

Tocilizumab for the treatment of rheumatoid arthritis

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Practice Points

- IL-6 is a cytokine with a very important role in the pathogenesis of rheumatoid arthritis (RA).
- Tocilizumab (TCZ) is a biologic agent directed against the IL-6 receptor.
- TCZ is indicated in patients with moderate-to-severe RA that have an inadequate response/intolerance to TNF- α agents or disease-modifying antirheumatic drugs.
- Although TCZ is indicated in association with methotrexate, it has also been demonstrated to be effective as monotherapy.
- The highest efficacy of TCZ is reached at a dosage of 8 mg/kg every 4 weeks, although a lower dose of 4 mg/kg every 4 weeks can also be effective.
- RA patients treated with TCZ experience a rapid clinical and analytical response as well as an important reduction in structural damage; benefits that are sustained over time and seen even in RA patients with previous fails to other biologic agents.
- The efficacy of TCZ in RA is similar to that seen with other biologic agents and in some situations is even superior, such as when it is used as monotherapy.
- TCZ has a relatively good safety profile, similar to that observed with other biologic agents.

SUMMARY Tocilizumab (TCZ) is a humanized monoclonal antibody against the IL-6 receptor, approved in Japan, Europe and the USA for the treatment of severe rheumatoid arthritis. Several Phase III trials have shown a clinical efficacy of TCZ, such as in treatment of rheumatoid arthritis patients with no previous methotrexate failures both in combination with methotrexate and in monotherapy (the AMBITION trial); and rheumatoid arthritis patients who are resistant to disease-modifying antirheumatic drugs (the TOWARD, OPTION and LITHE trials) and anti-TNF- α agents (the RADIATE trial). Some of these Phase III trials have also

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demonstrated the radiologic efficacy of TCZ (the LITHE and SAMURAI trials) as well as its good safety profile, similar to other biologic agents. The effectiveness and safety of TCZ in a setting closer to clinical practice than that typically described in Phase III studies have recently been revealed by some Phase IIIb studies (the TAMARA, ROSE, ACT-SURE, ACT-RAY and ACT STAR studies) and the nationwide Danish registry.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint pain and swelling, as well as stiffness and fatigue, resulting in progressive joint damage with loss of function and increased morbidity and mortality [1]. Treatment comprises disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), which improve inflammatory processes and can slow disease progression [2,3]. Biologic agents such as TNF- α inhibitors are frequently used in patients with inadequate response or intolerance to traditional DMARDs. However, in spite of these agents, there are patients who do not achieve an optimal control of disease activity [4–11]. A novel target for RA treatment is IL-6, a pleiotropic proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes and fibroblasts, with an important role in the pathogenesis of RA [12].

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the receptors of IL-6, both soluble and membrane bound. It was indicated in Japan for RA, Castleman's disease and juvenile idiopathic arthritis. In Europe it has been approved, in combination with MTX, for the treatment of adult patients with moderate-to-severe RA who responded inadequately or were intolerant to previous treatment with one or more DMARD or TNF- α antagonist. However, TCZ can be given as monotherapy in cases of intolerance to MTX or when continuation with MTX is contraindicated.

This article reviews the most relevant aspects related to the pharmacology, clinical efficacy and safety profile of TCZ, according to data obtained not only from the Phase III trial program but also from a setting close to real-life medical care.

Pharmacology

■ Pharmacodynamics

The IL-6 receptor (IL-6R) complex is composed of IL-6R (either soluble IL-6R or membrane-bound IL-6R) and a signal-transducing

molecule called gp130. When IL-6 binds any of both forms of IL-6R, the complex IL-6–IL-6R associates with gp130, which transduces the IL-6 signal into the cell [13]. TCZ is a molecule composed of four polypeptide chains, two heavy chains consisting of 448 amino acids and two light chains of 214 amino acids [101]. TCZ binds selectively and competitively to soluble IL-6R and membrane-bound IL-6R, preventing dimerization of gp130 molecules on the cell membrane, blocking IL-6 signal transmission into cells and, therefore, inhibiting the biologic activity of IL-6 [14].

IL-6 is implicated in multiple immunologic processes relevant to RA, such as the differentiation of B cells into immunoglobulin-secreting plasma cells or the activation of T cells [15,16]. It is involved in Th17 cell polarization and in the production of IL-17, a cytokine that potentially plays an important role in RA [12]. It also induces the proliferation of synovial fibroblasts [17] and osteoclast differentiation, which contribute to joint destruction and osteoporosis [18]. In addition, results from animal models suggest an important role for IL-6 in the induction and maintenance of chronic synovitis [19,20]. IL-6 also contributes to the systemic manifestations of RA, such as the development of anemia by means of the hyperproduction of hepcidin [21] or the decrease in the blood lipid concentrations [22]. IL-6 is also implicated in the mechanisms leading to production of acute-phase proteins [23] and increase in the number of platelets [24].

The Phase II CHARISMA trial, a multicentric double-blind randomized study, encompassed seven therapeutic arms with different doses of TCZ (2, 4 and 8 mg/kg) every 4 weeks with or without MTX, and a placebo group treated only with MTX. TCZ 8 mg/kg, besides obtaining the highest clinical efficacy when combined with MTX, was the only dose capable of decreasing both inflammatory pharmacodynamic markers (erythrocyte sedimentation rate and CRP) and maintaining normal CRP levels [25]. Also, using this

dosage, sustained improvements in markers of bone resorption and cartilage turnover were observed after 24 weeks of treatment [26].

■ Pharmacokinetics

Data from 1793 RA patients treated with TCZ 4 and 8 mg/kg every 4 weeks for 24 weeks were used to determine the pharmacokinetic properties of TCZ [102]. The predicted steady-state area under the curve and the maximum concentration were found to be higher with the dose of TCZ 8 mg/kg than with 4 mg/kg. The elimination half-life of TCZ is concentration dependent, which explains why at steady state it ranged from 11 (4 mg/kg every 4 weeks) to 13 days (8 mg/kg every 4 weeks) [102].

Age, gender and ethnicity did not affect the pharmacokinetic parameters of TCZ. In this RA population a mild renal impairment did not affect the parameters either, although further formal studies are needed to assess the effect of renal and hepatic impairment on the pharmacokinetics of TCZ [102]. TCZ clearance was not affected by concomitant administration of MTX, NSAIDs or corticosteroids [102].

TCZ has been found to normalize the expression of CYP isozymes (e.g., CYP2C19 and CYP3A4), which are frequently reduced in RA [27,102]. Therefore, drugs metabolized by these isozymes (i.e., atorvastatin, calcium channel blockers, warfarin or ciclosporin) should be monitored in case of initiating or discontinuing TCZ, and a dosage adjustment could be required to maintain its therapeutic effect.

Clinical efficacy

Since the clinical development of TCZ for RA in Japan is considerably different (e.g., TCZ is used as monotherapy and the highest recommended dose of MTX is 8 mg/week [28]), this article will mainly focus on the trials developed outside Japan where MTX is usually used at a highest dose of 25 mg/week, also when combined with TCZ. There are seven Phase III trials that show clear efficacy of TCZ in all the possible situations of RA (Table 1): RA with no previous MTX failure (AMBITION [29]), RA refractory to MTX (SATORI [30], OPTION [31] and LITHE [32]) or any DMARDs (TOWARD [33]), and finally RA resistant to anti-TNF- α (RADIATE [34]). Efficacy has generally been proven in combination with DMARDs, usually MTX, but also in monotherapy in Japan

(SAMURAI [35] and SATORI [30]) and outside Japan (AMBITION [29]).

Data obtained in these studies were subsequently confirmed in a setting close to real-life medical care by means of the recently published results of the Danish registry [36], as well as by data obtained from Phase IIIb studies: ROSE (patients with established RA resistant to DMARDs who were randomly assigned to TCZ plus DMARD or placebo) [37], ACT-SURE [38], TAMARA (two open-label studies of TCZ in patients with inadequate response to DMARDs or anti-TNF- α agents in the usual clinical practice) [39]; and the ACT-RAY [40,41] and ACT-STAR trials [42], both of which compared the efficacy of the combined treatment TCZ plus MTX with TCZ alone. The retrospective study REACTION also showed the efficacy of TCZ in clinical practice in Japan [43].

■ Phase III trials

The therapeutic arms of the Phase III trials were restricted to those of greater efficacy. Thus, the treatment group in the TOWARD and AMBITION trials received TCZ 8 mg/kg intravenously (iv.) every 4 weeks, while the RADIATE, OPTION and LITHE studies had a second therapeutic arm using TCZ 4 mg/kg iv. every 4 weeks. All these studies used TCZ in combination with MTX except for the TOWARD and AMBITION trials, which used TCZ associated with any DMARD and as monotherapy, respectively. The control arms received MTX at a stable dose, with the exception of the patients from the TOWARD study, who could be treated with any DMARD.

In general, the primary efficacy end point was the American College of Rheumatology (ACR) 20 response after 24 weeks, which ranged from 70% in the AMBITION trial to 50% in the RADIATE study. The difference between the trials can be explained by their different RA populations. Other secondary efficacy end points were the ACR50 and ACR70 responses, which were equally optimal, being approximately 40 and 20%, respectively, as well as clinical remission (defined as a Disease Activity Score in 28 joints [DAS28] <2.6), which was achieved in approximately 30% of patients after 24 weeks even in those with anti-TNF- α resistant RA (RADIATE) [34].

It is important to remark that the beneficial clinical and analytical effects of TCZ

Table 1. Phase III clinical trials with tocilizumab in rheumatoid arthritis.

Trial	Patients (n)	Design	Objective	Population	Therapeutic group	Comparison group	Duration of trial (months)	Ref.
Phase III: Japan								
SATORI	127	Double blind	Clinical efficacy	Failure to MTX	TCZ	MTX	6	[30]
SAMURAI	306	Open	Clinical and radiologic efficacy	Failure to DMARDs	TCZ	DMARDs	12	[35]
Phase III: outside Japan								
OPTION	623	Double blind	Clinical efficacy	Failure to MTX	TCZ + MTX	MTX	6	[31]
TOWARD	1220	Double blind	Clinical efficacy	Failure to DMARDs	TCZ + DMARDs	DMARDs	6	[33]
RADIATE	499	Double blind	Clinical efficacy	Failure to anti-TNF- α	TCZ + MTX	MTX	6	[34]
AMBITION	673	Double blind	Clinical efficacy	No previous failure to MTX	TCZ	MTX	6	[29]
LITHE	1196	Double blind	Clinical and radiologic efficacy	Failure to MTX	TCZ + MTX	MTX	12	[32]
Phase IIIb: outside Japan								
ACT-RAY	556	Double blind	Clinical and radiologic efficacy	Failure to MTX	TCZ + MTX	TCZ	6	[42]
ACT-STAR	883	Open	Clinical and radiologic efficacy	Failure to biologic and nonbiologic DMARDs	TCZ + MTX, TCZ	-	6	[41]
ACT-SURE	1681	Open, clinical practice	Clinical efficacy	Failure to DMARDs, failure to anti-TNF- α	TCZ + MTX, TCZ	-	6	[38]
ROSE	619	Double blind	Clinical efficacy	Failure to DMARDs	TCZ + DMARDs	DMARDs	6	[37]
TAMARA	286	Open, clinical practice	Clinical efficacy	Failure to DMARDs, failure to anti-TNF- α	TCZ + DMARDs	-	6	[39]

DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; TCZ: Tocilizumab.

occurred very rapidly. Clinical efficacy measured by a moderate European League against Rheumatism Response (EULAR) [31], as well as ACR20 [31] and ACR50 [33] response, was observed as early as week 2 in different Phase III clinical trials. In addition, after 2 weeks of treatment, CRP levels had normalized and the mean hemoglobin levels had significantly increased [29,33,34].

Other common parameters, such as physical function (Health Assessment Questionnaire – Disability Index), health-related quality of life and fatigue (Functional Assessment of Chronic Illness Therapy) were also significantly improved with TCZ after 24 weeks in all the different situations in which RA patients were treated with this drug. Interestingly, clinical improvement occurred early and was sustained throughout TCZ therapy [29–35].

Regarding the efficacy of TCZ over time, there are data available up to 3.5 years from long-term extension studies, which included 3368 patients from the five Phase III trials, except for AMBITION [44]. Patients with inadequate responses to DMARDs (the OPTION, TOWARD and LITHE trials) increased ACR50 and ACR70 responses up to 67 and 46%, respectively, and DAS28 remission up to 62%, after 180 weeks of treatment. RA patients refractory to TNF- α (the RADIATE trial) also experienced a significantly higher clinical response over time (ACR50: 56%; ACR70: 31%; DAS28 remission: 48% at week 144). Similar results were obtained from the AMBITION study after 3 years of treatment [45]. In the long-term extension study, a high number of patients treated with TCZ achieved ACR20, ACR50 and ACR70 responses (83, 66 and 43%, respectively) and DAS28 remission (57%) over time.

OPTION & TOWARD

When assessing the main Phase III trials in more detail, it can be seen that the OPTION [31] and TOWARD [33] studies had a similar design and obtained comparable results. Both trials included patients with long-standing, moderate-to-severe RA resistant to DMARDs (MTX in the OPTION trial and any DMARD in the TOWARD study). Patients from the OPTION trial were randomized to receive every 4 weeks either TCZ 8 mg/kg,

TCZ 4 mg/kg or placebo iv., in combination with MTX (10–25 mg/week). However, the TOWARD trial had only one therapeutic arm, in which patients received TCZ 8 mg/kg iv. associated to any DMARD (not only MTX). In both cases, the ACR20, ACR50 and ACR70 responses after 24 weeks of treatment were approximately 60, 40 and 20%, respectively (Figure 1), and a clinical DAS28 remission was achieved in approximately 30% (Figure 2). These results were significantly superior to placebo (ACR responses approximately 25, 10 and 2%, respectively, in both trials and a DAS28 remission of only 2.9% in the TOWARD trial and less than 1% in the OPTION trial).

Although the ACR20 and ACR50 responses obtained in these trials were similar to those reported with other biologic agents in RA patients resistant to DMARDs, ACR70 response and DAS28 remission rates obtained with TCZ in this setting were superior [46–48].

However, these high rates of remission may be overestimated because of the efficacy of TCZ in reducing acute-phase reactants, which have an important role in DAS28 remission. In fact, using other measures in which acute-phase reactants have a low weight (the Simplified Disease Activity Index) or are not even included (the Clinical Disease Activity Index), the clinical remission obtained with TCZ in patients from the OPTION, LITHE and TOWARD studies decreased to rates similar to those reported with TNF- α inhibitors [49].

AMBITION

The AMBITION trial also obtained interesting results [29]. TCZ 8 mg/kg used as monotherapy for RA patients with no previous failure to MTX disclosed a clinical efficacy clearly superior to MTX. The ACR20, ACR50 and ACR70 responses in both groups were 70 versus 55%, 44 versus 33% and 28 versus 14%, respectively, and DAS28 remission was 33 versus 12.1%, respectively (Figures 1 & 2). This is an important result taking into account that studies such as TEMPO (etanercept) or PREMIER (adalimumab) showed that TNF- α inhibitors were not superior to MTX when used as monotherapy [50,51].

RADIATE

The RADIATE trial included RA patients resistant to anti-TNF- α drugs and also reported

superior ACR responses with TCZ compared with placebo, although these were slightly inferior to those seen in the rest of the Phase III trials (Figure 1). The DAS28 remission was also approximately 30% after 24 weeks, even in those resistant to two or three anti-TNF- α inhibitors (Figure 2). Up to now, DAS28 remission was reported to be achieved in approximately 10% of RA patients refractory to TNF- α inhibitors who were treated with another anti-TNF- α agent or with a different biologic drug (rituximab or abatacept) [52–54]. The authors feel that, as shown in studies in RA patients resistant to DMARDs, the reduction in the levels of acute-phase reactants produced by TCZ when compared with the different biologic therapies could explain its superiority over other biologic agents in achieving DAS28 remission [49].

■ Phase IIIb trials & nationwide registries TAMARA & ROSE

The data discussed above from Phase III clinical trials have been confirmed in additional studies performed in clinical practice. In this regard, the TAMARA trial included 286 moderate-to-severe RA patients resistant to DMARDs or anti-TNF- α drugs who received TCZ 8 mg/kg

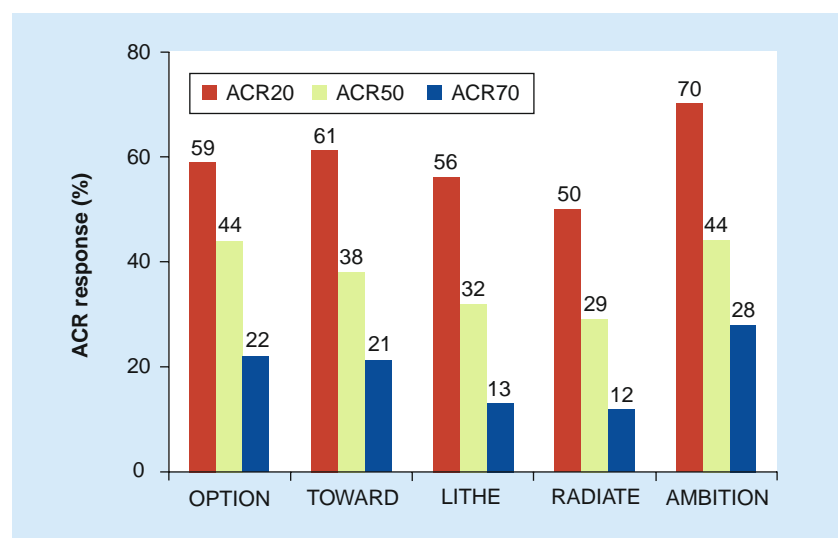


Figure 1. Proportion of patients with American College of Rheumatology responses 20, 50 and 70 in different Phase III studies with tocilizumab in rheumatoid arthritis performed outside of Japan. The results were observed at week 24. The results of the best therapeutic group of each study are shown: tocilizumab at dose of 8 mg/kg intravenously every 4 weeks either plus methotrexate (OPTION, LITHE and RADIATE), plus disease-modifying antirheumatic drugs (TOWARD) or as monotherapy (AMBITION). ACR: American College of Rheumatology.

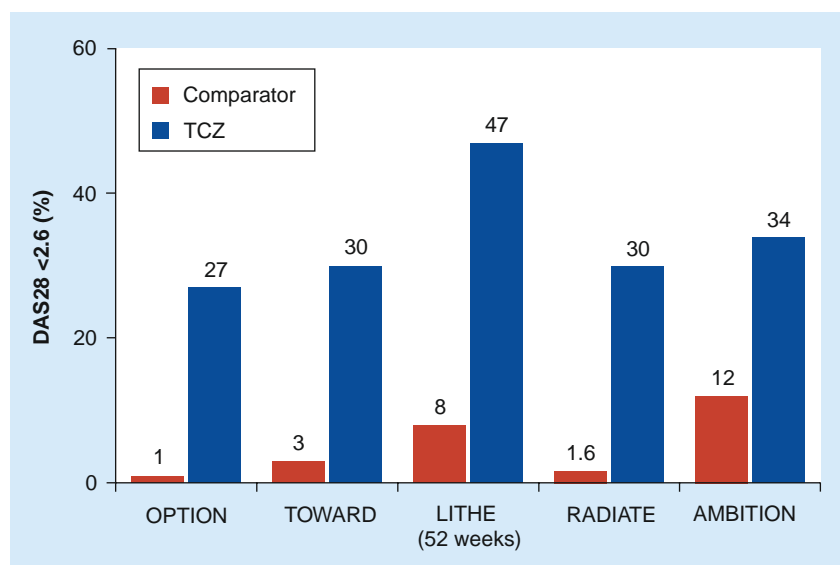


Figure 2. Proportion of patients in clinical remission (disease activity score 28 < 2.6). The results were observed after 24 weeks, except in the LITHE trial, in which results were observed after 1 year. The results of the best therapeutic group for each study are shown: TCZ at dose of 8 mg/kg intravenously every 4 weeks either plus methotrexate (OPTION, LITHE and RADIATE), plus disease-modifying antirheumatic drugs (TOWARD) or as monotherapy (AMBITION). DAS28: Disease activity score 28; TCZ: Tocilizumab.

iv. in combination with DMARDs every 4 weeks during 24 weeks [39]. This study confirmed and even improved the previously mentioned data of clinical efficacy, obtaining ACR20, ACR50 and ACR70 responses of 65, 50.7 and 33.9%, respectively, and a DAS28 remission of 47.6%. Similar results were reported in the ROSE study, a 24-week, randomized, double-blind trial performed with RA patients resistant to DMARDs, in which 30% of patients who received TCZ 8 mg/kg plus a DMARD achieved an ACR50 response [37]. As occurred in the Phase III trials, in participants in the TAMARA and ROSE studies TCZ had very early onset of action. As a result, TCZ-treated RA patients experienced a significant reduction of DAS28 and levels of CRP within 1 week. In addition, the TAMARA trial confirmed other important data regarding the efficacy of TCZ such as the significant improvement experienced in health-related quality of life in patients treated with TCZ, as well as the lower clinical response in RA patients who had previously failed to TNF- α antagonist use compared with TNF- α antagonist-naïve patients [39].

In addition, a *post-hoc* analysis performed with patients from the TAMARA trial also confirmed in clinical practice the influence of

acute-phase reactants in the high rates of DAS28 remission obtained with TCZ [55]. Thus, these rates decreased to the level observed with other biologic agents when remission criteria did not include CRP or erythrocyte sedimentation rate (Clinical Disease Activity Index, Simplified Disease Activity Index and ACR/EULAR criteria). The TAMARA trial not only confirmed the results obtained in the Phase III trial program but also showed new data, such as the comparable clinical response seen in rheumatoid factor-positive and rheumatoid factor-negative RA patients, which had not been reported previously.

REACTION

The efficacy of TCZ in daily clinical practice was also demonstrated in Japan in the retrospective study REACTION [43]. This trial reported a clinical remission of 43.7% in 232 RA patients treated during 52 weeks with TCZ 8 mg/kg iv. every 4 weeks, combined with MTX in 56% of cases. Remarkably, 62% of patients had previously been treated with TNF- α inhibitors.

ACT-RAY, ACT-STAR & ACT-SURE

The results of Phase IIIb trials recently presented during the last rheumatology meetings also show us new important data regarding TCZ [38,41,42]. Thus, the double-blind randomized Phase IIIb trial ACT-RAY concluded that the clinical and radiologic response to TCZ monotherapy at week 24 was not inferior to that observed with TCZ plus MTX in RA patients resistant to MTX [42]. Similarly, TCZ as monotherapy demonstrated an equivalent clinical efficacy to that obtained with the combined treatment TCZ plus DMARDs in RA patients with inadequate responses to DMARDs or TNF- α inhibitors [38,41]. The efficacy of TCZ monotherapy had already been demonstrated in the AMBITION study, although this trial did not include a therapeutic arm group with TCZ plus MTX, which would have allowed the comparison of both regimens, and the RA patients included had not failed to previous MTX or biologic agents [29]. The CHARISMA trial included seven therapeutic arms with RA patients resistant to MTX; of which one received TCZ monotherapy and another TCZ combined with MTX [25]. TCZ plus MTX was demonstrated to be the most effective regimen, as it was the only one to achieve significantly better ACR50 and ACR70

responses than MTX, differences that were not seen with TCZ monotherapy.

Danish registry

Besides Phase IIIb trials, the nationwide registries also provide us with interesting data on the efficacy of TCZ in a setting close to real-life medical care. The results of the Danish registry, including data of 97 RA patients treated with TCZ (of which 93% had previously received TNF- α inhibitors), have recently been published [36]. At week 24, clinical remission was achieved by 39% of patients, and this increased over time up to 58% after 1 year of treatment.

Radiologic efficacy

The radiologic efficacy of TCZ was demonstrated in two Phase III clinical trials, as monotherapy [35] and as combined therapy with MTX [32], and confirmed in clinical practice in the REACTION study [43].

The SAMURAI trial evaluated the radiologic progression (primary efficacy end point) in early (duration <5 years) RA patients from Japan with disease refractory to DMARDs [35]. Patients were randomly assigned to receive TCZ 8 mg/kg in monotherapy or traditional DMARDs. At week 52, patients in the TCZ group showed significantly less radiologic progression both in the total Sharp score modified by van der Heijde (2.3 [TCZ 8 mg/kg] vs 6.1 [placebo]) and in the erosive and joint space narrowing components. In addition, significantly more patients receiving TCZ compared with DMARDs had no radiologic progression after 52 weeks (56 vs 39%; $p < 0.01$). The 3-year extension study confirmed these data and also showed that the structural damage was more effectively suppressed in patients treated with TCZ from the beginning, compared with those who initially received DMARDs and switched to TCZ later [56].

The coprimary end point of the LITHE trial was to assess the radiologic disease progression after 52 weeks in RA patients refractory to MTX who received either TCZ 8 mg/kg, TCZ 4 mg/kg (both combined with MTX) or MTX as monotherapy [32]. There was significantly less radiologic progression in TCZ groups compared with placebo regarding total Genant-modified Sharp score (mean change of 0.29, 0.34 and 1.13, respectively) as well as in its components. The 2-year open-label trial confirmed this radiologic

efficacy over time, reporting that 81% of patients treated with TCZ 8 mg/kg did not experience radiologic progression after 2 years [57].

The Japanese REACTION study also demonstrated the efficacy of TCZ in preventing structural damage in clinical practice, since 62% of RA patients treated with TCZ for 52 weeks (56% in combination with MTX) did not show radiologic progression [43]. A significant decrease of synovitis at week 2 and osteitis at week 12 was detected by the use of MRI in MTX-resistant RA patients treated with TCZ, as described in the Phase IIIb clinical trial ACT-RAY [40].

Adverse events

A good safety profile of TCZ has been demonstrated in all the Phase III trials mentioned and subsequently confirmed in the studies performed in daily clinical practice [37–40]. A recent meta-analysis that included the combined data retrieved from the patients of the randomized controlled trials ratified the good results in terms of safety reported in each individual trial [58]. This study confirmed that the majority of the adverse events (AEs) attributed to TCZ after 24 weeks of treatment were mild or moderate, both in monotherapy and in combination therapy with DMARDs. In fact, compared with controls, the TCZ 8-mg/kg combination therapy group only showed a small increased risk of mild or moderate AEs such as nasopharyngitis, respiratory tract disorder, skin and soft tissue pathology (e.g., rash) or gastrointestinal (GI) side effects (e.g., nausea), but without differences in the rates of serious AEs or deaths. These promising results observed at week 24 were confirmed in open-label extension studies (median 2.4 years of treatment), which included 4009 patients combining the five Phase III trials and one clinical pharmacology study [59]. This study demonstrated that the rate of serious AEs remains stable over time (14.4/100 patient years), with a rate of withdrawal owing to AEs of 5.8/100 patient years, most occurring during the first 6 months. The most relevant AE data are discussed below.

■ Infections

Infections are the most common AEs and serious AEs in TCZ-treated patients [59]. In the randomized controlled trials the rates of infections after 24 weeks were slightly higher in the TCZ 8 mg/kg combined group compared with

controls, although the difference was not significant when the frequency of serious infections was analyzed [58,60]. It seems that the incidence of serious infections remains stable over time, with rates of 4.7/100 patient years in the open-label extension studies mentioned above [59] and 5.7/100 patient years in a 5-year extension Japanese study that used TCZ as monotherapy [61]. These rates are equivalent to those observed in daily clinical practice [37–39]. The most frequent serious infections were pneumonia, gastroenteritis, urinary tract infections and cellulitis, and these were more prevalent in patients with pre-existing pulmonary disease, diabetes, older age and higher BMI, as well as in those treated with steroids or previously treated with a TNF- α inhibitor [59]. The rate of serious infection observed in patients undergoing TCZ therapy is similar to that seen in patients with anti-TNF- α antagonists [62].

Opportunistic infections were reported in 22 patients (0.23/100 patient years) after a median duration of treatment of 2.4 years, but only nine of these were caused by mycobacteria [59]. By contrast, no cases of tuberculosis were reported after 5 years in the STREAM trial [61]. TCZ did not affect the response to influenza vaccination, which was similar to that observed in patients receiving DMARDs [63].

■ Malignancies

The different open-label extension studies did not show an increased incidence of malignancies in patients treated with TCZ. The overall rate of malignancy in the extension studies combining the five Phase III studies performed outside Japan was 1.1/100 patient years [59], which was comparable to the rate of 1.3/100 patient years observed in a cohort of RA patients from the USA [64]. Similarly, the Japanese STREAM trial found a low rate of malignancy (0.7/100 patient years), which was equivalent to that observed in a population of RA patients from Japan [65].

■ Infusion reactions

Infusion reactions (occurring within 24 h of the infusion) were reported in 7% of patients receiving TCZ 8 mg/kg plus DMARDs during 6 months compared with 5% in the placebo plus DMARD group [102]. Most of the reactions were mild and did not require discontinuation of treatment. The most common infusion reactions were nausea, exanthema, hypertension,

headache and pruritus. Severe anaphylactic reactions were reported in eight patients in the extension studies; most of them with the TCZ 4 mg/kg dose and during the first four infusions [59]. Postmarketing data also reported a case of fatal anaphylaxis. In addition, TCZ was associated with a low production of autoantibodies and immunogenicity [66].

■ Neutropenia

Treatment with TCZ was often associated with the development of neutropenia, which was generally mild, Common Toxicity Criteria grade 1 (>1500 cells/mm³) or grade 2 (1000–1500 cells/mm³), transient and not associated with infections. In this regard, Common Toxicity Criteria grade 3 (500–1000 cells/mm³) and 4 (<500 cells/mm³) neutropenia was reported in 4.1 and 0.6% of patients, respectively, leading to treatment discontinuation in most cases [59]. However, TCZ-related neutropenia was not associated with an increased rate of infections [59]. Neutropenia was found to be related to TCZ dose [25]. IL-6 physiologically increases the number of circulating neutrophils and its inhibition via TCZ can lead to the opposite effect [67].

■ Elevation of liver enzymes

Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin have often been reported and constitute the most common AEs leading to the discontinuation of TCZ [59]. However, most of the ALT and AST increases were mild (less than three-times above the upper limit of normal [ULN]), transient, unrelated to bilirubin increases and normalized either spontaneously or following the discontinuation of TCZ therapy [68]. Moreover, no cases of hepatitis or liver dysfunction were seen. The frequency of ALT and AST elevations greater than three-times the ULN occurring at any time in the extension studies was 9.5 and 3.1%, respectively [59]. Elevations of ALT and AST were observed more frequently in the high-dose TCZ group, especially when combined with MTX. Thus, increases in ALT greater than three-times the ULN occurred in 5.7% of patients treated with TCZ 8 mg/kg plus DMARD, compared with 3.7% of patients treated with MTX monotherapy and 1.9% of those treated with TCZ 8 mg/kg monotherapy [59]. It has been demonstrated that IL-6 has

an antiapoptotic physiological action on the liver, leading to its regeneration, but the mechanism of liver enzyme increase mediated by TCZ is still unknown [69].

■ Alteration of the lipid profile & cardiovascular events

Increases in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides as well as ApoA1 and ApoB have been reported in clinical trials [31,59,60,70]. This elevation is observed as early as week 6 [31], with no further elevation over time [59,60]. Elevations of low-density lipoprotein cholesterol from <130 mg/dl at baseline to >130 mg/dl occurred in 33.2% of patients not receiving lipid-lowering agents, compared with 14.2% in the control group [59]. By contrast to reports in dyslipidemia, serum levels of high-density lipoprotein cholesterol are increased in patients receiving TCZ, which contributes to the correction of the atherogenic index (plasma total cholesterol:high-density lipoprotein cholesterol ratio), an important prognostic marker for cardiovascular disease. Lipid-lowering therapy was initiated in 7.8% of patients during long-term TCZ treatment [59], leading to improvement of the lipid profile [71]. Interestingly, TCZ drastically decreased the inflammation markers [29,33,34]. This fact is of major relevance as it is known that inflammation plays a role in the development of subclinical atherosclerosis and cardiovascular events in patients with RA [72,73]. Therefore, the overall cardiovascular effect of both factors (lipid alteration and improvement in inflammatory parameters) remains unclear and somehow contradictory. However, the results of the different trials show that patients who have received TCZ for 2.4 years do not have an increased rate of stroke and myocardial infarction compared with those treated with placebo, and the rates of cardiovascular events seem to be similar to those observed in epidemiologic studies of RA [59]. In this regard, the 5-year extension study STREAM did not find evidence of an increased risk of cardiovascular disease related to TCZ either [61].

Similar alterations in the lipid profile and in the inflammatory parameters have also been described in RA patients undergoing anti-TNF- α therapy [74–76]. However, an important reduction in the incidence of cardiovascular events has been observed in these patients, in

particular in those who experienced a good therapeutic response following the use of TNF- α antagonists [77,78].

■ GI perforation

Concerns about an increase in lower GI perforations in patients receiving TCZ have been raised. However, a recent review showed that the rate of lower GI perforations observed in patients treated with TCZ (1.9/1000 patient years) is comparable to that observed in those treated with TNF- α inhibitors (1.3/1000 patient years), and lower than that seen with corticosteroids (3.9/1000 patient years) [79].

Place in therapy

■ Patient selection

The management of RA has significantly changed in recent years with the introduction of biologic agents directed against specific therapeutic targets with an important role in the pathogenesis of RA (e.g., TNF- α and IL-1). These drugs have allowed a much more effective control of the disease in cases of inefficacy or intolerance to traditional DMARDs. Usually, TNF- α inhibitors are used as first-line agents in patients refractory to conventional DMARD therapy but, regrettably, they do not control disease activity in all cases and are not free of side effects. When required, the anti-TNF- α agent can be replaced by another anti-TNF- α agent or by a biologic agent with a different target. However, in spite of this, some patients will still have persistently active disease, so other therapeutic options able to achieve an optimal control of RA activity are required. Since 2008, TCZ (an IL-6 inhibitor) has provided a new therapeutic tool to be used in moderate-to-severe RA patients either resistant to DMARDs or TNF- α antagonist agents, or intolerant of them. TCZ obtains a better response combined with MTX, although it can be used as monotherapy. Data discussed in this review indicate that TCZ is a drug that is at least as effective and safe as other biologic agents in patients with RA, and with some specific characteristics that allow us to consider TCZ to be a very good therapeutic option in certain situations. With respect to this, TCZ is the only biologic agent that, used alone, has demonstrated superiority over MTX [31]; therefore, it may be a good option in RA patients that must be treated with a monotherapy (e.g., patients with intolerance

of/contraindication to DMARDs). Owing to the important role of IL-6 in the systemic inflammatory response, TCZ should also be considered in RA patients with high levels of acute-phase reactants and severe anemia. In fact, the TAMARA trial found TCZ to be particularly beneficial in patients with high RA activity measured by DAS28, an index in which acute-phase reactants have an important role [41]. TCZ can also be a good alternative in RA patients resistant to TNF- α inhibitors [36], although its superiority over other biologic agents in achieving DAS28 remission seems to be overestimated because of its efficacy in decreasing levels of acute-phase reactants [49,55]. The subset of rheumatoid factor-negative RA patients with an inadequate response to anti-TNF- α drugs should be considered for receiving TCZ since, unlike other biologic agents used after a TNF- α inhibitor failure, TCZ is not less effective in seronegative RA [41]. Because of the important role of IL-6 in the pathogenesis of the AA amyloidosis, and the efficacy of TCZ in controlling the inflammatory process that causes this complication, TCZ could also be a good option in RA patients diagnosed with secondary amyloidosis [80,81]. TCZ may also be considered in RA patients who are candidates to receive a biologic agent and are diagnosed with latent tuberculosis, always after receiving the correct prophylactic therapy. Although more data are necessary to be able to recommend TCZ in this setting, IL-6, unlike TNF- α , does not have a pivotal role in granulomatous bacterial containment and cases of active tuberculosis with TCZ have been rarely reported [62]. In the authors' clinical experience, TCZ has also been effective in RA patients with refractory psoriasiform lesions induced by TNF- α inhibitors who did not respond to the discontinuation of the drug or to topical treatments. TCZ rapidly controlled both joint manifestations and skin involvement in two patients with this complication.

■ Dosing & administration

According to data mentioned above, TCZ 8 mg/kg every 4 weeks is considered the most effective dosage to achieve an optimal clinical and analytical response. However, TCZ at a dose of 4 mg/kg every 4 weeks has also been demonstrated to be superior to placebo in different scenarios of RA [31,32,34]. In fact, the US FDA recommends a starting dose of 4 mg/kg followed

by an increase to 8 mg/kg based on clinical response. Taking into account the recently communicated results of the Phase IIIb trials mentioned above [43,44,58], more data seem necessary to be certain that combining TCZ with MTX or other DMARDs is actually the best option and to discover what type of RA patients would benefit from this combination (RA with no previous failure to MTX, or resistant to MTX or TNF- α inhibitors).

■ Tolerability & AEs

TCZ is generally well tolerated, with a low rate of withdrawal, similar to that observed in other biologic agents. The majority of AEs are mild-to-moderate and consist mainly of infections (frequently involving the upper respiratory tract), GI side effects or cutaneous rash. However, severe AEs can also occur and physicians should be aware of serious infections (mainly pneumonia, gastroenteritis or urinary tract infections) and opportunistic infections such as tuberculosis or anaphylaxis reactions [59,60].

Laboratory alterations such as neutropenia, elevation of liver enzymes or alterations of the lipid profile are also frequently seen. However, in most cases they are mild and not related to an increase in the rates of infections, hepatitis or cardiovascular events [62]. However, laboratory values should be monitored every 4–8 weeks during treatment and TCZ should be discontinued in cases of ALT or AST greater than three-times the ULN and grades 3 or 4 neutropenia. In cases of alteration of the lipid profile, lipid-lowering therapy should be initiated when indicated.

The association between TCZ and other possible serious AEs such as GI perforations or malignancies remains unclear, meaning that clinicians should also be aware of them, as well as other rare but serious side effects observed with other biologic agents, such as demyelinating disorders or interstitial lung disease.

Conclusion

TCZ is an IL-6 inhibitor that constitutes a therapeutic option for the management of RA different from other biologic agents such as anti-TNF- α agents, rituximab or abatacept. Infusions of 8 mg/kg iv. every 4 weeks combined with MTX or with another DMARD or even in monotherapy seem to be the most adequate way of TCZ administration. Its efficacy in RA patients with an inadequate response to

DMARDs or TNF- α inhibitors has been discussed in the present review; it demonstrates similar results to those seen with other biologic agents, although higher end points such as ACR70 or DAS28 remission might be more easily achieved with TCZ, and its outcomes as monotherapy are unique. TCZ has also been demonstrated to have a safety profile similar to those of other biologic drugs, with its main AEs being infections, infusion reactions, neutropenia, elevations of liver enzymes and alterations of the lipid profile. However, further studies are necessary to assess other, less frequent, secondary effects such as malignancies, cardiovascular

events or demyelinating disease, as well as its use in some situations such as interstitial lung disease or amyloidosis.

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References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med.* 344, 907–916 (2001).
- 2 Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. *Am. J. Health Syst. Pharm.* 63, 2451–2465 (2006).
- 3 Maravic M, Bologna C, Daures JP. Radiologic progression in early rheumatoid arthritis treated with methotrexate. *J. Rheumatol.* 26, 262–267 (1999).
- 4 Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. *N. Engl. J. Med.* 350, 2167–2179 (2004).
- 5 Lipsky PE, van der Heijde DM, St Clair EW *et al.*; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N. Engl. J. Med.* 343, 1594–1602 (2000).
- 6 Weinblatt ME, Kremer JM, Bankhurst AD *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N. Engl. J. Med.* 340, 253–259 (1999).
- 7 Weinblatt ME, Keystone EC, Furst DE *et al.* Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48, 35–45 (2003).
- 8 Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al.* The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a Phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 54, 1390–1400 (2006).
- 9 Jiang Y, Genant HK, Watt I *et al.* A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum.* 43, 1001–1009 (2000).
- 10 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144, 865–876 (2006).
- 11 Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. *Rheumatology (Oxford)* 46, 975–979 (2007).
- 12 Hashizume M, Mihara M. The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis* 2011, 765624 (2011).
- 13 Taga T, Kishimoto T. gp130 and the interleukin-6 family of cytokines. *Annu. Rev. Immunol.* 15, 797–819 (1997).
- 14 Mihara M, Kasutani K, Okazaki M *et al.* Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. *Int. Immunopharmacol.* 5(12), 1731–1740 (2005).
- 15 Muraguci A, Hirano T, Tang B *et al.* The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. *J. Exp. Med.* 167, 332–344 (1988).
- 16 Lotz M, Jirik F, Kabouridis P *et al.* B cell stimulating factor 2/interleukin 6 is a costimulant for human thymocytes and T lymphocytes. *J. Exp. Med.* 557, 417–435 (1989).
- 17 Mihara M, Moriya Y, Kishimoto T, Ohsugi Y. Interleukin-6 (IL-6) induces the proliferation of synovial fibroblastic cells in the presence of soluble IL-6 receptor. *Br. J. Rheumatol.* 34, 321–325 (1995).
- 18 Tamura T, Udagawa N, Takahashi N *et al.* Soluble interleukin-6 receptor triggers osteoclast formation by interleukin 6. *Proc. Natl Acad. Sci. USA* 90, 11924–11928 (1993).
- 19 De Hooge AS, van de Loo FA, Arntz OJ, van den Berg WB. Involvement of IL-6, apart from its role in immunity, in mediating a chronic response during experimental arthritis. *Am. J. Pathol.* 157, 2081–2091 (2000).
- 20 Hata H, Sakaguchi N, Yoshitomi H *et al.* Distinct contribution of IL-6, TNF- α , IL-1, and IL-10 to T cell-mediated spontaneous autoimmune arthritis in mice. *J. Clin. Invest.* 114, 582–588 (2004).
- 21 Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood* 101, 2461–2463 (2003).
- 22 Hashizume M, Yoshida H, Koike N, Suzuki M, Mihara M. Overproduced interleukin 6 decreases blood lipid levels via upregulation of very-low-density lipoprotein receptor. *Ann. Rheum. Dis.* 69(4), 741–746 (2010).
- 23 Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H. Interferon β 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proc. Natl Acad. Sci. USA* 84(20), 7251–7255 (1987).

- 24 Ishibashi T, Kimura H, Uchida T, Kariyone S, Friese P, Burstein SA. Human interleukin 6 is a direct promoter of maturation of megakaryocytes *in vitro*. *Proc. Natl Acad. Sci. USA* 8, 3546–3549 (1989).
- 25 Maini RN, Taylor PC, Szechinski J *et al.*; CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 54, 2817–2829 (2006).
- 26 Garnero P, Mareau E, Thompson E *et al.* The antiinterleukin-6 receptor inhibitor tocilizumab combined with methotrexate has beneficial effects on bone and cartilage metabolism in patients with rheumatoid arthritis: results of a Phase III 24-week randomised placebo-controlled study. Presented at: *2008 Annual European Congress of Rheumatology*. Paris, France, 11–14 June 2008 (Abstract THU0178 plus poster).
- 27 Terao K, Tsuru T, Suzaki M *et al.* Drug–disease interaction study of tocilizumab in patients with rheumatoid arthritis: IL-6 signal inhibition normalized cytochrome P-450 enzymes expression which was reduced by inflammation. *Ann. Rheum. Dis.* 67(Suppl. II), 339, Abstract FRI0166 (2008).
- 28 Ito S, Gross WL, Reinhold-Keller E *et al.* Rheumatology in Japan, Germany, and Egypt: a comparison of medical practices. *Acta Med. Biol.* 54, 51–58 (2006).
- 29 Jones G, Sebba A, Gu J *et al.* Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann. Rheum. Dis.* 69, 88–96 (2010).
- **Demonstrated the efficacy of tocilizumab (TCZ) as monotherapy versus methotrexate outside of Japan.**
- 30 Nishimoto N, Miyasaka N, Yamamoto K *et al.* Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod. Rheumatol.* 19(1), 12–19 (2009).
- 31 Smolen JS, Beaulieu A, Rubbert-Roth A *et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 371, 989–997 (2008).
- 32 Kremer JM, Blanco R, Brzosko M *et al.* Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum.* 63(3), 609–621 (2011).
- **Showed that treatment with TCZ plus methotrexate resulted in inhibition of joint damage progression compared with methotrexate alone.**
- 33 Genovese MC, McKay JD, Nasonov EL *et al.* Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 58(10), 2968–2980 (2008).
- **First study to prove the additive effect of TCZ on any disease-modifying antirheumatic drug.**
- 34 Emery P, Keystone E, Tony HP *et al.* IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann. Rheum. Dis.* 67, 1516–1523 (2008).
- **Demonstrated the efficacy of TCZ in rheumatoid arthritis patients with an inadequate response to anti-TNF- α agents.**
- 35 Nishimoto N, Hashimoto J, Miyasaka N *et al.* Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI). Evidence of clinical and radiographic benefit from an X-ray reader-blinded randomized controlled trial of tocilizumab. *Ann. Rheum. Dis.* 66, 1162–1167 (2007).
- 36 Leffers HC, Ostergaard M, Glinborg B *et al.* Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. *Ann. Rheum. Dis.* 70(7), 1216–1222 (2011).
- 37 Yazici Y, Curtis JR, Ince A *et al.* Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann. Rheum. Dis.* 71(2), 198–205 (2012).
- 38 Bykerk V, Östör A, Román Ivorra JA. Comparison of tocilizumab as monotherapy or with add-on disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and an inadequate response to previous treatments. Presented at: *75th Annual Scientific Meeting of the American College of Rheumatology*. Chicago, IL, USA, 4–9 November 2011 (Abstract 2218).
- 39 Burmester GR, Feist E, Kellner H, Braun J, Iking-Konert C, Rubbert-Roth A. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first Phase IIIb real-life study (TAMARA). *Ann. Rheum. Dis.* 70(5), 755–759 (2011).
- **Main study demonstrating the efficacy of TCZ in clinical practice.**
- 40 Peterfy C, Troum O, Olech E *et al.* Discriminative power of different combinations of bones and joints for assessing change in rheumatoid arthritis with low-field MRI. *Ann. Rheum. Dis.* 69(Suppl. 3), 119 (2010).
- 41 Dougados M, Kissel K, Amital H *et al.* Double-blind study of tocilizumab plus methotrexate vs tocilizumab plus placebo in patients with active rheumatoid arthritis despite prior methotrexate: progression of structural damage, quality of life, and physical function at 24 weeks. Presented at: *75th Annual Scientific Meeting of the American College of Rheumatology*. Chicago, IL, USA, 4–9 November 2011 (Abstract 2628).
- 42 Weinblatt ME, Kremer JM, Cush JJ *et al.* Efficacy and safety of tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: a 24-week randomized study in a United States population. Presented at: *75th Annual Scientific Meeting of the American College of Rheumatology*. Chicago, IL, USA, 4–9 November 2011 (Abstract 2213).
- 43 Takeuchi T, Tanaka Y, Amano K *et al.* Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients – REACTION 52-week study. *Rheumatology (Oxford)* 50(10), 1908–1915 (2011).
- 44 Smolen J, Gomez-Reino JJ, Vernon E, Rubbert-Roth A, Emery P. Efficacy of tocilizumab in patients with RA and inadequate response to DMARDs or TNF inhibitors: up to 3.5-year data from ongoing extension studies. *Ann. Rheum. Dis.* 69(Suppl. 3), 386 (2010).
- 45 Jones G, Sebba A, Calvo A *et al.* Efficacy of tocilizumab in patients with rheumatoid arthritis who had never been exposed to or had never failed methotrexate: analysis of up to 3 years of treatment in a long-term extension study. *Ann. Rheum. Dis.* 69(Suppl. 3), 386 (2010).

- 46 Keystone EC, Genovese MC, Klareskog L *et al.* Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann. Rheum. Dis.* 68(6), 789–796 (2009).
- 47 Heiberg MS, Rødevand E, Mikkelsen K *et al.* Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. *Ann. Rheum. Dis.* 65(10), 1379–1383 (2006).
- 48 Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. *Semin. Arthritis Rheum.* 39(6), 425–441 (2010).
- 49 Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. *Arthritis Rheum.* 63(1), 43–52 (2011).
- 50 Breedveld FC, Weisman MH, Kavanaugh AF *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 54, 26–37 (2006).
- 51 Klareskog L, van der Heijde D, de Jager JP *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363, 675–681 (2004).
- 52 Smolen JS, Kay J, Doyle MK *et al.* Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 374(9685), 210–221 (2009).
- 53 Cohen SB, Emery P, Greenwald M *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumour necrosis factor therapy. *Arthritis Rheum.* 54, 2793–2806 (2006).
- 54 Genovese M, Becker JC, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N. Engl. J. Med.* 353, 1114–1123 (2005).
- 55 Iking-Konert C, Aringer M, Wollenhaupt J *et al.* Performance of the new 2011 ACR/EULAR remission criteria with tocilizumab using the Phase IIIb study TAMARA as an example and their comparison with traditional remission criteria. *Ann. Rheum. Dis.* 70(11), 1986–1990 (2011).
- 56 Nishimoto N, Hashimoto J, Miyasak N *et al.* Three-year extension of the SAMURAI study confirms tocilizumab to prevent joint destruction in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 67(Suppl. 2), 335 (2008).
- 57 Fleischmann R, Burgos-Vargas R, Skopouli FN *et al.* Tocilizumab inhibits radiographic progression, improves physical function, and gains efficacy over time: LITHE 2 year. *Ann. Rheum. Dis.* 69(Suppl. 3), 384 (2010).
- 58 Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford)* 50(3), 552–562 (2011).
- **Demonstrated the safety of TCZ in rheumatoid arthritis patients.**
- 59 Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res. Ther.* 13(5), R141 (2011).
- **Demonstrated the safety of TCZ in rheumatoid arthritis patients over time.**
- 60 Smolen JS, Beaulieu AD, Dikranian A *et al.* Safety of tocilizumab in patients with rheumatoid arthritis: pooled analysis of five Phase 3 clinical trials. *Arthritis Rheum.* 58(9 Suppl.), 1669 (2008).
- 61 Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long term safety and efficacy of tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Ann. Rheum. Dis.* 68(10), 1580–1584 (2008).
- 62 Dixon WG, Watson K, Lunt M *et al.*; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 54, 2368–2376 (2006).
- 63 Shinoki T, Kikuchi M, Kaneko U *et al.* Safety and response to influenza vaccine in patients with juvenile rheumatoid arthritis receiving tocilizumab. *Arthritis Rheum.* 58(9 Suppl.), 1495 (2008).
- 64 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum.* 56, 2886–2895 (2007).
- 65 Yamanaka H, Nishimoto N, Inoue E *et al.* Incidence of malignancies in Japanese rheumatoid arthritis patients treated with tocilizumab in comparison to those in an observational cohort of Japanese patients and a Japanese population database. Presented at: 2007 Annual European Congress of Rheumatology. Barcelona, Spain, 13–16 June 2007 (Abstract OP0228).
- 66 Genovese MC, Harrell RA, Woodworth T, Alecock E. Low immunogenic potential of tocilizumab in patients with rheumatoid arthritis: analysis of four Phase 3 clinical trials. *Arthritis Rheum.* 58(9 Suppl.), 993 (2008).
- 67 Suwa T, Hogg JC, English D, van Eeden SF. Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow. *Am. J. Physiol. Heart Circ. Physiol.* 279, 2954–2960 (2000).
- 68 Kremer JM, John AK, Malamet R, Keystone EC. Hepatic aminotransferases and bilirubin levels during tocilizumab treatment of patients with rheumatoid arthritis: pooled analysis of five Phase 3 clinical trials. *Arthritis Rheum.* 58(9 Suppl.), 1667 (2008).
- 69 Taub R. Liver regeneration: from myth to mechanism. *Nat. Rev. Mol. Cell Biol.* 5, 836–847 (2004).
- 70 Genovese MC, Smolen JS, Emery P *et al.* Lipid and inflammatory biomarker profiles in patients receiving tocilizumab for rheumatoid arthritis: analysis of five Phase 3 clinical trials. *Arthritis Rheum.* 58(9 Suppl.), 987 (2008).
- 71 Genovese MC, Smolen JS, Emery P *et al.* Concomitant use of statins in tocilizumab-treated patients with rheumatoid arthritis with elevated low density lipoprotein cholesterol: analysis of five Phase 3 clinical trials. *Arthritis Rheum.* 58(9 Suppl.), 1672 (2008).
- 72 Gonzalez-Gay MA, Gonzalez-Juanatey C, Piñeiro A *et al.* High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. *J. Rheumatol.* 32, 1219–1223 (2005).

- 73 Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ *et al.* HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum.* 57, 125–132 (2007).
- 74 Serio B, Paolino S, Sulli A, Fasciolo D, Cutolo M. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. *Ann. NY Acad. Sci.* 1069, 414–419 (2006).
- 75 Popa C, van den Hoogen FH, Radstake TR *et al.* Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. *Ann. Rheum. Dis.* 66, 1503–1507 (2007).
- 76 Dahlqvist SR, Engstrand S, Berglin E, Johnson O. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. *Scand. J. Rheumatol.* 35, 107–111 (2006).
- 77 Jacobsson LT, Turesson C, Gülfe A *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J. Rheumatol.* 32, 1213–1218 (2005).
- 78 Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register Control Centre Consortium. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 56, 2905–2912 (2007).
- 79 Gout T, Ostör AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. *Clin. Rheumatol.* 30(11), 1471–1474 (2011).
- 80 Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. *Arthritis Rheum.* 54(9), 2997–3000 (2006).
- 81 Magro-Checa CS, Casado AN, Borrego-Garc AE *et al.* Successful use of tocilizumab in a patient with nephrotic syndrome due to a rapidly progressing AA amyloidosis secondary to latent tuberculosis. *Amyloid* 18(4), 235–239 (2011).

■ Websites

- 101 Genentech Actemra® Prescribing Information. www.gene.com/gene/products/information/actemra/pdf/pi.pdf
- 102 EMA. RoActemra (tocilizumab): summary of product characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf