

Efficacy of tocilizumab, a humanized anti-IL-6 receptor antibody, in rheumatoid arthritis

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Evaluation of: Smolen JS, Beaulieu A, Rubbert-Roth A et al.; OPTION Investigators: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet* 371, 987–997 (2008). Evidence accumulated suggests a major role of for IL-6 in the pathogenesis of rheumatoid arthritis (RA). Several clinical trials have demonstrated that IL-6 signaling blockade with an anti-IL-6 receptor antibody (tocilizumab) is clinically effective in treating patients with RA. In this study, Smolen *et al.* report the results of a randomized, double-blind, controlled study that assessed the efficacy of tocilizumab in combination with methotrexate. Active RA patients who were refractory to methotrexate treatment were treated with 8 or 4 mg/kg of tocilizumab, or placebo, intravenously every 4 weeks in combination with methotrexate. At 24 weeks, a 20% improvement of signs and symptoms of RA according to the American College of Rheumatology criteria (ACR20 response) was observed in more patients receiving tocilizumab. This study confirmed the results of the previous investigations, concluding that tocilizumab could be an effective therapeutic approach in patients with moderate to severe active RA.

Smolen *et al.* report the results of the double-blind, placebo-controlled, randomized Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders (OPTION), which assessed the efficacy of a humanized anti-IL-6 receptor antibody (tocilizumab) in the treatment of patients with rheumatoid arthritis (RA) [1]. RA is a chronic and progressive autoimmune inflammatory disease that is associated with joint damage of the hands and feet. Although the etiology of RA is not fully understood, it is believed that inflammatory cells, such as macrophages and lymphocytes, infiltrating into synovium cause proliferation of synovial cells, joint swelling, stiffness and pain. In a proportion of patients, this finally results in irreversible destruction of cartilage and bone in the joints, which leads to disability. RA is a systemic disease with symptoms including fever, fatigue, anemia, anorexia, osteoporosis, weight loss and muscle weakness. In the adult population, 0.3–1.0% suffer from RA worldwide. A total of 40% of patients are unable to work 5 years postdiagnosis, rising to over 50% at 10 years postdiagnosis. Life expectancy is reduced by up to 10 years. Therapy for RA typically escalates from the use of disease-modifying antirheumatic drugs (DMARDs) to biological agents [2]. Approximately 30–40% of patients do not achieve adequate disease control with

currently available therapies. In recent years, biological therapy has focused on the use of agents directed against TNF- α , a proinflammatory cytokine associated with disease pathogenesis. However, in up to 50% of patients, TNF blockers fail to improve disease status significantly [3]. Hence, the social impact of RA as an unmet medical need is high. It is clear that new therapies are required to arrest the RA disease process.

Evidence has recently accumulated that the cytokine IL-6 is involved in RA pathogenesis [4]. Tocilizumab is a humanized monoclonal antibody that targets the IL-6 signaling pathway. The mouse monoclonal antibody, which binds to the human IL-6 receptor, neutralizing IL-6 function, was humanized by means of complementarity-determining region grafting technology [5].

Multicenter, double-blind, randomized, placebo-controlled Phase II trials conducted in both Japan [6] and Europe [7] demonstrated that tocilizumab is effective in the treatment of patients with active RA who had an inadequate response to DMARDs/methotrexate therapy, in monotherapy or combination therapy with methotrexate.

Based on the results, including two pivotal Japanese Phase III studies [8,9], tocilizumab was approved in Japan for patients with RA in April

Keywords: ACR score, anemia, chronic inflammation, fatigue, humanized anti-IL-6 receptor antibody, IL-6, rheumatoid arthritis, tocilizumab

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2008. In addition, the biologics license application was submitted to the US FDA in November 2007 to reduce the signs and symptoms in adults with moderate to severe RA, and was also submitted to the European Medicines Agency in December 2007.

Results & significance of the findings

Results of this multinational Phase III study (the OPTION study) have confirmed the previously reported clinical efficacy and safety of tocilizumab in the treatment of RA. In this double-blind, randomized, placebo-controlled, parallel-group Phase III study, 623 patients with moderate-to-severe active RA, despite long-term treatment with methotrexate, were randomly assigned to receive tocilizumab 8 mg/kg (n = 205), tocilizumab 4 mg/kg (n = 214) or placebo (n = 204) intravenously every 4 weeks, with methotrexate at stable pre-study doses (10–25 mg/week). At week 24, a significantly higher proportion of patients receiving tocilizumab with methotrexate achieved a 20% improvement in signs and symptoms of RA according to the American College of Rheumatology criteria (ACR20 response) when compared with the placebo plus methotrexate group (8 mg/kg: 120 [59%] patients; 4 mg/kg: 102 [48%]; placebo: 54 [26%]; $p < 0.0001$). In addition, significantly more patients treated with 8 mg/kg tocilizumab achieved ACR50 and ACR70 responses compared with controls ($p < 0.0001$). By week 24, patients treated with either dose of tocilizumab also achieved significant reductions from baseline in the Disease Activity Score (DAS)28 and improved European League Against Rheumatism responses compared with placebo. DAS28 remission (< 2.6) at 24 weeks was seen in significantly more patients in the 8 mg/kg tocilizumab group than in the placebo group (27.5 vs 0.8%). A clinically meaningful improvement in health-related quality of life was observed: health assessment questionnaire disability index scores, both physical and mental components of the medical outcomes short-form 36-item survey, and the functional assessment of Chronic Illness Therapy Fatigue Scale all improved in the tocilizumab groups.

It was found that a greater number of patients receiving tocilizumab plus methotrexate, when compared with those receiving methotrexate alone, had at least one adverse event (143 [69%] in the 8 mg/kg group; 151 [71%] in the 4 mg/kg group; 129 [63%] in the placebo group). The most common serious adverse events were

serious infections, reported by six patients in the 8 mg/kg group, three in the 4 mg/kg group and two in the placebo group. The authors also found that tocilizumab did not cause reactivation of *Mycobacterium tuberculosis* infection.

The authors concluded that tocilizumab could be an effective therapeutic approach in patients with moderate to severe active RA.

Reviewer's perspective

A wide variety of activities of IL-6 reflect various signs and symptoms in RA patients [4]. For example, IL-6 induces autoantibodies through B-cell activation, and also acts on naive T cells to induce Th17 cells that play major roles in RA pathogenesis [10]. IL-6 also induces the synthesis of VEGF [11] and RANK ligand [12] in synovial cells, which results in the development of synovitis with neovascularization, and finally leads to bone destruction via osteoclast formation [13]. Moreover, since IL-6 acts on hepatocytes to induce an acute phase reaction, serum levels of C-reactive protein (CRP) and serum amyloid A (SAA) increase [14]. It also enhances synthesis of hepcidin (an iron-regulatory peptide secreted by liver cells) [15], resulting in anemia of chronic inflammation. Hypoalbuminemia can be explained by the inhibitory effect of IL-6 on albumin synthesis in the liver.

As demonstrated in this paper, all the above-mentioned clinical abnormalities have improved in the patients treated with tocilizumab. These results clearly indicate the benefits of using tocilizumab to block IL-6 signaling in the treatment of RA.

It should be emphasized that tocilizumab treatment almost completely normalized CRP and SAA levels. This may contribute to the improvement in secondary amyloidosis [16] that is seen in 5% of RA patients in Europe and difficult-to-treat patients, and the prevention of the development of cardiovascular diseases in which high CRP is involved [17].

Importantly, this study clearly demonstrated that tocilizumab treatment benefited patients' quality of life, partly resulting from improvement of anemia and hypoalbuminemia.

However, as described by the authors themselves, there are several limitations to the present work. First, a 6-month trial time is not long enough to judge persistence of clinical and functional improvement; a long-term follow-up study will be needed. Second, prevention of structural damage was not assessed in this study.

Although the Study of Active Controlled Monotherapy for Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI) trial [9] carried out in Japan suggested that tocilizumab monotherapy delayed and inhibited radiographic progression of joint destruction, this study is an open-label trial and the combination of tocilizumab with methotrexate was not assessed. Third, this trial does not provide information on the long-term safety.

Very recently, it has been reported that IL-6 signaling blockade with anti-IL-6 receptor antibodies inhibited the development of experimental allergic encephalomyelitis as well as experimental arthritis in mice. It is thought that the inhibition may be attributable to prevention of Th17 cell development [18,19]. Although results obtained in animal studies should be carefully considered, tocilizumab is possibly more than just an anti-inflammatory agent and could affect the underlying etiology of RA. In fact, long-term treatment has demonstrated that serum IL-6 levels gradually decreased, becoming undetectable in some patients despite the fact that tocilizumab is not known to directly inhibit IL-6 synthesis [20]. It should also be pointed out that IL-6 itself does not have the ability to promote acute inflammation, and IL-6 transgenic mice do not develop arthritis, while it is the most important marker of inflammation. This may suggest that IL-6 does not play a role in the efferent arc of immune-mediated inflammation.

Tocilizumab is safe and generally well tolerated, with similar frequencies and types of adverse events as seen with conventional DMARD treatment. The most frequent adverse events reported included upper respiratory tract infections, headache, nasopharyngitis and hypertension. Antibodies to tocilizumab have been detected in only 3–5% of the treated patients without concomitant use of immunosuppressants, and did not lead to infusion reactions in the vast majority of patients.

All clinical studies, including this study, clearly demonstrate that targeting the IL-6 receptor with tocilizumab should therefore be seen as an attractive and innovative therapeutic option for RA. The scope of involvement of IL-6 in the pathogenesis and progression of the disease is highlighted by the magnitude of efficacy consistently achieved in clinical trials. Moreover, an international study demonstrated efficacy in tocilizumab-treated patients refractory to TNF blockers [21].

Financial & competing interests disclosure

Yoshiyuki Ohsugi is an employee of Chugai Pharmaceutical Co. Ltd., developers of tocilizumab. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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