Clinical Trial Commentary
Future Rheumatology

The OPTION trial: inhibition of the interleukin-6 receptor with tocilizumab in patients with rheumatoid arthritis

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Rheumatoid arthritis (RA) is a disease that patients may suffer for decades. RA is a complex syndrome with an increasing number of cell types, cellular mediators and signaling pathways implicated in the inflammatory networks of the disease. Interleukin (IL)-6 is a proinflammatory cytokine. Thus, targeting IL-6 has a biological congruence as a therapeutic option in RA patients. Tocilizumab is a humanized monoclonal antibody that binds to the IL-6 receptor. A study to assess the effect of tocilizumab in 622 patients with moderate-to-severe active RA (OPTION) was a Phase III, three-arm, randomized, double-blind, placebo-controlled study. Efficacy was assessed using standard composite criteria (ACR, EULAR) at 24 weeks. Safety was assessed at regular intervals during the study. A 70% improvement according to the ACR (ACR70) was achieved in more patients treated with tocilizumab than with placebo. Higher responses were seen in the tocilizumab high-dose group than in the tocilizumab low-dose group. The most common adverse events were infections. Blocking IL-6 is a novel therapeutic approach that could be effective in moderate-to-severe active RA patients. The long-term efficacy and safety profile of tocilizumab remains to be determined.

Rheumatoid arthritis (RA) is a disease that patients may suffer for 30 or more years [1], with a multidimensional impact ranging from pain and stiffness and the development of comorbid conditions such as cardiovascular diseases or cancer, to family distress and high societal costs [2,3]. For example, although some patients may not have progressive disease, eight out of ten will be partially or completely disabled after just 12 years of having the disease [4]; in other words, many patients may be bedridden or in a wheelchair for the last 15 to 35 years of their lives. Although these figures may change with the new therapeutic armamentarium, including biologic agents, other poor outcome determinants must be addressed first to make it happen [5,6].

The outcome predictors in RA are separated into three domains: individual, such as genes and gender; contextual, such as formal education and social network; and behavioral, such as helplessness and therapeutic adherence. However, the essential mechanism to produce a multidimensional impact is the disease itself, for example, the inflammatory process.

Rheumatoid arthritis is a complex autoimmune syndrome with an increasing number of cell types, cellular mediators and signaling pathways implicated in the inflammatory networks of the disease [7,8], such as CD4 T cells, B cells, CD8 T cells, dendritic cells and macrophages. These cells produce different cytokines including TNF-α, IL-1β, IL-6, leukotriene-α and leukotriene-β; chemokines, including CXCL13 and CCL21; and survival factors, such as APRIL and BAFF. All of these promote influx, expansion and activation of cells in the synovium, leading to the immunoinflammatory and destructive response of RA. However, the participation of these cells and mediators are not equal in all patients. This is one of the main reasons why we cannot assure the patient that even the best biological agent or any other DMARD that is available today is going to work for them. For example, only a small proportion of patients achieve 70% improvement according to the ACR (ACR70) with the use of TNF blockers. Moreover, the frequency of patients who do not achieve even the weakest response (20% improvement) with TNF blockers varies from 28 to 48% [8].

Considering the multidimensionality of the disease, the diversity and variability of its mechanisms of inflammation, and the limited clinical response produced by the available pharmacologic armamentarium, including TNF agents, seeking novel therapies is warranted.

Keywords
interleukin-6 ■ interleukin-6 receptor inhibition ■ OPTION study ■ rheumatoid arthritis ■ tocilizumab

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Introduction to the trial

The OPTION study, which has been recently published, was carried out to assess the therapeutic effect of blocking IL-6 by inhibition of the IL-6 receptor with a novel agent named tocilizumab (developed by F Hoffmann-La Roche, Basel, Switzerland and Chugai Pharmaceutical, Tokyo, Japan) in patients with RA [9].

Background & rationale

Interleukin-6 is a proinflammatory cytokine that can be induced by both TNF and IL-1. IL-6 may have various important activities in the pathogenesis of RA, including induction of antibody production by B cells, activation of T cells, macrophages and osteoclasts. It is also a major activator of the hepatic acute-phase response. The effects of IL-6 are mediated by binding to the IL-6 receptor (CD126, IL6Rα chain), which is expressed on cell surfaces and as a circulating soluble form. Thus, targeting IL-6 has a biological congruence as a therapeutic option in RA patients.

Tocilizumab is a humanized monoclonal antibody that binds to both forms of the IL-6 receptor and has shown clinical efficacy in an early-phase study conducted in Japanese patients. On this basis, it was decided that the OPTION randomized controlled trial should be conducted as a pivotal study.

Design

OPTION was a Phase III, three-arm, randomized, double-blind, placebo-controlled, parallel group study; it complied with the principles of Good Clinical Practice and was registered at regulatory agencies.

Patients were recruited in 73 centers from 17 countries. All participants had RA diagnosed according to ACR criteria, with a disease duration of at least 6 months, and had an inadequate response to methotrexate at a stable dose of 10 to 25 mg/week; all other concomitant DMARDs were discontinued before the start of the study. Patients were not included if they had functional class IV RA, other autoimmune diseases, infections including TB, hepatitis B and C, active liver disease or previous unsuccessful treatment with an anti-TNF agent, among others. Randomization was stratified by site and carried out centrally with an interactive voice response system.

The primary efficacy end point was the proportion of patients with an ACR20 response at 24 weeks. The ACR criteria is a composite index that includes seven different disease activity measurements:

- Tender joint count
- Swollen joint count
- Patient's assessment of pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Patient's assessment of physical function
- Acute-phase reactant value

The ACR20 means a 20% or greater improvement in swollen joint count, plus a 20% or greater improvement in tender joint count, plus a 20% or greater improvement in at least three of the following measures:

- Patient's assessment of pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Patient's assessment of physical function and acute-phase reactant value.

This study also included several secondary efficacy end points at 24 weeks, such as ACR50 (50% improvement in the ACR criteria), ACR70 response, disease activity score using 28 joint counts (DAS28), the proportion of patients in DAS28-remission (DAS28 <2.6), and the individual disease activity scales that compose the ACR criteria (e.g., Health Assessment Questionnaire–Disability Index), among others. The DAS28 is expressed as a continuous variable. The EULAR response criteria classify good, moderate and nonresponders based on DAS28 changes from baseline. A cut-off level of the DAS28 of less than 2.6 (DAS28 remission) corresponds with being in remission for RA disease activity.

Patients were scheduled for routine clinic visits at weeks 2, 4, 8, 12, 16 and 24 for efficacy-related assessments. A dual-assessor approach for efficacy and safety assessments was used to maintain the double-blind status. Joint counts were carried out by trained assessors blinded to patient data. A physician blinded to patient treatment made all treatment decisions on the basis of the patient's clinical response and safety data. Safety parameters were assessed at regular intervals at ten different times through clinical interviews and diverse laboratory tests.

Enrolled patients were randomly assigned to receive placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg intravenously at baseline and thereafter every 4 weeks for 24 weeks, in combination with weekly administration of their stable dose of methotrexate, folic acid and any other allowed

concomitant drugs (e.g., NSAIDs). Patients who had not achieved at least 20% improvement in both swollen joint count and tender joint count by week 16 were eligible for rescue therapy with tocilizumab 8 mg/kg. Patients completing the 6-month trial were allowed to transfer to an open-label extension trial for assessment for long-term safety and efficacy durability.

Data analysis

The sample size was calculated to provide 90% power to detect a difference between tocilizumab and placebo, assuming ACR20 responses of 60% with the study drug versus 40% with placebo. The primary efficacy analysis was carried out on the intention-to-treat population (ITT) (i.e., all patients randomized who received at least one infusion of study drug). Patients who withdrew before week 24, patients who received rescue therapy and patients whose week 24 categorical end points could not be determined due to insufficient data were deemed to be nonresponders in the analysis. The safety population included all randomized patients who received at least one infusion of study medication and who had at least one assessment of safety after randomization.

Results

Of the 812 screened patients, 622 (76.6%) patients met the selection criteria and were included in the ITT population. Baseline patient demographics and clinical characteristics were similar in all three groups: the mean age was around 50 years, most were females and the mean disease duration was 7.5 years; rheumatoid factor was positive in approximately 75%, the DAS28 score was 6.8 ± 0.9, and the mean swollen joint count was around 20 ± 11.

More patients in the 4 mg/kg group than in the 8 mg/kg group or the placebo group withdrew from the study prematurely. Major reasons for withdrawal were adverse events (14 patients in the 4 mg/kg group, 12 in the 8 mg/kg group, and six in the placebo group), insufficient response (two patients in the 4 mg/kg group, none in the 8 mg/kg group, and three in the placebo group), and refusal of treatment (six patients in the 4 mg/kg group, one in the 8 mg/kg group, and two in the placebo group). More patients in the placebo group than in the 4 mg/kg group or than the 8 mg/kg group switched to rescue therapy (33, 14 and 9%, respectively).

By week 24, significant differences were found in the efficacy end point among the three groups. More patients receiving tocilizumab had an ACR20 response than did those receiving placebo (48% in the 4 mg group, 59% in the 8 mg group and 26% in the placebo group). The ACR70 response was also achieved in a greater proportion of patients receiving tocilizumab than in those receiving placebo (12% in the 4 mg group, 22% in the 8 mg group and 2% in the placebo group). Numerical differences between the placebo and tocilizumab 8 mg/kg group were observed at week 2 for ACR20, at week 4 for ACR50 and at week 8 for ACR70.

The same trends occurred with the proportion of patients in remission as per EULAR definition (DAS28 <2.6; 12% in the 4 mg group, 27% in the 8 mg group and 0.8% in the placebo group). No response as per EULAR definition was observed in 38% of patients in the 4 mg group, 20% in the 8 mg group and in 65% in the placebo group.

By week 24, significantly better responses in all core set variables, whether physician-, patient- or laboratory-derived, were seen with both doses of tocilizumab than with placebo. For example, mean C-reactive protein concentrations normalized by week 2 of treatment with tocilizumab 8 mg/kg and remained below the upper limit of normal until the end of the study; erythrocyte sedimentation rate showed the same trend. Mean hemoglobin concentrations increased from baseline by 6–7 g/l by 4 weeks in both tocilizumab groups, but not in the placebo group, and continued to increase until week 24.

Safety & tolerability

More patients receiving tocilizumab reported at least one adverse event than did those receiving placebo (71% in the 4 mg group, 69% in the 8 mg group and 63% in the placebo group), and adverse events deemed to be related to study treatment were also more frequent in the tocilizumab groups than in the placebo group (43% in the 4 mg group, 47% in the 8 mg group and 30% in the placebo group). Of the patients in each group, 6% had serious adverse events, and 11 of the 41 serious adverse events led to discontinuation of treatment. No cases of TB occurred during the study period. For example, the rate of all infections was 98.7 per 100 patient-years of treatment in the 4 mg/kg group, 101.9 per 100 patient-years in the 8 mg/kg group, and 96.1 per 100 patient-years in the placebo group. Most of the abnormal laboratory results reported as adverse events were transient increases in the concentrations of hepatic aminotransferase, increases in lipid concentrations, or transient decrease in absolute neutrophil counts. However, mean plasma concentrations of total cholesterol, high-density lipoprotein

cholesterol and low-density lipoprotein cholesterol were increased from baseline in the tocilizumab groups at the first scheduled assessment at week 6; such levels were unchanged in the placebo groups. Plasma cholesterol levels remained raised at weeks 14 and 24 in the two tocilizumab groups, and increases to more than 6.2 mmol/l (an indication for intervention) at the last observation was noted more often in the tocilizumab groups than in the placebo groups (26% of patients in the 4 mg group, 21% in the 8 mg group and 3% in the placebo group). Increases in the ratio of total to high-density lipoprotein cholesterol of more than 30% above baseline were recorded in 8% of the patients in the 4 mg group, 17% in the 8 mg group and 5% in the placebo group. Other adverse events occurred with comparable frequency in all groups. Infusions were generally well-tolerated, with minor incidences of nausea, rash or hypertension occurring during or within 24 h of infusion.

Anti-tocilizumab antibodies were detected in five patients: one in the 4 mg/kg group and four in the 8 mg/kg group. Two hypersensitivity reactions leading to withdrawal were recorded, one in each tocilizumab group. Readers are invited to review the original article for complete safety data.

Conclusion

The OPTION study provides evidence that inhibition of IL-6-mediated proinflammatory effects significantly and rapidly improves the signs and symptoms of RA. Tocilizumab produced a marked improvement from baseline in all efficacy end points, including ACR core set variables and EULAR definition. The arithmetic differences between study drug and placebo (absolute benefit) to achieve ACR70 was 20%, to achieve EULAR good response was 35% and to achieve DAS28-remission was 26% for the tocilizumab 8 mg/kg group when compared with placebo. The number needed to treat with tocilizumab 8 mg/kg to attain an ACR70 response is five, for DAS28-remission is four and for EULAR good response is three.

So far, with the data presented in the OPTION study, the performance of tocilizumab in RA patients is encouraging. However, as is acknowledged in this study, there are limitations inherent to study design and duration. The 6-month period of the intervention is sufficient to assess short-term efficacy, but not persistence of the clinical improvement over time; the impact of tocilizumab treatment on structural damage was not assessed, and safety data is only available for this period. However, data on these issues are rapidly emerging as the results from other studies are available.

Diverse abstracts from ongoing studies were presented during the 2008 EULAR meeting. These results suggest that tocilizumab has a very good long-term (5 years) efficacy and safety profile. However, we have to wait until these results are published in peer-reviewed journals for a deep analysis.

Meanwhile, the Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor (SAMURAI) study showed that the effect of monotherapy with tocilizumab in preventing joint damage was greater than with conventional DMARDs in Japanese RA patients [10], and after 3 years of follow-up, the mean erosion score did not increase at all in the second and third year of tocilizumab treatment [11].

Future perspective

The OPTION findings have potentially important implications for the management of patients with RA. This study raises the possibility that blocking IL-6 by inhibition of the IL-6 receptor could be an effective therapeutic approach in patients who had an inadequate response to methotrexate. If the emerging data from ongoing studies confirms the long-term efficacy and a good safety profile, tocilizumab will represent a true option in the treatment of patients with RA.

We hypothesized that tocilizumab may be particularly useful in RA patients where IL-6 is the main mechanism of inflammation, for example, RA patients with anemia [12]. Tocilizumab may also be combined with other biologics that target different pathways in RA patients, for example, RA with partial response to anti-TNF agents, or it may be used as an 'induction' therapy.

However, the main challenge in the future of this new drug, as well as with the others in the therapeutic armamentarium, is community effectiveness. Efficacy is mainly based on the pharmacological effects of a therapy, but effectiveness takes into account many other aspects, such as individual patient characteristics, health system features, costs and social influences [5]. The long delays in referrals from general practitioners to rheumatologists, the projected deficit of rheumatologists relative to demand in several countries [13], the use of alternative therapies to 'cure' RA, the low therapeutic adherence, and poor positioning of rheumatic diseases and rheumatologists among patients will limit the community effectiveness of any drug [14].

Dealing with these complex problems in a 'consortium' of pharmaceutical industries, rheumatologists, policy makers and patients would improve the therapeutic effectiveness in RA patients in the community.

Executive summary

Background

- Rheumatoid arthritis (RA) is a complex syndrome with an increasing number of cell types, cellular mediators and signaling pathways implicated in the inflammatory networks of the disease.
- Only a small proportion of patients achieve clinically significant improvement with commercially available drugs, including anti-TNF agents.
- Interleukin (IL)-6 is a proinflammatory cytokine. Thus, targeting IL-6 has a biological congruence as a therapeutic option in RA patients. Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptor.

Methods

- A study to assess the effect of tocilizumab in 622 patients with moderate-to-severe active rheumatoid arthritis (OPTION) was a Phase III, three-arm, randomized, double-blind, placebo-controlled study.
- Efficacy was assessed using standard composite criteria (ACR, EULAR) at 24 weeks. Safety was assessed at regular intervals during the study.

Results

- ACR70 was achieved in more patients treated with tocilizumab than with placebo. Higher responses were seen in the tocilizumab high-dose group than in the tocilizumab low-dose group.
- The most common adverse events were infections.
- One main concern is the clinical significance of increased cholesterol levels in tocilizumab-treated patients.

Significance

- Blocking IL-6 is a novel therapeutic approach that could be effective in moderate-to-severe active RA patients.
- The long-term efficacy and safety profile of tocilizumab remains to be determined.

Financial & competing interests disclosure

Cesar Ramos-Remus participated in the OPTION clinical trial and is coauthor of the published results. Rodolfo Muriel-Vizcaino has no conflict of interest to disclose. The authors have 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.

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