mAbs 1:5, 432-438; September/October, 2009; © 2009 Landes Bioscience

Tocilizumab

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Key words: rheumatoid arthritis, Crohn disease, Castleman disease, IL-6 receptor, tocilizumab, interleukins for rheumatoid arthritis

Roche is co-developing tocilizumab (Actemra, RoActemra), a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody, with Chugai Pharmaceutical. Tocilizumab is marketed in Japan for Castleman disease and several types of arthritis. The product is approved in the European Union for treatment of moderate-to-severe rheumatoid arthritis, and is currently undergoing review by the US Food and Drug Administration for this condition. Tocilizumab has also been studied for potential use in the treatment of other IL-6 related disorders including Crohn disease.

Introduction

The field of rheumatology has seen a number of novel treatments over the last decade. These treatments have mainly targeted T and B lymphocytes, as well as cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)-6, IL-1β and IL-15.[1] These cytokines are pro-inflammatory and expressed in large amounts in patients with rheumatoid arthritis (RA). They are also detectable in the joints and circulatory pathways of RA patients. A number of marketed protein therapeutics target TNFα, including monoclonal antibodies (mAbs) infliximab and adalimumab, and etanercept, a soluble TNF receptor fusion protein. Patients having an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX), have benefited from these three drugs,[2] but 20–40% of patients do not respond well to these anti-TNFα drugs. Therapeutics with different mechanisms of action are required to address this unmet need.

Targeting the cytokine IL-6 presents such an opportunity. IL-6 binds to its soluble and membrane-bound receptor, IL-6R. The IL-6 receptor complex is involved in intracellular signaling through its interaction with membrane-bound gp130. This intracellular signaling is responsible for gene activation and a wide-range of biologic activities. The link between IL-6 and RA has been shown in previous preclinical and human studies. The influence of IL-6 on phenomena typical of RA such as activation of T cells,[3] proliferation of synovial fibroblasts,[4] osteoclast differentiation, and chronic synovial inflammation[5] has been demonstrated. Thus, IL-6 represents an attractive target for therapeutic inhibition of RA.

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Submitted: 07/10/09; Accepted: 07/10/09
Previously published online:
www.landesbioscience.com/journals/mabs/article/9497

Tocilizumab, also known as MRA, is a humanized anti-IL-6 receptor antibody of the IgG1 subclass. The molecule was humanized by the grafting of the complementarity-determining regions of a mouse anti-human IL-6 receptor mAb onto human IgG1. It inhibits the binding of IL-6 to its receptors, and thus reduces the cytokines pro-inflammatory activity by competing for both the soluble and membrane-bound forms of the human IL-6 receptor. While IL-6 levels are relatively low in a healthy person, levels increase during an immune response to such an extent that the cytokine causes inflammation by acting on various immune cells such as T cells, B cells, monocytes, macrophages.[6] A few key factors have played a major role in the interest in IL-6 as a target. One factor was the observation that patients suffering from Castleman disease, in which benign tumors overproducing IL-6 are produced, exhibit the same symptoms of RA. It was later observed from murine models that IL-6-deficient mice were incapable of producing an inflammatory response.[6] Further, the success of rituximab in RA demonstrates the importance of the role of B cells in autoimmune pathology. IL-6 is believed to be a major factor for differentiating B cells into antibody-producing plasma cells.[6]

The product was originally developed by Chugai Pharmaceutical Co., Ltd., (Tokyo, Japan), in collaboration with researchers at Osaka University. In December 2001, Hoffmann LaRoche (Basel, Switzerland) gained opt-in rights on tocilizumab in the US, and later entered into an agreement with Chugai to co-develop and promote tocilizumab in all countries except Japan, South Korea and Taiwan. Tocilizumab was approved as an orphan drug in Japan for the treatment of Castleman disease, a rare lymphoproliferative disease involving expansion of plasma cell numbers, in 2005. The product also received approval for RA, systemic-onset juvenile idiopathic arthritis (sJIA) and polyarticular-course juvenile arthritis in Japan.

For the US and European markets, Roche filed marketing applications with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) in late 2007, for reduction of the signs and symptoms of moderate-to-severe RA. While the drug received approval in Europe for this indication in January 2009,[7] the regulatory review path in the US has not been straightforward. The FDA has asked for more animal model data, a risk evaluation and mitigation strategy (REMS) to ensure that the drug is prescribed and administered correctly, as well as further documentation regarding product manufacture and final labeling.

Table 1. Phase 3 clinical studies in rheumatoid arthritis

Clinical phase	Study details	Results	National clinical trial (NCT) number; Status
Phase 3—OPTION[8]	A total of 623 patients received tocilizumab intravenously (either 4 or 8 mg/kg) or placebo infusions plus MTX (10–25 mg/week) every 4 weeks for 24 weeks.	At week 24, ACR20 response was achieved by 59, 48 and 26% of patients administered 8 mg/kg tocilizumab, 4 mg/kg tocilizumab or placebo plus MTX, respectively.	NCT00106548; Completed
Phase 3—TOWARD[9]	A total of 1,220 patients were randomized (2:1 ratio) in this study. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks.	At week 24, the proportion of patients achieving an ACR20 response was significantly greater in the tocilizumab plus DMARD group than in the control group (61% versus 25%; $p < 0.0001$). Systemic markers such as the C-reactive protein and hemoglobin levels showed superiority of tocilizumab plus DMARDs over DMARDs alone.	NCT00106574; Completed
Phase 3—RADIATE[10]	A total of 499 patients with inadequate response to one or more TNF antagonists were administered 4 or 8 mg/kg tocilizumab or placebo IV every 4 weeks with stable MTX for 24 weeks. ACR20 responses, secondary efficacy and safety endpoints were assessed.	More patients treated with 4 or 8 mg/kg tocilizumab plus MTX achieved a ACR20 response following 24 weeks of treatment compared with patients receiving placebo plus MTX. ACR20 was 50, 30 and 10% for the 8 mg/kg mAb, 4 mg/kg mAb and placebo groups, respectively.	NCT00106522; Completed
Phase 3—AMBITION[11]	Double-blind, double-dummy, randomized 24 week study of 673 patients received either 8 mg/kg tocilizumab every 4 weeks (iv) plus placebo capsules weekly or placebo infusions every 4 weeks plus MTX at 7.5 mg/week	After 24 weeks, tocilizumab was associated with a significantly greater rate of improvement than MTX, with 70% of tocilizumab recipients achieving a 20% improvement in signs and symptoms of RA compared with 53% of patients receiving MTX alone	NCT00109408; Completed
Phase 3—LITHE[12]	Three-arm, placebo-controlled study to compare safety and efficacy for prevention of joint damage. Tocilizumab (8 mg/kg or 4 mg/kg), every four weeks plus MTX at 10–25 mg/week. Patient group sizes: tocilizumab 8 mg/kg n = 398, tocilizumab 4 mg/kg n = 399, control n = 393.	At 52 weeks, ACR20 was achieved by 56, 47, and 25% of patients who received 8 mg/kg, 4 mg/kg or placebo, respectively. ACR70 was achieved by 20%, 16% and 4% of patients who received 8 mg/kg, 4 mg/kg or placebo, respectively. DAS28 remission was achieved in 47% and 30% of patients treated with tocilizumab 8 mg/kg and 4 mg/kg, respectively, at week 52, compared with 8% of patients treated with placebo.	NCT00106535; Completed
Phase 3—SAMURAI[13]	In a study of 306 RA patients in Japan, tocilizumab was administered IV at 8 mg/kg every 4 weeks for 52 weeks as monotherapy to RA patients in Japan. Control treatment was DMARDs. Radiographs of hands and feet were used to evaluate treatment effects.	Mean total Sharp, erosion and joint space narrowing scores were 2.3, 0.9 and 1.5, respectively, for tocilizumab-treated patients compared to 6.1, 3.2 and 2.9, respectively, for control treated patients. ACR20, ACR50 and ACR70 response rates were 78, 64 and 44%, respectively, for patients who received tocilizumab. The corresponding response rates for control treated patients were 34, 13 and 6%, respectively.	NCT00144508; Completed
Phase 3—SATORI[14]	A total of 125 patients in Japan received either 8 mg/kg tocilizumab monotherapy or 8 mg/kg MTX every 4 weeks for 24 weeks.	ACR20 response was achieved by 80% of patients administered tocilizumab and 25% of those who received control. Decreases in mean serum vascular endothelial growth factor levels were observed.	NCT00144521; Completed
Phase 3—STREAM[15]	Long-term study of the safety and efficacy of tocilizumab treatment. As of March 2007, a total of 94 patients had been administered 8 mg/kg tocilizumab every 4 weeks for five years.	At 5 years, ACR20, ACR50 and ACR70 responses were achieved by 84, 69 and 44%, respectively, of the patients.	NCT00144651; Active, not recruiting

ACR, American College of Rheumatology; DAS, disease activity score; DMARD, disease-modifying anti-rheumatic drugs; MTX, methotrexate.

Overview of Clinical Studies

As of June 2009, tocilizumab was the study agent in 37 studies listed as recruiting, active but not recruiting or completed at www.clinicaltrials.gov. Of these studies, 29 were Phase 3 studies of RA (24 studies), sJIA (3 studies), juvenile idiopathic arthritis (1 study), or polyarticular juvenile idiopathic arthritis (1 study) patients. Details of the patients, materials, methods and results of six completed Phase 3 studies and one ongoing long term Phase 3 study are summarized in **Table 1**. The molecule has also been studied as a treatment for other indications such as Castleman disease, Crohn disease (CD), systemic lupus erythematosus, Takayasu arteritis and mutirefractory adult-onset Still disease, although only one or a few studies were done in each indication, and the studies involved relatively small numbers of patients.

Clinical Studies in Rheumatoid Arthritis

Numerous Phase 3 studies have been performed to establish the safety and efficacy of tocilizumab in alleviating the signs and symptoms of RA. Studies with published results include OPTION (NCT00106548; Tocilizumab pivotal trial in MTX inadequate responders), TOWARD (NCT00106574; Tocilizumab in combination with traditional DMARD therapy), RADIATE (NCT00106522; Research on Actemra determining efficacy after anti-TNF failures), AMBITION (NCT00109408; Actemra versus MTX double-blind investigative trial in monotherapy), and LITHE (NCT00106535; Double-blind trial to investigate inhibition of joint damage by tocilizumab in combination with MTX), SAMURAI (NCT00144508; Investigation of the effects of tocilizumab monotherapy on inhibition of joint damage), SATORI (NCT001445221; Tocilizumab as monotherapy for RA patients with inadequate response to MTX) and STREAM (NCT00144651; Tocilizumab as monotherapy for RA patients).

The primary aim of these trials was to investigate tocilizumab either as a monotherapy or in combination with DMARDs in RA patients with inadequate response to MTX or anti-TNF therapies, and patients who had not been treated with MTX in the last 6 months. The primary outcome measure of these trials was the percentage of patients with a 20% improvement in tender or swollen joint counts, an improvement criteria defined by the American College of Rheumatology (ACR) and referred to as the ACR20 response. Patients' disease activity score based on 28 joints (DAS28) were also assessed. Eligible subjects for these studies were patients 18 years or older.

The OPTION[8] study (NCT00106548) was the first to demonstrate the clinical benefit of tocilizumab for patients with an inadequate response to MTX. The study showed that a greater proportion of RA patients treated with tocilizumab achieved a significant improvement in disease signs and symptoms as assessed by ACR20 scores at week 24, compared to the MTX control group. Tocilizumab was administered intravenously (IV) at 8 mg/kg (205 patients), 4 mg/kg (214 patients). An additional 204 patients received placebo. MTX was administered at stable pre-study doses (10–25 mg/week). At 24 weeks, ACR20 was achieved by 59% patients in the 8 mg/kg group and 48% in the 4 mg/kg group compared to 26% in the control group. Inhibition of structural damage, which is an important aspect of RA treatment, was not investigated in this study. Remission, as assessed by DAS28 scores, was achieved by 25% of the patients on the 8 mg/kg dose compared to 1% for the control group. Further, the higher dose of 8 mg/kg provided a more robust therapeutic effect as compared to the 4 mg/kg dose. Adverse events (AEs) were reported in 69 and 71% of patients administered 8 and 4 mg/kg tocilizumab, respectively, compared to 63% of those who received placebo.

The TOWARD study[9] (NCT00106574) results showed that tocilizumab in combination with DMARDs such as MTX, leflunomide, azathioprine, sulfasalazine, chloroquine was safe and effective in reducing articular and systemic symptoms in patients with active RA with inadequate response to these drugs alone. The study had a double-blind design and a total enrollment of 1,220 patients who either received 8 mg/kg tocilizumab or placebo every 4 weeks for 24 weeks. In addition to the ACR20 primary endpoint, secondary measures of ACR50 and ACR70, DAS28 and systemic markers like C-reactive protein (CRP) and hemoglobin levels were also compared. Tocilizumab in combination with DMARDs demonstrated superiority over DMARDs only. Out of 1,200 patients, 16 patients began lipid-lowering therapy during the study. Grade 3 neutropenia also occurred in 3.7% of the patients, while none was reported in the control group.

The primary objective of the RADIATE[10] study (NCT0010 6522) was to investigate the safety and efficacy of tocilizumab for patients with inadequate response to anti-TNF therapy. The study compared tocilizumab in combination with MTX to placebo plus MTX administered every 4 weeks for 24 weeks. A total of 499 patients enrolled, with 175, 163 and 160 assigned to the 8 mg/kg, 4 mg/kg, and placebo groups, respectively. Overall, the ACR response rates for the tocilizumab arm were higher than that of the placebo arm. At 24 weeks, ACR20 was achieved by 50, 30 and 10% of patients in the 8 mg/kg, 4 mg/kg and placebo groups, respectively. Failure to respond to either etanercept, adalimumab or infliximab, or the number of failed treatments did not affect response to tocilizumab. DAS28 remission, defined as DAS28 <2.6, rates were dose related; DAS28 was achieved by 30.1, 7.6 and 1.6% of 8 mg/kg, 4 mg/kg and placebo groups at week 24. Most AEs were mild or moderate. In total, AEs were reported by 84.0, 87.1 and 80.6%, respectively, of patients receiving 8 mg/kg, 4 mg/kg and placebo. Study results indicated a greater proportion of patients treated with tocilizumab plus MTX (either 4 or 8 mg/kg mAb) achieved a significant reduction in ACR20-measured reductions in the signs and symptoms of RA following 24 weeks of treatment compared to patients receiving placebo plus MTX.

The main objective of the AMBITION trial[11] (NCT00109408) was to investigate the efficacy and safety of tocilizumab as a monotherapy compared to MTX in patients with moderate-to-severe RA, not treated with MTX for the past six months, and who had not previously failed either MTX or a biologics treatment. The monotherapy group achieved a higher ACR20 response than the MTX group (69.9% compared to 52.5%).

Levels of high-sensitivity CRP were within the normal range for patients receiving tocilizumab alone, while they were higher in the MTX-treated group. Tocilizumab-treated patients also had a lower incidence of serious AEs (3.8% compared to 2.8% for MTX) and serious infections (1.4% compared to 0.7%). This study showed that tocilizumab as a monotherapy was superior to MTX monotherapy for the patient population studied.

The LITHE trial[12] (NCT00106535) focused on investigating the prevention of structural joint damage, improvement in physical function and disease signs and symptoms in moderate-to-severe active RA patients with inadequate response to MTX. The study had a three-arm, randomized, double-blind, placebo-controlled design and evaluated tocilizumab IV-dosed at either 8 or 4 mg/kg every 4 weeks for 52 weeks compared to placebo. All three groups of patients (tocilizumab 8 mg/kg n = 398, tocilizumab 4 mg/kg n = 399, control n = 393) also received MTX. At week 52, study results indicated that tocilizumab plus MTX significantly inhibited structural joint damage, as assessed by joint erosion, joint space narrowing and total Genant-modified Sharp scores, in RA patients compared to MTX alone. ACR20 was achieved by 56, 47 and 25% of patients who received 8 mg/kg tocilizumab, 4 mg/kg tocilizumab or placebo, respectively. ACR70 was achieved by 20, 16 and 4% of patients who received 8 mg/kg tocilizumab, 4 mg/kg tocilizumab or placebo, respectively. Disease remission as assessed by DAS28 score was achieved in 47 and 30% of patients treated with tocilizumab dosed at 8 and 4 mg/kg, respectively, at week 52, compared to 8% of patients treated with placebo plus MTX. The safety profile was noted as consistent with previous studies, and did not change from 6 to 12 months. The study concluded that tocilizumab significantly inhibited the progression of structural joint damage, improved physical function (as per a health assessment questionnaire-disability index) and the signs and symptoms of RA significantly more than control, and that the treatment had an acceptable safety profile.

The objective of the SAMURAI study[13] (NCT00144508) was evaluation of tocilizumab's ability to inhibit progression of joint damage in RA patients. The mAb was administered IV at 8 mg/kg every 4 weeks for 52 weeks as monotherapy. The control treatment was conventional DMARDs. The effects of treatment were assessed through radiographs of the hands and feet, which were scored by the van der Heijde modified Sharp method. The study included 306 Japanese patients over 20 years old, with 148 receiving control and 158 receiving tocilizumab treatment. At week 52, 56% of tocilizumab-treated patients had no radiographic progression compared to 39% of those who received control treatment. The mean total Sharp, erosion and joint space narrowing scores were 2.3, 0.9 and 1.5, respectively, for tocilizumab-treated patients compared to 6.1, 3.2 and 2.9, respectively, for control treated patients. ACR20, ACR50 and ACR70 response rates were 78, 64 and 44%, respectively, for patients who received tocilizumab. The corresponding response rates for control treated patients were 34, 13 and 6%, respectively. AEs were reported for 89 and 82%, respectively, for tocilizumab and control treated patients. The study results suggested that tocilizumab monotherapy was superior to DMARDs in preventing joint damage in Japanese RA patients.

The SATORI study[14] (NCT00144521) evaluated 8 mg/kg tocilizumab monotherapy for Japanese RA patients with inadequate response to low dose (8 mg/kg) MTX, which was used as the control treatment. A total of 125 patients received study drugs (64 in control group and 61 in tocilizumab-treatment group) every 4 weeks for 24 weeks. At 24 weeks, an ACR20 response was achieved by 80% of patients administered tocilizumab and 25% of those who received control treatment. Decreases in mean serum vascular endothelial growth factor (VEGF) levels were observed. The mean change from baseline VEGF level was -346.9 pg/mL and -74.0 pg/mL for patients administered either tocilizumab or control drug, respectively, at 24 weeks. AEs were reported for 92% and 72%, respectively, for tocilizumab and control treated patients. The study conclusion was that tocilizumab monotherapy was generally well-tolerated, and had excellent efficacy with a positive benefit-risk ratio in the patient population studied.

The objective of the STREAM study[15] (NCT00144651) is to assess the safety and efficacy of long term tocilizumab monotherapy for RA patients who had previously participated in a 3-month Phase 2 study. As of March 2007, a total of 94 patients (of 143 enrolled) had been administered 8 mg/kg tocilizumab every 4 weeks for five years. At 5 years, ACR20, ACR50 and ACR70 responses were achieved by 84, 69 and 44%, respectively, of the patients. Remission, as defined as a DAS28 less than 2.6, was achieved by 55% of the patients. Safety data indicated that long-term treatment with tocilizumab was well-tolerated and most AEs were mild.

Investigations have also been carried out on the effects of tocilizumab in RA patients at risk of heart disease.[16] The Phase 1 study NCT00365001 was a drug interaction study between tocilizumab, MTX and simvastatin administered to RA patients. The on-going Phase 3 study NCT00535782 will evaluate the effect of tocilizumab on markers of atherogenic risk in patients with moderate-to-severe RA. Patients are currently being recruited to investigate the effects of tocilizumab on lipids, arterial stiffness and markers of atherogenic risk in patients. The primary endpoints of this study are the LDL-1 particle numbers and changes in pulse wave velocity.

Clinical Studies in Other Indications

Tocilizumab has also been investigated for other arthritic conditions such as systemic-onset juvenile idiopathic arthritis (sJIA), as well as other indications, including Castleman disease and Crohn disease (CD). **Table 2** provides details of the clinical phase, indication and dose studied, and a brief summary of results from selected studies published in peer-reviewed literature.

Systemic-Onset Juvenile Idiopathic Arthritis

The main aim of this study was to evaluate the efficacy and safety of tocilizumab in patients with sJIA, a subtype of juvenile idiopathic arthritis.[17] The disease is resistant to MTX, and anti-TNF treatments are thought to be less beneficial than in other types of arthritis. The primary outcome measures in this study were the percentage of patients achieving a American

Table 2. Clinical studies in additional indications

Clinical phase and indication	Study details	Results of study
Phase 3—Systemic juvenile idiopathic arthritis[17]	Three doses of tocilizumab (8 mg/kg IV dose) were administered to 56 systemic juvenile idiopathic arthritis patients in Japan every 2 weeks during a 6-week open-label lead-in phase; patients were then assignment to placebo or continued tocilizumab treatment for 12 weeks in the double-blind phase. Patients responding to tocilizumab were enrolled in an open-label extension phase for at least 48 weeks.	At the end of the lead-in phase, ACR Pedi30, 50 and 70 responses were achieved by 91, 86 and 68% of patients, respectively. At 48 weeks, ACR Pedi 30, 50 and 70 responses were achieved by 98, 94 and 90% of patients, respectively.
Pilot study—Castleman disease[18]	Initial treatment with increasing doses (1, 10, 50 and 100 mg per patient) of tocilizumab administered IV twice weekly; tocilizumab (50 or 100 mg) then administered IV either once or twice weekly to seven Castleman disease patients.	Treatment was well tolerated except for a transient and mild decrease in granulocyte counts. Fever and fatigue disappeared, and laboratory index improved.
Phase 2—Castleman disease[19]	Twenty-eight patients with multicentric Castleman disease were administered 8 mg/kg tocilizumab every 2 weeks for 16 weeks during the initial phase; treatment was individualized during an open-label extension period in which the maximum dose was 8 mg/kg and the minimum treatment interval was 1 week.	Within 16 weeks, improvement was observed in lymphadenopathy and inflammatory parameters. CRP, immunoglobulin G, and serum amyloid A protein levels decreased; hemoglobin, serum albumin and total cholesterol levels increased; Significant improvement in fatigue compared to baseline was observed, and the treatment was well-tolerated
Pilot trial—Crohn disease[20]	Thirty-six patients with active Crohn disease (CDAI ≥150) were randomly assigned to receive biweekly intravenous infusion of either placebo, tocilizumab, or tocilizumab/placebo alternately for 12 weeks at a dose of 8 mg/kg. The study's primary end point was a clinical response rate that was defined as a reduction of CDAI ≥70.	Serum concentrations of tocilizumab were detected at 2 weeks after every infusion, at which time acute phase responses were completely suppressed; however, they were not suppressed at 4 weeks. Endoscopic and histologic examination showed no difference between tocilizumab and placebo groups. The incidence of AEs was similar in all the groups.

ACR Pedi, American College of Rheumatology Pediatric; AE, adverse events; CDAI, Crohn Disease Activity Index; CRP, C-reactive protein.

College of Rheumatology Pediatric (ACR Pedi) 30 response, defined as at least a 30% improvement in at least three of six variables with no more than one variable worsening by 30%, and improvement in C-reactive protein (CRP) levels. Another measure of efficacy was the percentage of patients in whom these effects were maintained. The age requirement for enrollment was between 2 and 19 years.

The study was divided into three phases: an open-label lead-in phase of 6 weeks, a double-blind, randomized, placebo-controlled phase of 12 weeks, and an open-label extension phase of at least 48 weeks. The study was registered as NCT00144599 for the open-label lead-in and double-blind phases, and as NCT00144612 for the open-label extension phase. A total of 56 patients were enrolled in the open-label lead-in phase. All patients received three doses of 8 mg/kg tocilizumab IV every 2 weeks. ACR Pedi 30, 50 and 70 responses were 91, 86 and 68%, respectively, at the end of the open-label lead-in phase.

In the double-blind phase, 44 patients who completed the open-label lead-in phase and achieved ACR Pedi 30 response and CRP concentrations of less than 5 mg/mL were a assigned to receive tocilizumab 8 mg/kg IV or placebo every 2 weeks for 12 weeks. At the end of the double-blind phase, 80% of tocilizumab-treated patients and 17% of the placebo group had completed the phase and maintained the ACR Pedi 30 response and CRP concentrations of less than 5 mg/mL.

Patients responding to tocilizumab were then enrolled in an open-label extension phase in which 8 mg/kg doses of tocilizumab were administered IV every 2 weeks for at least 48 weeks. At 48 weeks, ACR Pedi30, 50 and 70 responses were achieved by 98, 94% and 90% of patients, respectively. Overall, the study showed a sustained clinical improvement with the use of tocilizumab and a favorable risk-benefit profile.

Castleman Disease

In a pilot study18 of seven Castleman disease patients, three of which had amyloidosis secondary to the disease, increasing doses (1, 10, 50 and 100 mg per patient) of tocilizumab were administered IV twice weekly. No dose-limiting toxicity was observed in this initial phase. Fifty to 100 mg tocilizumab was then administered either once or twice weekly for 5 to 42 weeks as maintenance therapy. On a per patient basis, the maximum amount of tocilizumab administered was 4,561 mg (total of 67 administrations) and the minimum amount was 410 mg (total of 10 administrations). After the first treatments, symptoms such as fever and malaise were improved, and anemia, serum levels of CRP, fibrinogen and albumin were reduced. After 3 months, hypergammaglobulinemia and lymphadenopathy were reduced, as were renal function abnormalities in patients with amyloidosis. The study results indicated that patients had achieved marked responses without significant adverse reactions or the development of neutralizing antibodies.

In a Phase 2 study,[19] twenty-eight patients with multicentric Castleman disease were administered 8 mg/kg tocilizumab every

2 weeks for 16 weeks during the initial study phase. Treatment was individualized during an open-label extension period in which the maximum dose was 8 mg/kg and the minimum treatment interval was 1 week. The primary end point was improvement in disease activity, which was assessed by biochemical markers including CRP, hemoglobin and serum albumin. General fatigue was also measured using a visual analog scale. Within 16 weeks, improvement was observed in lymphadenopathy and inflammatory parameters. CRP, immunoglobulin G, and serum amyloid A protein levels decreased; decreases were significant compared to baseline and were maintained through week 60. Hemoglobin, serum albumin and total cholesterol levels increased; increases were significant compared to baseline and were maintained through week 60. Significant improvement in fatigue compared to baseline was observed and the treatment was well tolerated.

Crohn Disease

A pilot study in which 36 patients with active CD were treated with tocilizumab suggested a benefit.[20] Patients were administered placebo or IV tocilizumab at either 8 mg/kg every 2 weeks or 8 mg/kg doses every 4 weeks for 12 weeks. Patients with CD activity index greater than 150 and with abnormal CRP levels were enrolled. IL-6 augments production of the acute-phase reactant CRP, which might serve as an appropriate marker for individuals likely to respond to IL-6 blockade.[21] A total of 80% (8/10) of patient who received 8 mg/kg every 2 weeks showed a clinical response, defined as a reduction of CD activity index more than 70, compared to 31% (4/13) of the placebo group. The treatment was generally well-tolerated. However, only two patients receiving tocilizumab achieved remission.

Future Prospects

Tocilizumab represents a major advance as an alternative strategy to anti-TNF therapy for the treatment of RA. Three marketed anti-TNF therapeutic proteins, infliximab, adalimumab and etanercept, have a combined global market share of $6.7 billion (as of 2006),[22] and another anti-TNF mAb, golimumab, was approved in the US in April 2009. These facts indicate the market potential for biologic RA therapeutics, but also suggest that the market is competitive.

Tocilizumab has strong therapeutic potential for the treatment of RA as demonstrated by Phase 3 study results. One of the biggest advantages from a clinical and economic standpoint is its strong showing as a monotherapy. However, head-to-head comparisons of anti-IL-6 monotherapy, TNF antagonists and combinations of these would help to further define the effectiveness of the molecule. The product could have strong global sales, especially if tocilizumab shows greater effects in combination with TNF antagonists.

The delay in the approval of tocilizumab by the FDA is already having an impact on revenue expected to be generated by the molecule. This delay could also potentially be crucial because second-generation IL-6 inhibitors are currently in clinical trials.[6] From a medical perspective, a potential impediment to the capture of a large market share could be the safety profile of the molecule. Clinical trials have indicated changes in lipid levels and liver abnormalities as the molecule targets the IL-6 receptor found on hepatocytes.[3] One strategy to reduce these side-effects would be to produce human mAbs targeting IL-6 and not its receptor, a strategy currently being explored by GlaxoSmithKline.[6] Despite these potential problems, tocilizumab is expected to be a blockbuster with some analysts predicting that it would net $800 million to $4 billion in revenue.[6]

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