IL-6 Inhibition for the Treatment of Rheumatoid Arthritis and Other Conditions

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Abstract

New data published or presented in the past year has expanded our understanding of the clinical use of interleukin 6 (IL-6) inhibitors and their role in the management of rheumatoid arthritis (RA) and other rheumatic diseases. Data has become available on the use of tocilizumab (TCZ) in comparison to adalimumab, as therapy in RA patients with an inadequate response to TNF inhibitors and on its role as monotherapy. Early data on the efficacy and safety of subcutaneously administered TCZ suggests a potential role for this formulation of the drug. Extension studies of the use of TCZ in systemic juvenile inflammatory arthritis have confirmed the long-term efficacy of the drug in this illness, while studies on the use of TCZ and other IL-6 inhibitors in spondyloarthropathies has been less encouraging. Finally, new agents targeting the IL-6 pathway have entered late stage clinical trials, and the early results are promising.

The treatment of rheumatoid arthritis (RA) has advanced tremendously in the past 10 years. An array of biologic medications are available that inhibit different components of the inflammatory pathway, including T cell activation (abatacept), B cells (rituximab), and cytokines. Tumor necrosis factor alpha inhibitors (TNFi) are the most widely used cytokine inhibitors; however, the use of tocilizumab (TCZ), a humanized antibody directed against the interleukin-6 receptor (IL-6R), is growing steadily, particularly in patients with an inadequate response to other biologic therapies. Within the past year, a number of newly published or presented studies in patients with RA have addressed the efficacy of TCZ as monotherapy and in direct comparison with a TNFi (adalimumab), as well as the overall safety of this agent. Additional recent information on TCZ includes trials in patients with spondyloarthropathies and new data on the efficacy and safety of TCZ in patients with juvenile idiopathic arthritis (JIA). Finally, data has become available on the efficacy of other agents targeting the IL-6 pathway, including sarilumab, a fully human IL-6Rα antibody and BMS945429, a humanized anti-IL-6 antibody.

Efficacy in Rheumatoid Arthritis

Although TNFi inhibitors revolutionized the treatment of RA, a substantial number of patients still fail to respond to this treatment. TCZ has been shown to be effective in patients who are inadequate responders to TNFi and methotrexate.1,4 Until now, however, there have been no “head-to-head” trials comparing these agents.

The ADACTA trial, presented in abstract form at the 2012 EULAR congress, is the first large clinical trial to demonstrate significant differences in treatment effectiveness between two different biologic agents.3 In this trial, 326 biologic naïve patients with RA who were intolerant of, or unable to use, methotrexate (MTX) were randomized to receive, in a blinded fashion, adalimumab (ADA) subcutaneously (SC) 40 mg every other week or TCZ 8 mg/kg intravenously (IV) every 4 weeks. Both treatments were administered as monotherapy, without background MTX. At 24 weeks, the change in mean DAS28 score (primary endpoint) was significantly greater in patients taking TCZ than in those taking ADA (-3.3 vs. -1.8, p < 0.0001). The TCZ group also had statistically higher DAS28 remission rates compared to the ADA group (38.8% vs. 10.5%), and more TCZ patients achieved low disease activity than the
ADA patients (51.5% vs. 19.8%). Two deaths were reported in the TCZ group; one from an unrelated drug overdose, and one from an unknown cause. Other safety data, including serious infection rates, were comparable between the two agents.

Current standard practice in RA treatment is to add a biologic agent to MTX (or another DMARD) when a patient has not achieved an adequate response. However, up to 30% of patients taking TNFi may be using them as monotherapy, and there is evidence that TCZ monotherapy may be as effective as TCZ/MTX combination therapy, observations that prompted the ACT RAY trial. In this 2-year, double-blind study, 565 MTX-inadequate responders (high DAS28 scores) were randomized to receive TCZ with either placebo or MTX.

At 24 weeks, there was no difference in the primary endpoint of remission (DAS28 < 2.6), although there was a modest difference in the percentage of patients with low disease activity (DAS28 < 3.2), favoring the use of methotrexate (61.7% versus 51.4%, p = 0.029). At 24 weeks, there were also no differences in percent of patients with radiographic change between the two groups. The 1 year data from this trial has been presented in abstract form only. By 1 year, there was a significant difference in the percentage of patients achieving remission (45.5% versus 36.6%, p = 0.025). Most other endpoints were not different, except for percentage of patients with no radiographic progression (92.4% versus 85.5%, p = 0.007). ACR 20, 50, and 70 responses remained similar after 1 year in both groups. Although these data do show that combined therapy with MTX produced a statistically significant difference in a few key areas, it remains unclear whether these differences are clinically meaningful, and whether TCZ may be the one biologic therapy that is truly as effective alone as with MTX.

The past year has seen additional data on the use of TCZ in patients previously treated with TNF inhibitors. ACT-SURE was an open label trial in RA patients with moderate to severe activity who had had inadequate response to DMARDs and TNF-inhibitors. The trial enrolled 1,680 patients who were treated with TCZ 8mg/kg with stable DMARDs. Patients were categorized as TNF naïve, TNF-recent (not currently taking a TNFi), or TNF-previous (requiring a washout prior to TCZ initiation). At 24 weeks, 61.6% (TNF-naïve), 50.4% (TNF-recent), and 48.5% (TNF-previous) of patients achieved DAS28 remission, confirming previous data showing that TCZ is efficacious even in patients with inadequate response to TNF inhibitors.

To date, TCZ has been administered only by IV infusion. In a recent presentation, though, TCZ dosed at 162 mg every 2 weeks subcutaneously was shown to be non-inferior to TCZ dosed at 8 mg/kg IV every 4 weeks. The study included 315 patients who completed 24 weeks of therapy. Change from baseline in DAS28 score, the primary endpoint, was similar in both groups (-3.4 vs. -3.7 with SQ and IV, respectively). Similar rates of serious infection were seen as well (1.2% vs. 2.9% with SQ and IV, respectively).

Beyond clinical disease, there is great concern in RA patients about the erosive joint damage that can occur with ongoing disease. TCZ has previously been shown to slow or halt radiographic progression of RA. Two recent trials have investigated changes in bone physiology and structure in RA patients taking TCZ and have even raised the question of whether this agent may allow for healing of already damaged bone. In one study, microcomputerized tomography was used to assess erosions in 20 RA patients undergoing treatment with TCZ. A total of 133 erosions were identified (all at metacarpophalangeal joints). After 1 year, large erosions (> 1.6 mm) or those showing sclerosis at baseline were found to have significant decreases in width. In a separate, post-hoc analysis of 299 patients from the RADIATE trial of TCZ in MTX inadequate responders, there was evidence of a positive effect of TCZ treatment on bone metabolism. Matrix metalloproteinase-6 levels and type I collagen degradation products were reduced, suggesting decreased catabolism in joint tissue, and net bone balance was improved, as indicated by the ratio of C terminal peptides of type I collagen (CTX-1) to osteocalcin (OC), suggesting a reduction in bone turnover.

### Safety

In the open-label ACT-SURE study of 1680 RA patients with inadequate response to non-biologic DMARDs, TNFi, or both, the incidence of infection and other adverse events was similar to that previously seen in RA patients treated with TNFi. In particular, the rate of 5.2 serious infections per 100 patient-years was similar to that previously reported in patients taking TNF inhibitors. There was no significant difference in rates of serious infections in patients who switched from a TNFi with or without a washout period, suggesting that such a washout may not be necessary.

Safety reports from registry studies and other clinical trials do not always paint a full picture of the true risk of a new medication. Registry data often helps to clarify both the nature and the extent of the risks seen with clinical use; such data have proven to be important sources of information with other biologic medications in RA. The first registry data on TCZ is coming from Japan, where the drug has been available longer than in the United States and Western Europe. Outcomes were recently reported for 7,901 patients enrolled in the Japanese national biologics registry who were taking
TCZ 8 mg/kg for at least 28 weeks. Overall, the most common adverse events were laboratory abnormalities and infections. Serious adverse events were more likely in patients with long-standing RA (more than 10 years) compared to those with less than 10 years of disease (p < 0.001). Although patients who had previously taken TNF inhibitors were not at higher risk of serious adverse events, patients taking concomitant MTX were more likely to develop them (p < 0.001). Serious infections occurred in 3.8% of patients. Five patients developed tuberculous (0.06%) and 13 patients developed gastrointestinal perforation (0.2%).

Response to routine vaccination remains a concern with the use of biologic therapy. In a recent report on 194 RA patients treated with MTX, TCZ/MTX, or TCZ alone, appropriate seroconversion rates were seen in all groups, although MTX did seem to have a negative impact on vaccine efficacy overall. Another concern with biologic therapy has been the use of these agents in patients with viral hepatitis. A recent case report described successful TCZ treatment of a patient with severe RA, incidentally found to have chronic hepatitis C, with no untoward liver effects, although it would be premature to consider this agent safe in the setting of hepatitis C.

Juvenile Idiopathic Arthritis

TCZ was approved in 2011 for treatment of systemic juvenile idiopathic arthritis (sJIA). A recent report on patients in the pivotal TENDER trial found continued efficacy and no changes in safety signals after 1 year. After 12 weeks, ACR 70 and 90 rates for patients taking TCZ 8 mg/kg were 71% and 31%, respectively. At 52 weeks, the ACR 70 and 90 rates were 89% and 65%, respectively. There were 12 serious adverse events considered at least possibly related to TCZ itself for a rate of 0.23 events per patient years. Two year data from the same trial was reported at the 2012 EULAR congress. Among 65 patients who remained in the extension trial, 57 achieved an ACR 70 (88%) and 46 achieved an ACR 90 (71%). At 2 years, 55% of patients had no active joints. Safety results (adverse events) were reported to be similar to the 52-week data.

Patients with sJIA may sustain joint damage. In a small series of 9 patients with sJIA treated with TCZ 8 mg/kg every 2 weeks for a mean of 82 weeks, evidence of radiographic improvement, and not just stabilization, was noted. However, some joints did worsen, even when improvement in inflammatory and disease markers was seen.

Macrophage activation syndrome (MAS) is a rare but important complication in patients with sJIA. Treatment with TCZ, which produces profound reduction in acute phase reactants, may make monitoring for this syndrome problematic. In a recent series of five sJIA patients treated with TCZ, these patients generally had more subtle presentations of MAS and no significant CRP elevations. The investigators suggested that monitoring of IL-6 and IL-18 levels may be beneficial for improved surveillance of both JIA disease activity and MAS in patients on TCZ.

Spondyloarthropathies

Two reports in the past year addressed TCZ use in patients with spondyloarthropathies. In the first, TCZ was given at a dose of 8 mg/kg every 4 weeks for a total of 12 weeks to patients with ankylosing spondylitis (AS). A total of 99 patients completed the trial (48 TCZ, 51 placebo). Improvement with TCZ relative to placebo was seen in only one of the disease activity scores measured, the ASDAS score that includes CRP. In an on-line survey of French rheumatologists and internal medicine physicians, treatment with TCZ was reported to lead to no significant or meaningful improvements in 13 patients with axial spondyloarthopathy (SpA), although 4 of 8 patients with peripheral spondyloarthropathy had some response in their peripheral joint disease. Overall, targeting of the IL-6 pathway has not provided encouraging results in the spondyloarthropathies.

Other Agents

The clinical efficacy of TCZ has generated interest in other agents targeting the IL-6 pathway, and the first large clinical trials with these agents are being reported. Sarilumab is a fully human monoclonal antibody against IL-6Rα. In a blinded trial of 301 patients with AS, it proved no more effective than TCZ in this population; there was no statistical difference from placebo in the primary endpoint of ASAS20, nor in any of the secondary endpoints measured. Sarilumab has also been studied in RA, and there it proved more effective. In the Phase 2 MOBILITY study, 306 RA patients with an inadequate response to MTX were randomized to placebo or 1 of 5 dose regimens of sarilumab, all with background MTX. At week 12, the ACR20 response to sarilumab 150 mg weekly was statistically greater than placebo, and several of the ACR core measurements showed greater improvement with 150 mg and 200 mg every 2 weeks, the doses that will be taken forward into phase 3. The toxicity profile was similar to TCZ and included infections, neutropenia, and elevations in lipids.

Another agent in development is BMS945429, a monoclonal antibody against IL-6 itself, rather than its receptor. In a phase 2 trial involving 127 RA patients with an inadequate response to MTX, the ACR 20 response to BMS945429 was as high as 82%, compared with 27% in the placebo arm, when given with background MTX. Adverse events included transaminase and cholesterol elevations.

Conclusion

As biologic therapies become an increasingly important element of the standard of care in the management of RA, updated data on their safety and efficacy is a critical element
to ensuring their proper use. New data on TCZ helps to inform the role of this agent in the management of RA, either alone or in combination with MTX and other DMARDs. Comparative data with adalimumab and other agents in the future may begin to identify the specific place in the treatment armamentarium for TCZ. Similarly, new information on trials of TCZ in SJIA helps to place it in the proper place in the treatment paradigm for this disease. Data on the use of IL-6 targeting therapies in spondyloarthropathies has been disappointing to date, although other agents besides TCZ show promise as future therapies for RA.

Disclosure Statement
Robert S. Woodrick, M.D., does not have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony. Eric M. Ruderman, M.D., has been a consultant for Abbott Laboratories, Amgen, Genentech, and Pfizer, Inc., and has provided paid expert testimony for Pfizer.

References
20. Dragonas C, Ehrenstein B, Fleck M. Tocilizumab treatment in a patient suffering from rheumatoid arthritis and concomitant


