

Interleukin-6 inhibitors in the treatment of rheumatoid arthritis

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Abstract: Recent developments in understanding the immunopathogenesis of rheumatoid arthritis (RA), combined with progress in biopharmaceutical development, have facilitated the introduction of novel immune modulating therapies for this progressive debilitating disorder. Efficacy achieved with certain agents, particularly the TNF inhibitors, has spurred the development of additional biologic agents targeting other components of the dysregulated immune response relevant to the etiology and sustenance of immune driven systemic inflammation characteristic of RA. Among these other potential targets is IL-6, a cytokine with effects on numerous cell types, including those involved in the pathogenesis of RA. Based on its activities, IL-6 appeared to be a viable target for autoimmune disease. Inhibitors of IL-6 were successful in animal models of autoimmune disease paving the way for subsequent studies in humans. The greatest experience to date has been with tocilizumab, a humanized monoclonal antibody specific for the IL-6 receptor (IL-6R). Beginning with open label studies, and progressing through larger and more rigorous controlled trials, tocilizumab has been shown to have significant efficacy in patients with RA. Additional studies analyzing its effects in varied populations of RA patients, as well as greater detail concerning its longer-term tolerability and safety, will help define the ultimate role of tocilizumab and other future inhibitors of IL-6 activity as potential therapies for RA.

Keywords: rheumatoid arthritis, IL-6, tocilizumab, biologic agents

Introduction to targeted treatments in rheumatoid arthritis: TNF and IL-6

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterized by progressive, symmetric joint inflammation and subsequent destruction. Left untreated, RA is associated with significant patient morbidity and accelerated mortality. Treatment with traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) can be efficacious for a number of RA patients. However, appreciation of the severity of the disease has led to elevation in the goals of treatment of RA. The desire for more complete control of disease, coincident with advances in understanding the underlying immunopathogenesis of RA, and progress in biopharmaceutical development, has spawned the introduction of novel biologic agents. Perhaps the greatest success has come with targeting those inflammatory cytokines that exhibit key roles in the activation and continuation of the destructive process occurring in the rheumatoid synovium. To date, the most notable clinical success in the treatment of RA has been achieved through inhibition of tumor necrosis factor alpha (TNF α). Patients receiving anti-TNF agents have not only exhibited significant improvement in arthritis signs and symptoms, but also better quality of life, less functional disability, and abrogation of joint damage (Gartlehner et al 2006). Despite these benefits, as with DMARDs not all patients respond or maintain efficacy to desired standards. Therefore, new therapies for RA are needed.

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Interleukin-6 (IL-6) is a pleiotropic cytokine that is abundant in both the synovium and serum of RA patients. Locally in the joint, the major source of IL-6 may be synovial fibroblasts, with additional amounts released by activated macrophages and lymphocytes (Yoshizaki et al 1998). Originally identified as a B-cell differentiation factor, IL-6 is now known to regulate a diverse array of activities that may underlie both systemic as well as local symptoms of RA. For example, IL-6 initiates the acute-phase response inducing the hepatic synthesis of acute phase proteins including C-reactive protein (CRP), serum amyloid, haptoglobin, and fibrinogen among others (Cronstein 2007). IL-6 can also activate vascular endothelial cells, upregulating expression of certain chemokines and adhesion molecules, and facilitating leukocyte recruitment directly to sites of inflammation (Lipsky 2006). Excess production of IL-6 also contributes to the anemia of chronic disease common in active RA by increasing hepcidin production, and induces thrombocytosis through increased megakaryocyte differentiation (Ishibashi et al 1993; Andrews 2004). Its ability to induce B-cell differentiation may lead to hypergammaglobulinemia as well as the production of autoantibodies such as rheumatoid factor (RF) and autoantibodies to citrullinated peptides (Yoshizaki et al 1998). Additionally, IL-6 may prompt synovial fibroblast differentiation and osteoclast activation, contributing to pannus formation and cartilage and bone destruction (Kudo et al 2003; Park and Pillinger 2007).

Dysregulation of IL-6 may provide an explanation for some of the common clinical manifestations associated with active RA, including fever, weight loss, fatigue, and poor appetite (Yoshizaki et al 1998). Significant correlations between elevated levels of IL-6 and disease activity parameters including duration of morning stiffness and the Ritchie articular index have also been reported (Madhok et al 1993a). Furthermore, treatment of RA patients with methotrexate or gold therapy results in decreased levels of IL-6 in patients with concomitant improvement in additional measures of disease activity (Madhok et al 1993b; Straub et al 1997).

Given its many possible contributions to the pathogenesis of rheumatoid inflammation, IL-6 would appear to be an attractive therapeutic target in RA. Tocilizumab, a monoclonal antibody (mAb) specific for the IL-6 receptor (IL-6R) is the first biologic agent targeting IL-6 that has progressed to late phase clinical trials.

Tocilizumab: pharmacology, mechanism of action, and pharmacokinetics

IL-6 mediates cell signaling by binding its cognate receptor (IL-6R; CD126). However, in order to transduce a signal,

the combination of IL-6/IL-6R must also bind a ubiquitous transmembrane protein, glycoprotein (gp) 130 (CD130). The binding of IL-6R complexed with IL-6 results in homodimerization of gp130 and signal transduction through Janus-activated kinase (JAK)/signal transducers and activators of transcription (STAT) pathways (Heinrich et al 2003). IL-6R is expressed on several cell types. However, IL-6 may also bind IL-6R in its soluble form. This complex can then bind gp130, which is expressed on a much wider variety of cell types. The presence of soluble IL-6R allows cell activation through gp130, a process known as trans-signaling, in tissues that do not constitutively express IL-6R (Rose-John 2003). This may help explain the diverse activities mediated by IL-6 in systemic inflammatory diseases such as RA.

Tocilizumab, previously known as myeloma receptor antibody (MRA), is a humanized, IgG1 IL-6 receptor monoclonal antibody that binds with high affinity to the 80 kDa component of IL-6R. This binding subsequently inhibits dimerization of the IL-6/IL-6R complex with membrane-bound gp130, preventing signaling.

The pharmacokinetics of tocilizumab were first established in a small, open-label study (Nishimoto et al 2003). Fifteen patients with active RA who had previously failed at least one DMARD or immunosuppressant received tocilizumab intravenously at doses of 2, 4, or 8 mg/kg biweekly for 6 weeks. The half-life of tocilizumab increased in a dose-dependent manner, as well as with repeated dosing. After the third dose of 8 mg/kg, half-life reached a maximum of ~240 hours. Serum tocilizumab concentrations were detectable during the entire study period in 4 of 5 patients in the 2 mg/kg group, 3 of 5 patients in the 4 mg/kg group, and all patients in the 8 mg/kg group, and decreased in a nonlinear manner. Those patients with detectable blood levels of tocilizumab maintained marked improvement in serum acute phase reactants such as CRP and amyloid A.

Clinical trials

After its promising success in early open label studies, the efficacy of tocilizumab in the treatment of RA was affirmed in larger double-blind, placebo-controlled randomized trials (DBPCRT) (Table 1) (Yoshizaki et al 1998; Nishimoto et al 2003). A dose escalation study by Choy et al (2002) randomized 45 patients with active RA to receive a single intravenous (IV) dose of tocilizumab 0.1, 1.0, 5.0, or 10.0 mg/kg or placebo. All patients had to have previously failed therapy with at least one DMARD. Improvement in disease activity was evaluated using the American College of Rheumatology (ACR) response criteria. At week 2, 55% of

Table 1 Clinical trials of tocilizumab in rheumatoid arthritis

Trial	Trial design	Number of patients	Average number of DMARDs failed	Protocol	Results
Nishimoto et al 2004, 2007a	DBRPCT	162	5	Tocilizumab 4 or 8 mg/kg iv or placebo q4weeks	At 3 months: ACR20: 8 mg/kg MRA – 78%, 4 mg/kg MRA – 57%, placebo – 11%. ACR50: 8 mg/kg MRA – 40%, placebo – 1.9%. At 5 years: ACR20: 8 mg/kg MRA – 84.2%, ACR50: 8 mg/kg MRA – 68.4%, ACR70: 8 mg/kg MRA – 44.7%
Maini et al 2006 CHARISMA	Phase II DBRPCT	359	2	Tocilizumab 2, 4, or 8 mg/kg monotherapy, or + MTX, or MTX + placebo	At week 16: ACR20: 2 mg/kg MRA – 31%, 4 mg/kg MRA – 61%, 8 mg/kg MRA – 63%, MTX – 41%, 2 mg/kg MRA + MTX – 64%, 4 mg/kg MRA + MTX – 63%, 8 mg/kg MRA + MTX + placebo – 74%. ACR50: 2 mg/kg MRA + MTX – 32%, 4 mg/kg MRA + MTX 37%, 8 mg/kg MRA + MTX 53%, MTX + placebo – 29%. ACR70: 8 mg/kg MRA + MTX 37%, MTX + placebo – 16%.
Smolen et al 2008 OPTION	Phase III DBRPCT	623	MTX	Tocilizumab 4 or 8 mg/kg iv q4weeks + MTX or placebo + MTX	At week 24: ACR20: 4 mg/kg MRA + MTX – 47.9%, 8 mg/kg MRA + MTX – 58.5%, MTX + placebo – 26.5%. ACR50: 8 mg/kg MRA + MTX – 43.9%, MTX + placebo – 10.8%. ACR70: 8 mg/kg MRA + MTX – 22.0%, MTX + placebo – 2.0%. EULAR good/moderate response: 8 mg/kg MRA + MTX – 79.5%, 4 mg/kg MRA + MTX – 61.9%, MTX + placebo – 34.8%. Mean Δ HAQ: 8 mg/kg MRA + MTX – 0.55, 4 mg/kg MRA + MTX – 0.52, MTX + placebo – 0.34 Δ SF-36 PCS: 8 mg/kg MRA + MTX – 9.5, 4 mg/kg MRA + MTX – 9.7, MTX + placebo – 5.0 Δ SF-36 MCS: 8 mg/kg MRA + MTX – 7.3, 4 mg/kg MRA + MTX – 5.7, MTX + placebo – 2.7 Δ FACIT-Fatigue: 8 mg/kg MRA + MTX – 8.6, 4 mg/kg MRA + MTX – 7.29, MTX + placebo – 4.0.
Genovese et al 2007; Gomez-Reino et al 2007 TOWARD	Phase III DBRPCT	1216	≥ 1	Tocilizumab 8 mg/kg + DMARD or DMARD + placebo	At week 24: ACR20: 8 mg/kg MRA + DMARD – 60.8%, DMARD + placebo – 24.5%. ACR50: 8 mg/kg MRA + DMARD – 37.6%, DMARD + placebo – 9.0%. ACR70: 8 mg/kg MRA + DMARD – 20.5%, DMARD + placebo – 2.9%. Mean Δ HAQ: 8 mg/kg MRA + DMARD – 0.47, DMARD + placebo – 0.20 Δ SF-36 PCS: 8 mg/kg MRA + DMARD – 8.9, DMARD + placebo – 4.1 Δ SF-36 MCS: 8 mg/kg MRA + DMARD – 5.3, DMARD + placebo – 2.3.
Nishimoto et al 2007b SAMURAI	Phase III DBRPCT	320	2	Tocilizumab 8 mg/kg iv q4weeks or DMARDs	At week 52: ACR20: 8 mg/kg MRA – 78%, DMARDs – 34%. ACR50: 8 mg/kg MRA – 64%, DMARDs – 13%. ACR70: 8 mg/kg MRA – 44%, DMARDs – 6%. Mean Δ TSS: 8 mg/kg MRA – 2.3, DMARDs – 6.1.

Abbreviations: MRA, tocilizumab; DBRPCT, double-blind randomized placebo-controlled trial; ACR, American College of Rheumatology; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; Δ , change; TSS, mean total modified Sharp score; EULAR, European United League Against Rheumatism; SF-36, Short Form 36 Health Survey; PCS, physical component score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue score.

patients receiving 5 mg/kg of tocilizumab met the primary efficacy endpoint (ACR20) compared with 0% in the placebo cohort. Efficacy was maintained through week 8. However, no significant difference could be observed between the other tocilizumab groups and placebo until week 6. Nonetheless, mean disease activity (assessed with the Disease Activity Score using a 28 joint count; DAS28) in the 5 mg/kg and 10 mg/kg tocilizumab groups was statistically significantly lower at day 14 than those in the 0.1 mg/kg and 1 mg/kg tocilizumab and placebo cohorts. Inflammatory markers including the erythrocyte sedimentation rate (ESR) and CRP also decreased significantly in the 5 mg/kg and 10 mg/kg tocilizumab groups and normalized after only 2 weeks of treatment.

A second multi-center DBPCRCT evaluated the efficacy and safety of tocilizumab in 164 RA patients who had been refractory to multiple DMARDs (Nishimoto et al 2004). Patients received tocilizumab at doses of 4 mg/kg or 8 mg/kg IV or placebo every 4 weeks over a 3-month period. The primary endpoint was achievement of an ACR20 response at week 12 using the last observation carried forward (LOCF) method. Secondary endpoints consisted of improvement in the DAS28, frequency of ACR50 and ACR70 responses, improvement of variables in the ACR core set, and overall improvement in the ACR criteria. Tocilizumab significantly improved all measures of disease activity in the ACR core set in a dose-dependent manner, with response obvious at week 4 and escalating through week 12. At 3 months, 78%, 57%, and 11% in the 8 mg/kg, 4 mg/kg, and placebo groups, respectively, achieved an ACR20. A statistically significantly higher percentage of patients in the 8 mg/kg group (40%) attained an ACR50 response compared with the placebo group (1.9%). Furthermore, complete normalization of CRP was observed in 76% and 26% of patients in the 8 mg/kg and 4 mg/kg groups versus only 1.9% of the placebo group. Of note, 5-year data from patients originally in this study that elected to continue tocilizumab in an open-label extension were recently reported (Nishimoto et al 2007a). Of the original 164 patients, 144 opted to continue treatment with tocilizumab at 8 mg/kg every 4 weeks. Importantly, 89 of these patients had received tocilizumab for >5 years. At the 5-year assessment, 84% of patients met ACR20 criteria. Sustained improvement was also noted in the mean DAS28 and Health Assessment Questionnaire (HAQ) scores, confirming the persistent clinical utility of tocilizumab in long-term treatment.

The European Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA)

trial was the first study to examine the effects of tocilizumab in conjunction with concomitant MTX (Maini et al 2006). Three hundred and fifty-nine patients with moderately severe RA who were refractory to MTX therapy were randomized to 1 of 7 treatment arms; tocilizumab 2 mg/kg, 4 mg/kg, or 8 mg/kg as monotherapy, the same doses in combination with MTX, or MTX plus placebo. Patients had failed an average of 5 DMARDs and almost 14% had received a TNF inhibitor prior to enrollment. The primary outcome measure at week 16 was a 20% improvement in ACR criteria, with mean change in DAS28 observed as the secondary endpoint. In the combination groups, an ACR20 response was achieved by a statistically significantly greater number of patients compared with MTX plus placebo. However, this could not be demonstrated in the group receiving 2 mg/kg of tocilizumab as monotherapy. Additionally, those patients receiving 4 mg/kg or 8 mg/kg of tocilizumab in combination with MTX also achieved an ACR50 and ACR70 response that was significantly increased in comparison with MTX alone. These results indicate that tocilizumab is effective as monotherapy at the 4 mg/kg and 8 mg/kg dose, but also appears to have a synergistic effect in combination with methotrexate. Significant changes in DAS28 scores were observed in a dose-dependent manner beginning at week 4 (maximum reduction in the 8 mg/kg groups), and were maintained throughout the treatment period in all tocilizumab groups except patients administered 2 mg/kg of tocilizumab as monotherapy. Of patients in the 8 mg/kg combination group, 34% achieved remission as defined by a DAS28 score <2.6, compared with only 8% of patients receiving MTX plus placebo (Prevoo et al 1996). Lastly, both ESR and CRP decreased markedly over time in all patients receiving tocilizumab except those assigned to 2 mg/kg monotherapy (ESR and CRP) and 4 mg/kg monotherapy (CRP only). Methotrexate plus placebo had very little effects on these parameters.

In the larger, more recent OPTION trial (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders), 632 RA patients with moderate to severe disease were randomly assigned to receive IV tocilizumab 4 mg/kg or 8 mg/kg or placebo every 4 weeks (Smolen et al 2008). Enrolled patients had average disease duration of 7.5 years, a DAS28 score of 6.8, swollen joint count (SJC) 20, and tender joint count (TJC) 32. Less than 10% of patients had received prior anti-TNF treatment. All three groups were continued on their pre-study dose of methotrexate (~15 mg/week) throughout the 24-week treatment period. The primary endpoint, an ACR20 response, was observed in a significantly higher proportion

of patients receiving tocilizumab 4 mg/kg or 8 mg/kg (48% and 59%) versus methotrexate alone (26%). Additionally, more patients in the 8 mg/kg tocilizumab group achieved an ACR50 or ACR70 response compared with placebo. CRP and ESR in this group also decreased significantly by week 2, and remained at normal levels throughout the study duration. Significant reduction in the DAS28 score was recorded as early as 2 weeks at both doses of tocilizumab, and continued to improve through 6 months of treatment. More patients allocated to tocilizumab therapy also achieved DAS28 remission (~25%) than those receiving DMARDs alone (<1%). Finally, a marked number of patients receiving tocilizumab also demonstrated good/moderate EULAR (European United League Against Rheumatism) response at 24 weeks (79.5% 8 mg/kg; 61.9% 4 mg/kg) compared with placebo (34.8%).

Investigation of tocilizumab in combination with a variety of DMARDs has also been recently reported. In the phase III, international TOWARD (Tocilizumab in Combination with Traditional DMARDs) trial, 1216 patients with moderate to severe RA who were inadequate responders to conventional DMARDs (MTX, sulfasalazine, leflunomide, chloroquine/hydroxychloroquine, azathioprine, or parenteral gold) were continued on their current therapy in addition to tocilizumab 8 mg/kg or placebo intravenously every 4 weeks for 24 weeks (Genovese et al 2007). Patients had an average disease duration of 9.8 years, DAS28 score of 6.6, TJC of 29, SJC of 19, HAQ score of 1.5, and a CRP of 2.6 mg/dL. At the primary evaluation point, patients receiving tocilizumab exhibited significantly higher ACR20/50/70 responses compared with placebo. ACR20 responses were seen in the tocilizumab group as early as week 2 as well as improvements in CRP and hemoglobin. Significant changes in the mean DAS28, HAQ score, and ESR were also documented in the tocilizumab group when compared to DMARDs alone. This trial was important in demonstrating the superior efficacy of tocilizumab in patients who are unable to tolerate methotrexate.

In addition to its clinical benefits, the ability of tocilizumab to alter the progression of joint damage in RA was examined in a prospective phase III study called SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor) (22). In this trial, 306 patients with RA of >5 years duration were randomized to receive either tocilizumab 8 mg/kg IV as monotherapy every 4 weeks or traditional DMARDs for 52 weeks. All patients had severe, active disease, with an average swollen and tender joint count 12 and 14, ESR >70, CRP of 4.8 mg/dL, and a mean DAS28

score of 6.5. The average number of DMARDs failed was 2 with average disease duration of 2.3 years. Radiographs of the hands and feet were performed at baseline, 28, and 52 weeks. Radiographic scoring was confirmed by 2 independent readers blinded to both treatment group and chronological order using the van der Heijde's modified Sharp method. The mean total Sharp score (TSS) at baseline was 29.4, with an estimated yearly progression rate of 13.3 Sharp units. Sixty seven percent of patients received MTX as monotherapy or in combination with other DMARDs. As in other studies, treatment with tocilizumab monotherapy proved to be clinically superior to conventional DMARD therapy. At week 52, patients allocated to treatment with tocilizumab achieved an ACR20, ACR50, and ACR70 response of 78%, 64%, and 44% in contrast to 34%, 13%, and 6% in the DMARD group, respectively. Clinical remission (DAS28 < 2.6) was achieved in 59% of patients receiving tocilizumab and only 3% of patients receiving DMARDs (Prevo et al 1996). Substantial improvements in radiographic progression were also documented. The mean change in TSS at week 28 was statistically significantly less in the tocilizumab group compared to patients treated with traditional DMARDs and exhibited constant improvement until week 52. These changes correlated with a higher ACR response in both the tocilizumab and DMARD cohorts. Furthermore, erosion and joint space narrowing scores also showed significantly less change in the tocilizumab group than in the DMARD group. These results indicate that tocilizumab is not only effective in managing the signs and symptoms of RA, but can help to sustain structural integrity of the joints.

Safety and tolerability

Safety remains an important concern for both physicians and patients when investigating any new therapy. To date, controlled trials and long-term follow-up of patients provide preliminary safety data on approximately 4000 RA patients who have received tocilizumab as monotherapy or in combination with other DMARDs, with more than 5000 patient-years of follow-up. The most frequent adverse events recorded to date are discussed below. In the future, post-marketing surveillance and pharmacovigilance may help to elucidate additional data relevant to adverse events and their potential clinical impact.

Infections have been the most frequently reported adverse event linked to tocilizumab therapy in RA. The most common documented infections include nasopharyngitis and upper respiratory tract infection of mild to moderate severity. Serious infections, that is those requiring antibiotics and/or

hospitalization, have been comprised of pneumonia, cellulitis, gastroenteritis, herpes zoster, herpes simplex, perianal abscess, osteomyelitis, infective arthritis, and sepsis (Maini et al 2006; Nishimoto et al 2007b). One patient in a trial died from disseminated Epstein-Barr virus (EBV) infection and subsequent hemophagocytic syndrome (Nishimoto et al 2004). In general, most studies show a small dose-dependent increase in the rate of serious infection associated with tocilizumab therapy compared with placebo. Larger studies with a more extensive period of exposure to study drug will be helpful to more accurately assess the risk of serious infection associated with tocilizumab treatment.

Increases in serum total cholesterol, LDL (low-density lipoprotein) and HDL (high-density lipoprotein) cholesterol, and triglycerides have been reported in many tocilizumab trials. In an earlier study, total cholesterol values in 44% of patients treated with tocilizumab increased in a dose-dependent manner (Nishimoto et al 2004). Comparable elevations were noted in serum HDL and triglyceride levels. More recently, mean plasma concentrations of total, HDL, and LDL cholesterol were noted to be increased in patients receiving tocilizumab within the first 6 weeks of treatment (Smolen et al 2008). These levels remained elevated through week 24, requiring 7 patients to begin lipid-lowering therapy according to protocol guidelines. Notably, there was no increase in cardiovascular events in this patient group compared with placebo. Moderate, but reversible changes in non-fasting total cholesterol, HDL, and triglycerides were also documented during the CHARISMA trial in patients treated with tocilizumab (Maini et al 2006). Levels steadied after initial treatment and did not continue to increase with subsequent dosing. Importantly, the mean atherogenic index remained largely unchanged. Increases in cholesterol have also been reported with TNF inhibitors and may be related to the degree of inflammatory suppression (Seriolo et al 2006). Improvement therefore in overall disease activity may outweigh known risks of high serum cholesterol (ie, cardiovascular disease). This, however, remains to be elucidated in longer-term studies.

Tocilizumab treatment has also been associated with moderate increases in serum transaminases. In the CHARISMA trial, the mean AST (alanine aminotransferase) and ALT (aspartate aminotransferase) in all 127 patients who received tocilizumab exhibited elevations above normal levels (Maini et al 2006). This increase was accentuated in patients receiving concurrent MTX (2% of patients in the combination group had elevations >3-fold the upper limit of normal (ULN)). Five patients had to be withdrawn from the study due to ALT

levels >100 IU/L. However, in the remaining patients, mean values returned to near-baseline within 8 weeks of the final infusion. A gradual rise in bilirubin levels was also recorded, but appeared to have no correlation with elevations in ALT. Patients receiving MTX plus placebo demonstrated no increase in serum bilirubin. Raised levels of transaminases were also recorded in the OPTION trial (Smolen et al 2008). Of the patients receiving tocilizumab, 6% in the 4 mg/kg group and 10% in the 8 mg/kg group had increases in ALT concentrations of more than $3 \times$ ULN compared with 4% of placebo patients. Eleven patients exhibited concentrations of $>5 \times$ ULN. None of these patients demonstrated a concurrent increase in total bilirubin or alkaline phosphatase. These increases declined or normalized spontaneously or after disruption of treatment in the majority of patients, with no recurrent increase in ALT after the resumption of therapy. In a larger RA cohort, only 1% of patients receiving tocilizumab in the TOWARD study had a transient ALT elevation $>3 \times$ ULN, with only 1 patient withdrawing (Genovese et al 2007). It is again important to note that these patients were also treated with concomitant DMARDs. No comments were made regarding elevations in serum bilirubin. To date, no cases of hepatitis or serious gastrointestinal (GI) events related to these fluctuations in liver enzymes have been reported.

Reductions in the mean neutrophil count have also been observed with tocilizumab therapy. The initial study by Nishimoto observed decreases in white blood cell counts in 16% of patients allocated to tocilizumab (grade 3 in 1 patient, grade 2 in 5 patients, and grade 1 in the remaining patients according to World Health Organization guidelines) (Nishimoto et al 2004). The decreases were transient and recovered without treatment within a few weeks. Only 1 patient withdrew from the study. Dose-dependent decreases in the neutrophil count were also reported in the CHARISMA trial, again with normalization after the treatment period ended (Maini et al 2006). Lastly, transient neutrophil decreases in the OPTION trial were seen more often in patients treated with tocilizumab than in those of placebo (37 patients in the 4 mg/kg group, 67 in the 8 mg/kg groups, and 4 in the placebo group) (Smolen et al 2008). It is noteworthy that only a few patients treated with tocilizumab have developed absolute neutropenia (<500 cells/mL) and that these decreases do not appear to increase susceptibility to infection.

Infusion reactions related to tocilizumab therapy have been mild to moderate, with 2 cases of nonserious anaphylaxis and hypersensitivity reactions described in one study (Maini et al 2006). Transient increases in blood

pressure, injection site erythema, headache, nausea, and pruritis have also been reported (Nishimoto et al 2007b). Less than 1% of patients among the controlled trials discontinued therapy due to these effects.

The occurrence of malignancy in patients treated with tocilizumab has been reported in a single study. In the SAMURAI trial, 2 patients were diagnosed with breast cancer and a third with colon cancer (Nishimoto et al 2007b). All patients improved with directed therapy. No malignancies were reported in the DMARD group. Though other trials have not demonstrated an increased risk of malignancy with tocilizumab exposure, as with other biologics more long-term data are required.

Patient-focused perspectives such as quality of life, patient satisfaction/acceptability/adherence

Patient-derived outcomes are essential in establishing the true efficacy of any investigational drug. The influence of tocilizumab on health-related quality of life (HRQOL) and physical function in patients with RA has been analyzed in several large studies. In the OPTION trial, outcome measures including HAQ-Disability Index (HAQ-DI) and Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) were performed every 4 weeks. The Short Form 36 Health Survey (SF-36) was also assessed at baseline, weeks 8, 16, and 24 (Smolen et al 2008). A significant improvement from baseline HAQ-DI score was noted as early as week 4 in the tocilizumab groups, with 61% of patients in the 4 mg/kg cohort and 59% of patients in the 8 mg/kg cohort achieving an increase of 0.3 points or more at week 24 compared with 47% of the placebo group. SF-36 physical component score (PCS) and mental component score (MCS) also dramatically improved in patients allocated to tocilizumab therapy ($p < 0.0001$). FACIT-Fatigue scores demonstrated considerable improvement in patients receiving tocilizumab compared to methotrexate alone (difference from placebo: 4 mg/kg 3.3, 8 mg/kg 4.6). Importantly, the change from baseline scores in patients receiving tocilizumab exceeded accepted thresholds for minimal clinically important difference (MCID) for these measures. The results of this study concluded that tocilizumab therapy provided clinically meaningful improvement in HRQOL and physical function in patients with RA.

Treatment with tocilizumab during the TOWARD trial also resulted in early significant and clinically relevant improvement in the HAQ, SF-36 score, and FACIT-Fatigue score at 24 weeks (Gomez-Reino et al 2007). Sixty percent

of patients receiving tocilizumab versus 34% of patients taking conventional DMARDs showed marked changes in the mean HAQ scores at 6 months. Improvement in the FACIT-Fatigue score in the tocilizumab groups was observed as early as week 8, with changes in the MCID increasing to well above accepted standards by week 24. Statistically significant improvements in the PCS and MCS and the individual domain scores of the SF-36 (physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health) were higher in the tocilizumab groups compared with placebo. Again, tocilizumab demonstrated significant benefit in patients with an inadequate response to DMARDs in all quality of life parameters.

Conclusions, place in therapy

Several published clinical trials have now established the efficacy of tocilizumab, both as monotherapy and in combination with traditional DMARDs, in the treatment of moderate to severe RA (Ohsugi and Kishimoto 2008). Significant early improvements in accepted disease outcome measures including the ACR response criteria, HAQ, and DAS28, as well as enhancement of quality of life and overall function indicate substantial clinical benefit over DMARD therapy alone.

Inhibition of radiographic progression and joint destruction in RA has also been suggested with tocilizumab monotherapy in open-label trials. Larger randomized controlled studies are needed to determine the effects of IL-6R blockade in erosive disease. These studies, as well as those to determine whether combination therapy with methotrexate will provide greater radiographic benefit, are in progress.

Based on their extensive record of efficacy and a safety accumulated for more than a decade, TNF inhibitors have become the biologic agent of choice for patients with RA, as well as for patients with other systemic inflammatory diseases. However, despite the substantial efficacy of these drugs, a subset of patients will exhibit a suboptimal response, either on account of incomplete or unsustained efficacy or related to tolerability. Of note, increasing observational and anecdotal data suggest that switching among different TNF inhibitors may be a viable option. As newer biologic agents are introduced to the clinic, it is important to understand their efficacy in patients who had previously been treated with TNF inhibitors. Such data have been published for biologic agents with other mechanisms of action, including the abatacept, an inhibitor of T-cell co-stimulation, and for rituximab, an anti-CD20 mAb that targets B cells. Similar

data for IL-6 targeted therapies, in particular tocilizumab, are eagerly awaited.

Several doses of tocilizumab have been assessed in clinical trials and testing for optimum efficacy at these and other levels continues. Evaluation of possible increased effectiveness with the addition of methotrexate or other DMARDs has also been previously estimated, but more studies to validate an observable difference are needed and are in progress. Combination therapy with other biologics may also be considered in prospective studies. However, because of current data surmised from published trials of combined biologic therapy, extreme caution will need to be implemented. Previous studies of a TNF inhibitor plus an IL-1 inhibitor or a T-cell costimulatory molecule antagonist showed no enhancement in efficacy but definite increases in toxicity (Kavanaugh et al 2004).

Tocilizumab appears to have an acceptable safety profile and is well-tolerated by most patients. Common laboratory abnormalities seen across clinical studies have included mild to moderate elevations in serum total cholesterol and its components (HDL, LDL, and triglycerides), AST and ALT, and decreases in absolute neutrophil count. To date, sequelae related to such events, such as increased cardiovascular events, hepatic failure, or increased susceptibility to infection, have not been reported. At this time, the rate of serious infections appears comparable to that seen with other immunomodulatory biologic agents. Longer-term studies with increased patient exposure time are needed to more fully understand the risk of these events.

In future, it may be expected that we may see additional methods to target IL-6 as well as the application of IL-6 inhibitors to systemic inflammatory diseases besides RA. For example, blockade of IL-6 trans-signaling with a soluble gp130 protein (sgp130Fc) is now in preclinical trials and showing promise in a number of inflammatory diseases (Rose-John et al 2007). In addition, tocilizumab has been approved in Japan for the treatment of RA, systemic onset juvenile idiopathic arthritis (JIA), and Castleman's disease, a rare, lymphoproliferative disorder characterized by excessive IL-6 production (Nishimoto et al 2000; Yokota et al 2008). Children and adolescents afflicted with JIA are often resistant to treatment, including TNF inhibitors. Recent studies examining its efficacy in Crohn's disease and systemic lupus erythematosus (SLE) have also shown promise (Rose-John et al 2007; Ito 2005).

In summary, tocilizumab appears to be an emerging therapy for RA. Early studies have provided an acceptable profile but conclusions about the true safety

of tocilizumab will need further evaluation through long-term studies.

Disclosures

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