Interleukin-6 Inhibition
Tolerability Profile and Clinical Implications

Vibeke Strand, M.D., and Yusuf Yazici, M.D.

Abstract

Tocilizumab, humanized monoclonal antibody to sIL-6R, is a promising new agent for the treatment of rheumatoid arthritis. Safety data from randomized controlled trials (RCT) to date have been overall reassuring with no evidence of increased opportunistic infections or malignancies, and some signals for elevated liver function tests and changed lipid profiles. The true implications of these signals in RCTs must be addressed in larger numbers of RA patients with longer term exposure before firm conclusions are reached.

Despite recent advances in the treatment of rheumatoid arthritis (RA) that have led to new therapies and also to new approaches to treatment, namely early and aggressive disease modifying antirheumatic drug (DMARD) regimens, a substantial number of RA patients still fail to respond to currently available medications. In addition, despite initial responses, many will ultimately lose responsivity, requiring supplementing with new DMARDs or switching to another.

Biologic agents that have resulted from advances in immunology and the understanding of the role various cytokines play in the underlying pathogenesis of RA have revolutionized the treatment of RA. Starting with cytokine inhibitors, including the tumor necrosis factor (TNF) inhibitors, and continuing with a T cell costimulation modifier and a B cell depleting agent, an inhibitor of interleukin-6 (IL-6) is now emerging as a promising new therapy. IL-6 is a proinflammatory cytokine that is produced in the liver and joints of RA patients and overexpressed in patients with autoimmune diseases, increasing circulating levels in serum.1 These levels result in the malaise, fatigue, and anemia characteristic of active disease. In addition to systemic effects, IL-6 and its soluble receptor (sIL-6R) activate endothelial cell production of chemokines and upregulate expression of adhesion molecules resulting in recruitment of leukocytes to inflammatory sites, and may well regulate IL-1 and TNFα synthesis through autocrine and paracrine loops.2 They also block trans-signalling through GP-130 in cells that do not express a membrane-bound IL-6 receptor.

Four RCTs with tocilizumab have been published to date, with abstract reports of an additional two. An initial phase I and phase II placebo-controlled dose-escalation trial randomized 45 patients to receive single intravenous (IV) doses of 0.1, 1.0, 5.0, and 10.0 mg/kg or placebo; patients were followed for 8 weeks.3 The most common AE reported was diarrhea and was seen in eight patients. Seven patients (three on placebo, four on the study drug) had severe AEs; one patient with preexisting ischemic heart disease had myocardial ischemia but the event was thought to be unrelated to the study drug administration. Mild elevations of liver enzymes and decreases in neutrophil counts were observed, but no values were reported. Antibodies to the mAb were not detected.

A second RCT examined the efficacy and safety of tocilizumab with monthly dosing x3 in 162 patients randomized to receive 4 or 6 mg/kg IV or placebo.4 Overall rates of AE...
reports were similar between placebo and treatment arms, and none led to discontinuation of study drug administration. Upper respiratory infections were the most commonly reported AE, with no differences between treatment groups. Five patients receiving tocilizumab reported skin rashes. Infusion reactions were few and mild in most cases. Five serious AEs were reported, three with active and two with placebo treatment. Of note, one patient died of disseminated Epstein-Barr virus (EBV) infection and consequent hemophagocytosis syndrome. She was noted to have increased EBV DNA in plasma before enrollment. Another patient had allergic pneumonitis and a third was hospitalized secondary to a lower extremity infection following grade III burn injuries. Serious AEs in the placebo group included a subarachnoid hemorrhage and a fracture of the femur. Elevated liver enzymes in the same trial were reported in 13% of tocilizumab treated patients; decreased neutrophil counts, which recovered spontaneously, were found in 16%. No serious infections were associated with these decreased counts. Overall increases in total cholesterol levels were observed in 44%, accompanied by increases in triglycerides and high-density lipoprotein (HDL) cholesterol. Anti-tocilizumab antibodies were observed in two patients.

In the larger phase II CHARISMA (Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody) trial, conducted in Europe, 359 RA patients with inadequate responses to methotrexate (MTX) were randomized to seven different treatment arms (2 mg/kg, 4 mg/kg, and 8 mg/kg of tocilizumab with MTX or as monotherapy as well as MTX plus placebo) and placebo only. The most frequently reported AEs included infections, bacterial and viral; gastrointestinal events; and rashes, including erythema. Serious AEs were reported in 30 patients: highest in the 2 mg/kg tocilizumab monotherapy group and lowest in the 4 mg/kg tocilizumab plus MTX cohort. Most common events consisted of a worsening of RA, seen in three patients, and infection, seven being diagnosed in six patients (one patient developed a limb abscess and osteomyelitis). Two patients developed sepsis. No cases of tuberculosis or opportunistic infections occurred. Five cases of anaphylaxis and hypersensitivity, simultaneous or as separate reactions, were reported: four in the 2 mg/kg and one in the 4 mg/kg monotherapy groups. Aside from the aforementioned serious events, there was an apparent dose response pattern noted in AEs. Anti-tocilizumab antibodies were detected in 25 patients, all in the 2 mg/kg and 4 mg/kg monotherapy groups.

Three laboratory AEs noted in the CHARISMA trial have continued to attract attention. ALT (alanine aminotransferase) and AST (aspartate aminotransferase) elevations greater than upper limits of normal were observed in all 127 patients who received tocilizumab, increasing immediately following dosing and decreasing over the month between infusions (a sawtooth pattern) (Fig. 1). These normalized within 8 weeks following the final dose although specific normal values were not reported. Five patients discontinued treatment due to ALT levels greater than 100 IU/liter. ALT levels greater than 100 IU/liter were observed in 18 patients. Liver enzyme elevations greater than three times the upper limits of normal were more common in the combination treatment arms, occurring in 2% overall; increases in bilirubin levels were also noted, with normalization after the study drug was discontinued. Of interest, there was no apparent relationship between ALT and bilirubin elevations, as no patient had both simultaneously.

Dose dependent decreases in neutrophil counts were also reported, again with normalization after treatment was discontinued (Fig. 2). Of importance, those with decreased neutrophil counts did not have a higher incidence of infection. The lowest neutrophil count observed was 0.88 x 10⁹/liter at week 8.

As in earlier trials, moderate but reversible increases in nonfasting total cholesterol and high density lipoprotein (HDL) and triglycerides were observed. After the initial increases with treatment, levels stabilized and the atherogenic index remained unchanged (Fig. 3). In the higher dose regimens, there were some patients who had reductions in the index.

In the open label, long-term extension trial following the initial phase II RCT, 143 of 164 (87%) patients received 8 mg/kg of tocilizumab intravenously every 4 weeks. Ninety-six patients (67%) continued to receive tocilizumab as of January 2007, of which 89 have been treated for more than

Figure 1 Effects of tocilizumab on ALT in CHARISMA trial.

Figure 2 Effects of tocilizumab on neutrophil count in CHARISMA trial.
Laboratory test abnormalities were reported in 61% and zumab antibodies were detected in four patients (2.5%) and one each of vomiting, pruritus, and malaise. Anti-tocilizumab erythema, two headache, two nausea, two skin rashes, in blood pressure occurred as well as events of two injection (7.0%) patients, all considered mild; three transient increases in total cholesterol levels were frequently observed after treatment initiation and stabilized at a mean value of approximately 220 mg/dL at 12 months, compared with 185 at baseline and 213 mg/dL at 60 months.

In the prospective phase III RCT, SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor), 320 patients with active RA of less than 5 years disease duration participated and were randomized to receive tocilizumab monotherapy 8 mg/kg IV every 4 weeks versus stable doses of conventional DMARDs, excluding biologic agents, for one year. Most commonly reported AEs (equal or more than 5% of those tocilizumab treated) included nasopharyngitis, rash and eczema, diarrhea, headache, stomatitis, nausea, pruritus, paronychia, and vomiting. Serious AEs were reported in 18% of the tocilizumab and 13% of the DMARD groups. Twelve (10.1%) serious infections were reported: three (1.9%) cases of pneumonia, two (1.3%) upper respiratory tract infections, two (1.3%) cellulitis cases, and one (0.6%) each of gastroenteritis, herpes zoster, herpes simplex, perianal abscess, and unidentified infection. In the DMARDs group, eight (5.6%) serious infections were reported: three (2.1%) gastroenteritis, two (1.4%) pneumonia, and one (0.7%) each of upper respiratory tract infection, herpes zoster, and sepsis. All SAEs improved with supportive treatment. No cases of tuberculosis were observed in this one-year study, which did not require screening. Three malignancies occurred in the tocilizumab group (two breast and one colon cancer); none occurred in the DMARD group.

Treatment related infusion reactions were reported in 11 (7.0%) patients, all considered mild; three transient increases in blood pressure occurred as well as events of two injection site erythema, two headache, two nausea, two skin rashes, and one each of vomiting, pruritus, and malaise. Anti-tocilizumab antibodies were detected in four patients (2.5%).

Laboratory test abnormalities were reported in 61% and 31% of patients in the tocilizumab and DMARD groups, respectively. With tocilizumab treatment, increases in total cholesterol, triglycerides, low-density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol were reported in 38%, 17%, 26%, and 24%, respectively; most were considered grade 1, according to the National Cancer Institute Common Toxicity Criteria. Fifty patients received treatment and their cholesterol levels improved during the study. Atherogenic indices were not changed over 52 weeks of treatment.

In another phase III RCT, OPTION (Tocilizumab Pivotal Trial in methotrexate Inadequate resPOnders), 623 patients with moderate to severe active RA despite long-term treatment with MTX were randomized to receive 4 or 8 mg/kg tocilizumab IV every 4 weeks, or placebo. All patients continued stable MTX dosing throughout the study at doses of 10 to 25 mg weekly. Tocilizumab was generally well tolerated, with an AE profile consistent with that reported in previous studies. Serious infections occurred in six patients receiving 8 mg/kg, three receiving 4 mg/kg tocilizumab, and in two patients on placebo treatment.

Data from the four RCTs published so far, as well as in recent abstracts, provide preliminary safety information in approximately 1024 RA patients who have received tocilizumab with and without background MTX. Clearly, more detailed information from longer-term patient exposure is required before the initial safety profile of this new biologic agent can be completely characterized, which can then be refined as postmarketing surveillance and registry information become available. Nonetheless, as with TNF inhibitors, where opportunistic infections, lymphomas, and demyelinating disorders were observed in RCTs, albeit in small numbers, postmarketing surveillance and registry data have now offered us the ability to better understand their potential relationship to treatment versus the underlying disease.

Treatment associated elevations in ALT and AST are characteristic of MTX and leflunomide, and regular monitoring of these liver enzymes is required. Their administration is not associated with elevations in bilirubin or alkaline phosphatase.

Although mean neutrophil levels appear to decrease over time with repeated administration of tocilizumab, few if any patients develop absolute neutropenia (less than 500 cells/ml). To date, available data do not show a relationship between decreased neutrophil counts and susceptibility to infection; information from more patient exposure of longer duration is required before this can be better clarified.

Treatment associated elevations in cholesterol levels have recently been reported with TNF inhibitors, with and without MTX background therapy. In these reports, total cholesterol and HDL levels were increased with no apparent change in atherogenic index. These increases were closely correlated with significant decreases in C-reactive protein (CRP) levels and decreased disease activity, as has been pre-
viously observed in RCTs with synthetic DMARDs: MTX and leflunomide. Treatment associated changes observed in tocilizumab trials may at least, in part, reflect significant improvement in disease activity; thus, resolution of “RA cachexia” as it was formerly termed will require detailed analyses of data from the ongoing phase III RCTs. As has been repeatedly observed, disease control with traditional DMARD as well as TNF inhibitors reduces cardiovascular mortality. The benefits of better and sustained disease control may outweigh the effects on cholesterol and triglycerides; if the atherogenic index remains unchanged, this may reflect improved clinical status overall.

The true implications of these signals in RCTs, with not only tocilizumab but also possibly with TNF inhibitors and limited to earlier, smaller trials and retrospective analysis, must be addressed in larger numbers of RA patients, with longer term exposure before firm conclusions are reached.

References


Disclosure Statement

Yusuf Yazici, M.D., participates in the speaker bureaus for the companies of Pfizer, Amgen, Boehringer Ingelheim, Genentech, and BMS; consults for Roche, Celgene, and BMS; is an advisory board member to Centocor, BMS, and Genentech; and has received educational grants from Abbott, Centocor, and Genentech. Vibeke Strand, M.D., is an independent biopharmaceutical consultant in clinical development and regulatory affairs and is a consultant for the companies of Abbott Immunology, Amgen Corporation, Astellas, AstraZeneca, Bayhill, BiogenIdec, CanFite, Centocor, Chelsia, Cypress Biosciences, Inc., Dianippon Sumitomo, Genelabs, Genentech, Human Genome Sciences, Incyte, Novartis, Omeros, Pfizer, Pharmoecina, Procter and Gamble, Propius, Rigel, Roche, Sanofi-Aventis, Schering Plough, Serono, SKK, UCB, Wyeth Ayerst, Xdx. Dr. Strand serves as well on the advisory boards of Abbott, Amgen, Biogen, Idec, BMS, CanFite, Centocor, Chelsea, Novartis, Roche, Pfizer, Schering Plough, and UCB. In addition, Dr. Strand participates in the speaker bureaus of Abbott, Centocor, Amgen, and Pfizer. Dr. Stranddoes not and has never held stock in any company.