacy of Anti-TNF Failures (RADIATE) trial evaluated the effectiveness of tocilizumab plus methotrexate in patients with RA who failed treatment with 1 or more TNF-α antagonists. In this study, 499 patients were randomly assigned to recieve 4 mg/kg or 8 mg/kg tocilizumab or placebo plus methotrexate.[4] At 24 weeks, 50% of the 8 mg/kg tocilizumab group and 30.4% of the 4 mg/kg tocilizumab group achieved an ACR20 response, compared with only 10.1% of the placebo group.[4] Taken together, the results of CHARISMA and RADIATE demonstrate the potential benefit of tocilizumab when methotrexate or TNF-α antagonists fail to control RA.

Combination Biologic Therapy

Biologic DMARDs are typically prescribed for patients who have an inadequate response to methotrexate monotherapy because clinical and radiographic improvement can be achieved with combination regimens. Initially, combination biologic therapy was considered because it was thought that targeting multiple aspects of RA immunopathology would lead to improved clinical outcomes. In clinical trials, however, the combination of abatacept and etanercept produced no increase in efficacy over either agent alone. In addition, the combination treatment was found to increase infection rates over biologic monotherapy.[15] Therefore, combination therapy with biologic DMARDs is currently not recommended.

Perioperative Management

The current emphasis on DMARD therapy makes it highly likely that orthopedic surgeons will encounter RA patients needing surgery who are using immunosuppressive medications. The potential impact of these medications on surgical

site infection has been described previously and suggests that a break in medical therapy should be considered in the perioperative period.[16] However, the risk of disease flare during this reduction in therapy intensity, which may subsequently impair rehabilitative efforts, is an important competing concern.[17]

Methotrexate is the most studied DMARD in RA patients undergoing surgery. Results of initial studies suggested an increased risk of infection when methotrexate was continued perioperatively. In 1991, Bridges and colleagues reported 4 infections in 19 procedures on patients who continued methotrexate therapy during surgery and no complications in 34 procedures on patients who halted methotrexate therapy at least 4 weeks before surgery.[18] In 1996, Carpenter and colleagues reported a similar experience; they prospectively evaluated the effect of methotrexate on postoperative complications in 32 RA patients undergoing total joint arthroplasty.[16] Nineteen patients were assigned to stop methotrexate 1 week before and during the week of surgery. The remaining 13 patients continued methotrexate during the perioperative period. There were no postoperative flares of RA in either group. However, 4 postoperative infections were observed in the methotrexate arm and no postoperative infections were observed in the discontinuation arm.[16] Based on these reports, common practice was to temporarily discontinue methotrexate around the time of surgery.

More recent studies of methotrexate in RA patients undergoing orthopedic surgery report a much lower incidence of surgical site infections than previous trials. In the largest study to date, Grennan and colleagues studied 338 patients with RA undergoing elective orthopedic surgery: 88 patients continued methotrexate, 72 patients stopped methotrexate perioperatively, and 228 patients had never used methotrexate.[19] At 1-year follow-up, the methotrexate continuation group showed statistically lower infection and complication rates as compared with the other 2 groups.[19] Authors of 2 additional smaller studies also reported no increase in postoperative complications in patients using methotrexate compared with patients who either stopped methotrexate or who had never used it.[20,21] Authors from these studies concluded that methotrexate should not be stopped before elective orthopedic surgery.

The potential impact of biologic DMARDs on postoperative complications in RA patients undergoing orthopedic surgery also has been examined. At present, data are limited to TNF-α antagonists, with mixed results; no studies have evaluated the perioperative use of rituximab, abatacept, or tocilizumab. In a study of 16 patients, the rate of complications was not increased in patients who continued etanercept, infliximab, or adalimumab during surgery (n=4) compared with patients who stopped these medications (n=12).[22] A retrospective study of 1219 procedures in 768 patients showed perioperative use of anti-TNF-α agents was not associated with a statistically significant increase in surgical site infections compared with patients who did not receive or who had stopped anti-TNF-α therapy.[23] In contrast to these reports, results of a 2011 retrospective study of infection after total knee (n=339) or hip (n=81) arthroplasties in RA patients suggested an increased risk of surgical site infection in patients treated with infliximab or etanercept compared with patients who had not used these medications.[24]

Recommendations from Professional Organizations

Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have published guidelines for the use of traditional and biologic DMARDs in the treatment of RA. EULAR does not specifically make recommendations in its guidelines regarding the perioperative management of RA therapies.[2] Though the ACR guidelines recommend that biologic DMARDs should be stopped 1 month prior to surgery, the members of the expert panel did not feel available data were conclusive enough to make a recommendation for traditional nonbiologic DMARDs (e.g. methotrexate) in the perioperative period.[1]

Conclusion

Rituximab, abatacept, and tocilizumab provide additional therapeutic options for patients with RA who continue to have active disease despite therapy with methotrexate and a TNF-α antagonist. Like TNF-α inhibitors, these agents typically are used in combination with methotrexate. Despite the hypothetical appeal of blocking multiple immune system targets in RA, at present there is no evidence to support the use of combination biologic DMARD therapy.

The perioperative management of RA patients with increasingly complex medication regimens highlights another area for collaboration between orthopedic surgeons and rheumatologists. Recent clinical trials and clinical guidelines suggest the risk of surgical site infection, as a result of continuation of DMARDs in the perioperative period, is lower than previously thought. The author prefers the continuation of methotrexate around the time of surgery and recommends the temporary cessation of biologic DMARDs. Until more formal guidelines are issued by professional organizations, perioperative medication management should be individualized for each patient. The treatment approach should be based on a discussion of potential risks and benefits involving patients, surgeons, and rheumatologists.

Author's Disclosure Statement

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

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, or the U.S. Government

References

1. Saag KG, Teng GG, Patkar NM, et al; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762–784.

2. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69:964-975.
3. Keith MP. Perspectives on rheumatoid arthritis for the orthopedic surgeon: overview of early diagnosis and the tumor necrosis factor antagonists. *Am J Orthop.* 2011;40(9):E193-E195.
4. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biological: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* 2008;67:1516-1523.
5. Buch MH, Bingham SJ, Bejarano et al. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. *Arthritis Rheum*. 2007;57(3):448–453.
6. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *New Engl J Med*. 2004;350(25):2572–2581.
7. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al; DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of phase a IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 2006;54(5):1390–1400.
8. Cohen SB, Emery P, Greenwald MW, et al; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006;54(9):2793–2806.
9. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept, and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis.* 2009;68(1):25–32.
10. Sharpe AH, Abbas AK. T-cell costimulation—biology, therapeutic potential, and challenges. *New Engl J Med.* 2006;355(10):973–975.
11. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *New Engl J Med.* 2005;353(11):1114–1123.
12. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: A randomized trial. *Ann Int Med.* 2006;144(12):865–876.
13. Kishimoto T. Interleukin-6: from basic science to medicine- 40 years in immunology. *Annu Rev Immunol.* 2005;23:1-21.
14. Maini RN, Taylor PC, Szechinski J, et al. CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 2006;54(9):2817-2829.
15. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: A randomised clinical trial. *Ann Rheum Dis.* 2007;66(2):228–234.
16. Carpenter MT, West SG, Vogelgesang SA. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. *Orthopedics.*1996;19(3):207-210.
17. Steuer A, Keat AC. Perioperative use of methotrexate – a survey of clinical practice in the UK. *Br J Rheumatol.* 1997;36:1009-1011.
18. Bridges SL, Lopez-Mendez A, Han KH, et al. Should methotrexate be discontinued before elective orthopedic surgery in patients with rheumatoid arthritis? *J Rheumatol.* 1991;18(7):984-988.
19. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Ann Rheum Dis*. 2001;60:214-217.
20. Jain A, Witbreuk M, Ball C, Nanchahal J. Influence of steroids and methotrexate on wound complications after elective rheumatoid hand and wrist surgery. *J Hand Surg.* 2002;27A:449-455.
21. Murata K, Yasuda T, Ito H, et al. Lack of increase in post-operative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. *Mod Rheumatol.* 2006;16:14-19.
22. Talwalkar SC, Grennan DM, Gray J, et al. Tumor necrosis factor α antagonists and early post-operative complications in patients with inflammatory joint disease undergoing elective orthopedic surgery. *Ann Rheum Dis.* 2005;64:650-651.
23. den Broder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention to anti-tumor necrosis factor: a large retrospective study. *J Rheumatol.* 2007;34:689-695.
24. Momohara S, Kawakami K, Iwamoto T, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. *Mod Rheumatol.* 2011 Feb 12. [Epub ahead of print]