Interleukin 6 Inhibition
RA and Beyond

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Abstract
Three years after the approval of the interleukin 6 (IL-6) receptor antibody tocilizumab in the U.S. for the treatment of rheumatoid arthritis, data has continued to accumulate that can help guide its use for this indication. In particular, the structural benefit of therapy, previously shown in Japanese studies, has been confirmed in non-Japanese populations. Additional studies have identified markers, such as high titer rheumatoid factor, that may be associated with greater clinical response to this agent. While registry data with this therapy have not yet become available, more detailed analyses of clinical trial data have helped clarify the risk for certain toxicities, including injection and gastrointestinal perforation. Importantly, data have become available supporting the use of tocilizumab in diseases other than adult RA. Large clinical trials in systemic juvenile inflammatory arthritis have led to the approval of tocilizumab for this indication, and preliminary data suggests benefit in adult onset Still’s disease. Finally, there is interest in the potential of IL-6 inhibition in other diseases, although meaningful data has not yet become available.

Rheumatoid Arthritis
Structural Damage
Perhaps the most important data on tocilizumab to become available in the last year was the publication of the radiographic data from the LITHE trial. While structural outcomes with this therapy had been reported from Japanese trials, this was the first data on radiographic progression to come from North American and Western European populations. The LITHE study was a randomized, double-blind, placebo-controlled trial involving 1,196 patients who had had an inadequate response to methotrexate therapy. Study participants were randomized to one of two doses of tocilizumab (4 mg/kg or 8 mg/kg) or placebo infusions every 4 weeks for 2 years. Methotrexate therapy was continued, at a mean dose of 15 mg, and rescue therapy with active drug was available for non-responders from 16 weeks on. For patients going into rescue therapy, radiographic endpoints were extrapolated from radiographs obtained at the time they exited their assigned treatment arm. Patients in this study had an average disease duration of approximately 9 years, a mean DAS28 score of 6.5, and a mean HAQ score of 1.5, indicating very active disease.

At the 1-year planned interim analysis, composite endpoints, including ACR response and DAS28 improvement, and HAQ scores for both doses were statistically better than placebo. Also at one year, the mean progression in total Sharp score was 0.34 units for tocilizumab 4 mg/kg, 0.29 units for tocilizumab 8 mg/kg, and 1.13 units for placebo. The placebo group, 67% had no radiographic progression, compared with 81%, and 84% of the 4 mg/kg and 8 mg/kg
groups, respectively. Clinical endpoints also demonstrated superiority of tocilizumab over placebo. While radiographic benefit with tocilizumab had previously been reported in Japanese trials, notably the SAMURAI study,2 this is the first report in the peer-reviewed Western literature to demonstrate the structural benefit of this agent.

**Prognostic Factors**

Given the potential toxicities, as well as the costs, involved in the use of biologic therapy, one of the more important clinical concerns has been the identification of patients who would benefit most from this therapy. Two recent studies have examined the question of which RA patients might benefit most from tocilizumab. In the first, data was analyzed from 302 patients in the SAMURAI trial in RA patients with less than 5 years of disease.3 Study patients were assigned to high-risk or low-risk categories for joint damage based on urinary levels of C-terminal cross-linked telopeptide of type II collagen (uCTX-II), total pyridinoline/total deoxypyridinoline ratios (uPYD/DPD), joint-space narrowing (JSN) scores, and body mass index (BMI) at baseline, factors the investigators had previously shown to be predictive markers for radiographic damage in this population. At 1 year, patients with high levels of uCTX-II, uPYD/DPD ratios, JSN scores, and low BMI (i.e., high risk for joint damage) who were treated with tocilizumab had significantly less joint damage than those treated with conventional DMARDs. Patients in the low-risk group, however, did not have a significant difference in joint damage with tocilizumab compared with DMARD therapy. Such data, if confirmed, might help to identify patients who would have sufficient benefit from tocilizumab to justify its cost.

The second trial was a prospective analysis of 58 Japanese patients with RA followed for 24 weeks using the clinical disease activity index (CDAI) to measure disease activity. Among the baseline characteristics measured, including age, gender, disease duration, corticosteroid use, prior TNF inhibitor therapy, erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (CCP) antibody level, only high inhibitor therapy, erythrocyte sedimentation rate (ESR), anti-RA factor, gender, disease duration, corticosteroid use, prior TNF antagonist therapy, and presence of at least two other risk factors were predictive of radiographic damage. A unique, and potentially worrisome, adverse event seen in clinical trials of tocilizumab has been gastrointestinal (GI) perforation. Twenty-six events were reported, for a rate of 2.8 per 1000 patient-years, with no events reported in control or placebo groups.9 Interpretation of these events is difficult without knowing the absolute risk of gastrointestinal perforation in RA, as well as other risk factors. A recent study using an insurance database found that the greatest risk factors for gastrointestinal perforation in RA patients are treatment with corticosteroids and a history of diverticulitis.10 Interestingly, biologic use (not including tocilizumab, which had not been approved at the time of the analysis), was not a significant risk factor. Further data will help to identify the precise risk associated with tocilizumab use, but caution would seem to be indicated in patients with a history of diverticulitis or those on chronic steroids.

Although opportunistic infections were rare in tocilizumab trials, there have been several recent case reports of atypical infections associated with tocilizumab use in
RA patients, including an ophthalmic herpes zoster virus infection, a case of recurrent allergic bronchopulmonary aspergillosis, and a case of cytomegalovirus associated pneumonitis. 11-13

**Juvenile Idiopathic Arthritis**

An exciting recent development in the use of tocilizumab for rheumatic disease has been its approval for the treatment of systemic juvenile idiopathic arthritis (sJIA). IL-6 has been found to be elevated in the blood and synovial fluid of patients with JIA, and fluctuates with the spiking fever characteristic of sJIA, making it an attractive target for therapy. 14-16 Tocilizumab has been shown to be effective in sJIA in two recent phase III trials.

In a Japanese study of 56 children with sJIA, three doses of 8mg/kg were administered every 2 weeks in a lead in phase; responders entered a randomized, double-blind phase for an additional 3 months. Seventy five percent of the tocilizumab patients completing the double-blind portion of the study achieved an ACRPed 70 and low CRP levels, versus 13% of the patients in the placebo group. Hemoglobin and platelet counts of patients treated with tocilizumab increased significantly, and corticosteroid requirements were typically halved. Two serious events occurred (one case of colonic ulcer resulting in GI hemorrhage and one anaphylactoid reaction). 17

In a second trial, 112 children ages 2 to 17 with intolerance or inadequate response to prior treatment were randomized to receive tocilizumab (8 mg/kg for children < 30 kg, 12 mg/kg for children ≥ 30 kg) or placebo every 2 weeks for 12 weeks. At 12 weeks, 85% of the tocilizumab patients versus 24% of the placebo patients met the primary endpoint of ACRPed 30 and absence of fever. An ACRPed 70 was achieved by 71% of tocilizumab-treated patients and just 8% of the placebo group. The most common side effects in this study were upper respiratory infections, diarrhea, and headaches. Five serious adverse events in the tocilizumab group included pneumonia, varicella infection, septic arthritis, macrophage activation syndrome, and dehydration. As in adults, transaminitis and elevated cholesterol levels were seen in more tocilizumab treated patients than placebo. 18

Response to tocilizumab was sustained through 52 weeks in the extension phase of this study. 19

**Adult Onset Still’s Disease**

Adult onset Still’s disease (AOSD) shares many features with sJIA, including spiking fevers; arthritis and arthralgias; evanescent rashes; and elevated CRP, ferritin levels, and white blood cell counts. IL-6 levels have been shown to correlate with clinical disease activity, as well as white blood cell counts, ESR and CRP levels, and platelet counts in AOSD. 20 There have been several case reports of successful tocilizumab therapy in patients with AOSD. 21-26 The experience with tocilizumab in 14 French patients with AOSD refractory to other medications was described in a recent report. The treated patients all had chronic arthritis, eight with destructive changes; the mean disease duration was 13.7 years. Eleven of 14 patients completed 6 months of therapy; 8 of 14 patients achieved DAS remission. 27

**Systemic Lupus Erythematosus**

Tocilizumab has been studied in a small series of 16 patients with moderate lupus based on either chronic glomerulonephritis or extra-renal manifestations (mSELENA-SLEDAI score 3-10). 28 Patients received one of three doses of tocilizumab (2mg/kg, 4mg/kg, or 8mg/kg); one patient receiving the 8mg/kg dose withdrew due to grade 3 neutropenia. After 14 weeks, significant decreases were recorded in mean SLAM scores (7.1 to 5.0, p = 0.002) and SELENA-SLEDAl scores (9.9 to 5.5, p = 0.0001). In 8 of the 15 patients, a clinically significant decrease of at least 4 points in the SELENA-SLEDAI was achieved. Infections occurred in more than two-thirds of patients; most were mild, although there was one case each of herpes keratitis, severe gastroenteritis, and pyelonephritis.

**Other Diseases**

In the past two years, tocilizumab has been used as salvage or “off label” for the treatment of several other autoimmune conditions. There have been three case reports of patients with ankylosing spondylitis and one with reactive arthritis not responsive to standard therapy, for instance, who have responded to tocilizumab. 29-32 A report from Japan described the use of tocilizumab in two patients with presumed polymyositis who were refractory to corticosteroids and cyclosporine. Both had resolution of symptoms and normalization of CK levels. 33 Another report from Japan described a 47-year-old female with refractory Behcet’s disease who responded to tocilizumab. 34 Finally, tocilizumab has been used successfully in the treatment of Takayasu’s arteritis (TA) and giant cell arteritis (GCA). Seven patients (five with GCA, two with TA) were treated with tocilizumab (2 doses of 8mg/kg during the first month, then monthly for 4 to 8 months). All patients had resolution of symptoms and inflammatory markers. Response was rapid, with reduction of prednisone dose to a mean of 2.5 mg/day by 12 weeks; three patients were able to discontinue steroids completely by this point. 35

**Conclusion**

The IL-6 inhibitor tocilizumab has been shown to be effective and has received a labeled indication for rheumatoid arthritis and now systemic juvenile inflammatory arthritis. As seen previously with other biologic therapies, there is great interest in the potential of tocilizumab for the management of refractory patients with other rheumatic diseases. While currently available data is limited to case reports and small case series, larger studies are sure to follow. The positive results for tocilizumab have also prompted interest in the development of other therapeutic molecules targeting this
pathway, although it is likely to be several years before any of these are commercially available.

**Disclosure Statement**

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