

Tocilizumab for rheumatoid arthritis: results of the Phase III clinical trial program

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Tocilizumab (TCZ) is a humanized monoclonal antibody targeting the receptor for IL-6 that has been approved in Japan, Europe and the USA for the treatment of rheumatoid arthritis (RA). Several Phase III trials have shown clinical efficacy of TCZ in the majority of clinical situations; namely RA with no previous methotrexate failures (AMBITION study), RA resistant to disease-modifying antirheumatic drugs (TOWARD, OPTION and LITHE studies) and anti-TNF- α agents (RADIATE). TCZ is usually used in RA in combination with methotrexate but it may also be used as monotherapy (AMBITION study). Radiological efficacy has also been demonstrated (SAMURAI and LITHE studies). In general, TCZ has a good safety profile. This article will specifically review the Phase III clinical trials related to clinical and radiological efficacy as well as safety of TCZ in RA.

Keywords: biological therapy • IL-6 receptor • juvenile idiopathic arthritis • rituximab • TNF- α • tocilizumab

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 often includes disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide, salazopyrin or antimalarials that improve inflammatory processes and can slow disease progression [2,3]. Biologic agents, such as TNF- α inhibitors are indicated for patients with inadequate response to conventional DMARDs. However, even with anti-TNF- α inhibitors a proportion of patients do not achieve an adequate clinical response [4–11]. An alternative target for RA treatment is IL-6, a pleiotropic proinflammatory cytokine that is produced by a variety of cells types, including lymphocytes, monocytes and fibroblasts. IL-6 is involved in multiple immunologic processes relevant to RA, such as the differentiation of B cells into immunoglobulin-secreting plasma cells, activation of T cells, induction of acute-phase proteins by hepatocytes and production of platelets [12–15]. IL-6 also induces the proliferation of synovial fibroblasts [16] and osteoclast differentiation, both of which contribute to joint destruction and osteoporosis [17]. In addition, results from animal models suggest an important role of IL-6 in the induction and maintenance of chronic synovitis [18,19]. Furthermore, IL-6 serum level correlates positively with RA disease activity [20,21], and may have an important role in the development of anemia in RA, owing to the hyperproduction of hepcidina, an acute phase reactant that blocks ferroportin, preventing entry of iron into the blood both from the intestine and the reticuloendothelial system [22].

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the soluble as well as membrane-bound receptors of IL-6. TCZ has been jointly developed by the University of Osaka (Japan), the pharmaceutical company Chugai (Tokyo, Japan) and Roche headquartered in Basel (Switzerland). In Japan, TCZ has been indicated for Castleman's disease and juvenile idiopathic arthritis. In Europe it has

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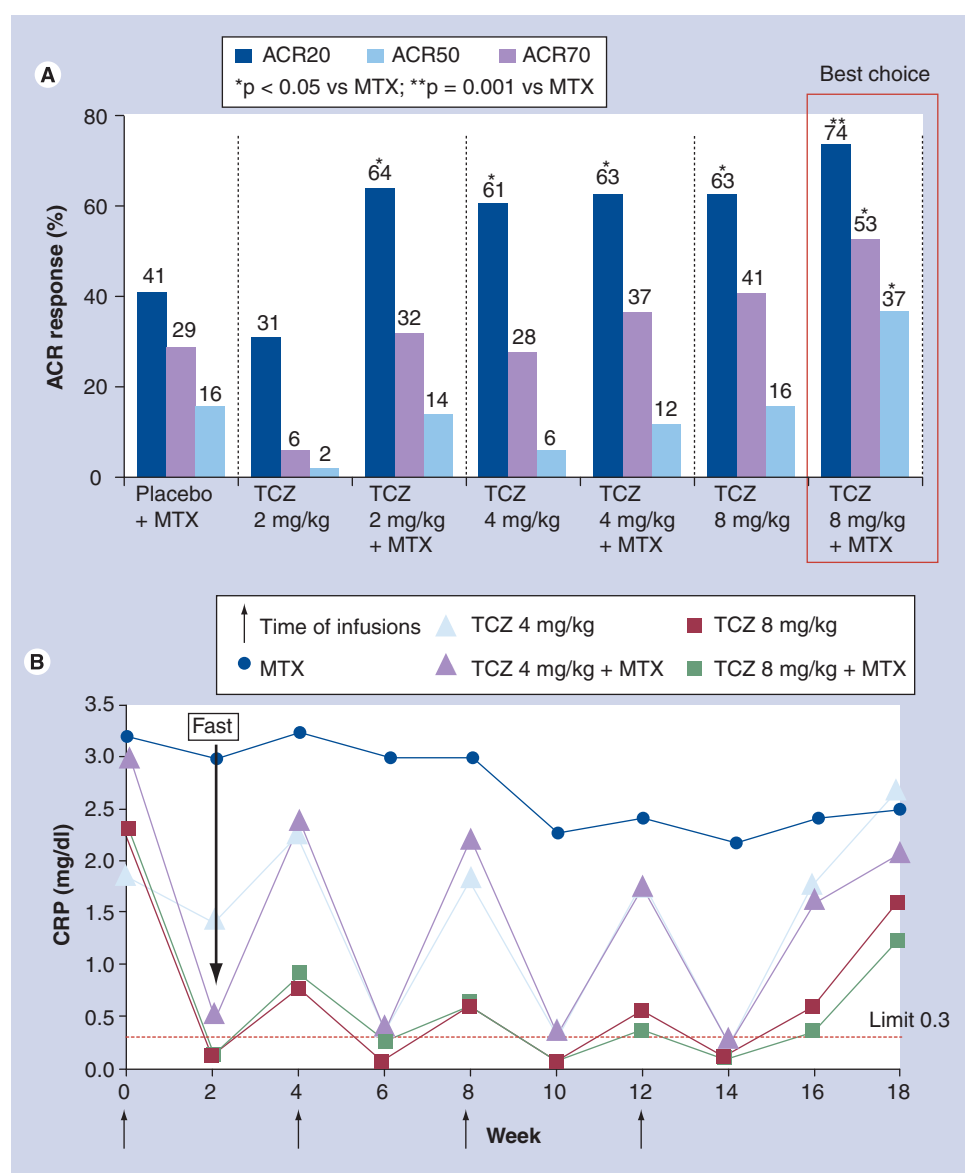


Figure 1. Results from the CHARISMA trial. (A) Improvement in the ACR responses in the different therapeutic groups with TCZ. Observed at week 16. **(B)** CRP response in the CHARISMA trial. TCZ 8 mg/kg is the only dose that produces a maintained reduction in CRP. ACR: American College of Rheumatology; CRP: C reactive protein; MTX: Methotrexate; TCZ: Tocilizumab. Data taken from [24].

been approved, in combination with MTX, for the treatment of adult patients with moderate-to-severe RA who had responded inadequately or were intolerant to previous treatment with one or more DMARDs or TNF- α antagonists. TCZ can be given as monotherapy in cases of intolerance to MTX or when continuation with MTX is contraindicated.

From the pharmacokinetic standpoint, TCZ 8 mg/kg infusions every 4 weeks is the most adequate dosage, according to the different studies that compared different

MTX (SATORI [26], OPTION [27], LITHE [28]) or any DMARDs (TOWARD [29]) and finally RA resistant to anti-TNF- α (RADIATE [30]). Efficacy has been proven generally in combination with DMARDs, usually MTX, but also in monotherapy in Japan (SAMURAI [31], SATORI) and outside Japan (AMBITION). In addition, results of four Phase IIIb studies have been presented recently including: the ROSE trial [32] (patients with established RA resistant to DMARDs treated with TCZ plus DMARDs), ACT-SURE [33] and TAMARA [34]

doses and intervals of TCZ administration. The initial data about the pharmacokinetic properties of TCZ came from a Japanese open-label Phase I–II dose-ascending study in which patients received treatment with TCZ 2, 4 or 8 mg/kg i.v. every 2 weeks [23]. This study demonstrated that the half-life of TCZ increased with dose increments and with the repetition of the dose [23], and a persistent reduction of C-reactive protein (CRP) was only observed with a dose of 8 mg/kg i.v. These data were supported by those from the Phase II CHARISMA trial, a multicenter double-blind randomized study that 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. This trial demonstrated that the efficacy based on the American College of Rheumatology (ACR) criteria (ACR20, -50, and -70 response) was significantly superior with TCZ 8 mg/kg with MTX and confirmed that normalized CRP levels were only maintained with this high TCZ dosage (Figure 1A & B) [24].

In this article we will focus on the more relevant aspects related to clinical efficacy, as well as its safety profile according to the results of the Phase III clinical trial program for TCZ.

Clinical efficacy

There are seven Phase III trials that show clear efficacy in the possible situations of RA (Table 1); namely: RA with no previous MTXs failure (AMBITION [25]), RA refractory to

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

Location	Phase	Trial	Number of patients	Design	Objective	Population	Therapeutic group	Comparison group	Duration of trial	Ref.
Japan	III	SATORI	127	Double blind	S & S	Failure to MTX	TCZ	MTX	6 months	[26]
		SAMURAI	306	Open	Radiologic damage S & S	Failure to DMARDs	TCZ	DMARDs	12 months	[31]
Outside Japan	III	OPTION	623	Double blind	S & S	Failure to MTX	TCZ + MTX	MTX	6 months	[27]
		TOWARD	1220	Double blind	S & S	Failure to DMARDs	TCZ + DMARDs	DMARDs	6 months	[29]
		RADIATE	499	Double blind	S & S	Failure to anti-TNF	TCZ + MTX	MTX	6 months	[30]
		AMBITION	673	Double blind	S & S	MTX naive >6 months	TCZ	MTX	6 months	[25]
		LITHE	1196	Double blind	Radiologic damage S & S	Failure to MTX	TCZ + MTX	MTX	1 year	[28]
	IIIb	ACT-RAY	63	Double blind	MRI	Failure to MTX	TCZ + MTX	MTX	12 weeks	[35]
		ACT-SURE	1669	Open clinical practice	S & S Safety	Failure to DMARDs Failure to anti-TNF	TCZ + MTX TCZ	-	6 months	[33]
		ROSE	619	Double blind	S & S	Failure to DMARDs	TCZ + DMARDs	DMARDs	6 months	[32]
		TAMARA	293	Open clinical practice	S & S	Failure to DMARDs Failure to anti-TNF	TCZ + DMARDs	-	6 months	[34]

DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; S & S: Signs and symptoms; TCZ: Tocilizumab.

(two open-label studies of TCZ in patients with inadequate response to DMARDs or anti-TNF- α agents in the usual clinical practice), and the ACT-RAY [35] (used MRI to determine the efficacy of TCZ) (Table 1).

Since the clinical development of TCZ for RA in Japan is considerably different (e.g., TCZ is used in monotherapy and the highest recommended dose of MTX is 8 mg/week [36]), this article will review mainly the trials developed outside Japan (Table 1). In the Phase III trials, the therapeutic arms were restricted to those of greater efficacy and the therapeutic arms were only the 8 mg/kg i.v. every 4 weeks in the TOWARD, AMBITION, ROSE, ACT-SURE and TAMARA trials while the RADIATE, OPTION and LITHE studies also used a 4 mg/kg i.v. arm. In general, the primary efficacy end point was the ACR20 response after 24 weeks, which was 70% in the AMBITION trial and 50% in the RADIATE study. This difference was somehow expected considering that the populations

of RA included in these studies were very different (Table 1). Other secondary efficacy end points were the ACR50 and -70 responses, which were equally optimal being approximately 40 and 20%, respectively, as well as the 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) (Figures 2 & 3). Clinical efficacy measured by a moderate European League against Rheumatism Response (EULAR) [27], ACR20 [27] and -50 [29] response was observed as early as week 2 in several Phase III clinical trials, whilst, a significant improvement in DAS28 was assessed at week 1 in the Phase IIIb ROSE study. Additionally, after 2 weeks of treatment, the CRP levels had been normalized and the mean hemoglobin levels had significantly increased [25,29,30]. A significant improvement in CRP was observed as early as week 1 (ROSE trial) [32].

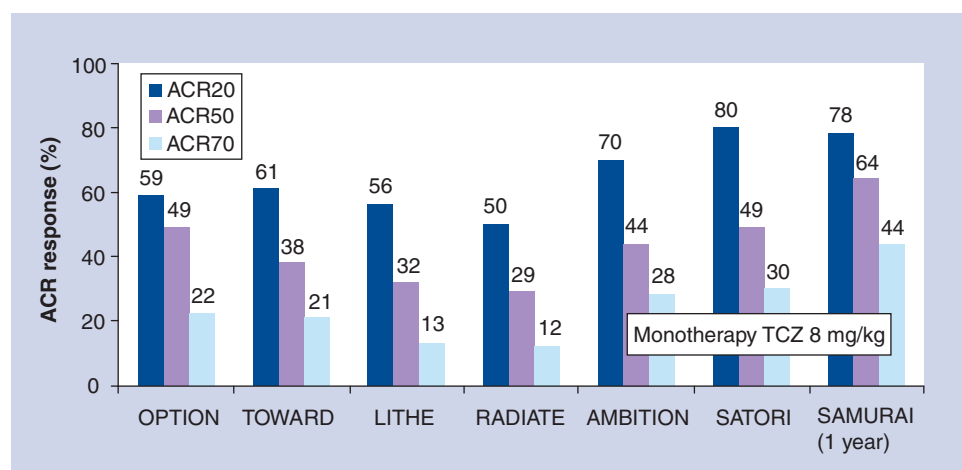


Figure 2. Proportion of patients with American College of Rheumatology responses 20, 50 and 70 in different Phase III studies with tocilizumab in rheumatoid arthritis. The results were observed at week 24 except in the SAMURAI trial, which was performed after 1 year. The results of the best therapeutic group of each study are shown, TCZ (at dose of 8 mg/kg every 4 weeks i.v.) associated to methotrexate or to disease-modifying antirheumatic drugs. The AMBITION, SATORI and SAMURAI trials, in monotherapy, express the results of TCZ at a dose of 8 mg/kg.

ACR: American College of Rheumatology; TCZ: Tocilizumab.

Data taken from [25–31].

Other common parameters, such as the physical function (HAQ-DI), health-related quality of life (HRQoL), and fatigue (FACIT) were also significantly improved with TCZ after 24 weeks. Interestingly, clinical improvement occurred rapidly and it was sustained throughout with TCZ therapy [25–31].

In assessing the main Phase III trials in more detail we can see that the OPTION study included patients with long standing, moderate-to-severe RA resistant to MTX, who were randomized to receive TCZ 8, 4 mg/kg or placebo i.v. every 4 weeks, with MTX (10–25 mg/week). The TOWARD trial was similar to OPTION but in this study RA patients were resistant to any DMARD (not only restricted to MTX) and there was only one therapeutic group receiving TCZ 8 mg/kg i.v. plus DMARD. In both cases, the results after 24 weeks were very similar, with the ACR20, -50 and -70 responses being approximately 60, 40 and 20% respectively, and a clinical DAS28 remission approximately 30%, which was significantly superior to placebo (25, 10 and 2% respectively in the ACR responses, and a DAS28 remission of only 3% [29]).

The RADIATE trial, which included patients that were resistant to anti-TNF- α drugs, reached a slightly inferior ACR response (Figure 2). However, the DAS28 remission was also approximately 30% after 24 weeks (Figure 3), even in those resistant to two or three anti-TNF- α inhibitors. Up to now, other biologic drugs indicated in anti-TNF- α resistant RA patients (rituximab or abatacept), independent of whether they

were assessed in different studies, obtained results that were lower than those obtained with TCZ regarding remission (~10% in both cases) (Figure 4) [37–39].

The AMBITION trial, which included patients with no previous MTX failure (67% patients were MTX naive and 40% DMARD naive) also obtained interesting results. TCZ 8 mg/kg in monotherapy demonstrated a clinical efficacy measured as ACR20, -50, -70, DAS28 remission and HAQ clearly superior to MTX, which was different from other biological agents [25]. It must be remembered that clinical efficacy in studies such as TEMPO (etanercept) or PREMIER (adalimumab), the anti-TNF is clearly superior when combined with MTX and is similar to MTX when anti-TNF is used in monotherapy [40,41].

The data discussed previously from Phase III clinical trials have been confirmed in additional studies performed in the clinical practice such as the ACT-SURE or TAMARA Phase IIIb studies (Table 1) [33,34].

Another feature of TCZ is that its efficacy increases continuously over time. There are already data from 3.5 years of long-term extension studies, which included 3368 patients from the OPTION, RADIATE, TOWARD and LITHE trials [42]. Patients with inadequate response to DMARDs (OPTION, TOWARD and LITHE) increased ACR50 and -70 responses up to 67 and 46% respectively, and DAS28 remission up to 62%, after 180 weeks of treatment. Data from patients with inadequate response to TNF- α (RADIATE) were analyzed separately and also experienced a significantly higher clinical response over time (ACR50: 56%, -70: 31% and DAS28 remission: 48% at week 144). Similar results were obtained from the AMBITION study after 3 years of treatment [43]. In this long-term extension study a high number of patients treated with TCZ achieved ACR20, 50 and 70 responses (83%, 66% and 43%) and DAS28 remission (57%) over time.

Radiological efficacy

The radiological efficacy of TCZ has been evaluated in two Phase III clinical trials, SAMURAI [31] and LITHE [28]. The SAMURAI trial evaluated the radiological progression (primary efficacy end point) in early RA patients (<5 years duration) resistant to DMARDs in Japan. 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 radiographic 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 (Figure 5A). In addition, significantly more patients receiving TCZ than DMARDs had no radiological progression after 52 weeks (56 vs 39%; $p < 0.01$) [31]. These data were confirmed in the 3-year extension study [44].

The coprimary end point of the LITHE trial was to assess the radiographic disease progression after 52 weeks in RA patients refractory to MTX who received TCZ 4 and 8 mg/kg combined with MTX or placebo (MTX alone). There was also significantly less radiological progression in both TCZ groups compared with placebo, regarding the total Genant-modified Sharp scores as well as in its components (Figure 5B). Data obtained in the 2-year open-label trial confirmed these results (Figure 5C) [45].

A significant decrease in synovitis at week 2 and osteitis at week 12 was detected with the use of MRI in patients with erosive RA despite MTX receiving TCZ (both with MTX and in monotherapy), as concluded the Phase IIIb clinical trial ACT-RAY [35].

Adverse events

The clinical program for TCZ has demonstrated that TCZ is a safe and well-tolerated drug, both in monotherapy [25,26,31] and in combination with DMARDs [27–30,32–34]. Combined data retrieved from 3324 patients of the five Phase III studies performed outside Japan with a duration of 24 weeks ratify these results in terms of safety reported in each individual trial [46]. Overall, all these results confirm that the majority of the adverse events attributed to TCZ were mild-to-moderate both as monotherapy and in combination with DMARDs. The most common

serious adverse event (SAE) was the development of infections, without differences in the rate of SAEs or deaths between groups treated with TCZ and the control groups (Table 2). These promising results at week 24 described previously were confirmed in open label extension studies (median 2.6 years of treatment) which included 4009 patients combining the five Phase III

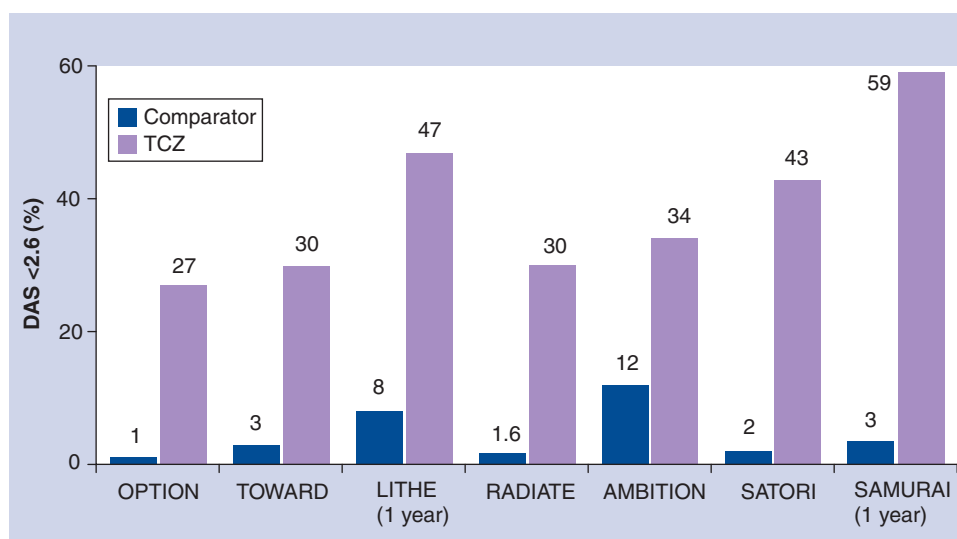


Figure 3. Proportion of patients in clinical remission (disease activity score 28 < 2.6). The results were observed after 24 weeks, except in the LITHE and SAMURAI trials, which were done after 1 year. The results of the best therapeutic group for each study are shown, TCZ (at dose of 8 mg/kg every 4 weeks i.v.) associated to methotrexate or to disease-modifying antirheumatic drugs. The AMBITION, SATORI and SAMURAI trials, in monotherapy, express the results of TCZ at a dose of 8 mg/kg.

DAS: Disease activity score; TCZ: Tocilizumab.

Data taken from [25–31].

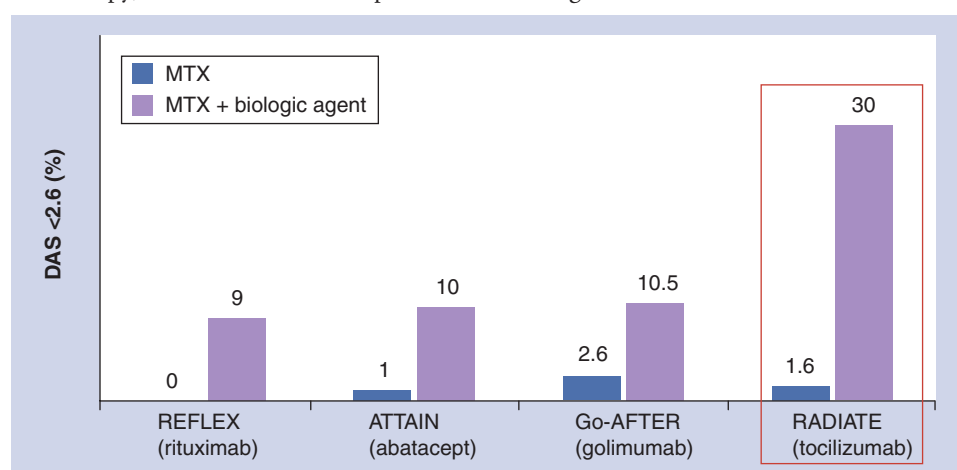


Figure 4. Disease activity score 28 remission in RA patients resistant to one anti-TNF- α drug treated with other biologic agents.

DAS: Disease activity score; MTX: Methotrexate.

Data taken from [30,37–39].

trials [47]. This study demonstrated that the rate of SAEs was stable over time (14.6/100 patient-years), with a rate of withdrawal because of adverse events of 5.4/100 patient-years [47]. The most relevant adverse data are discussed.

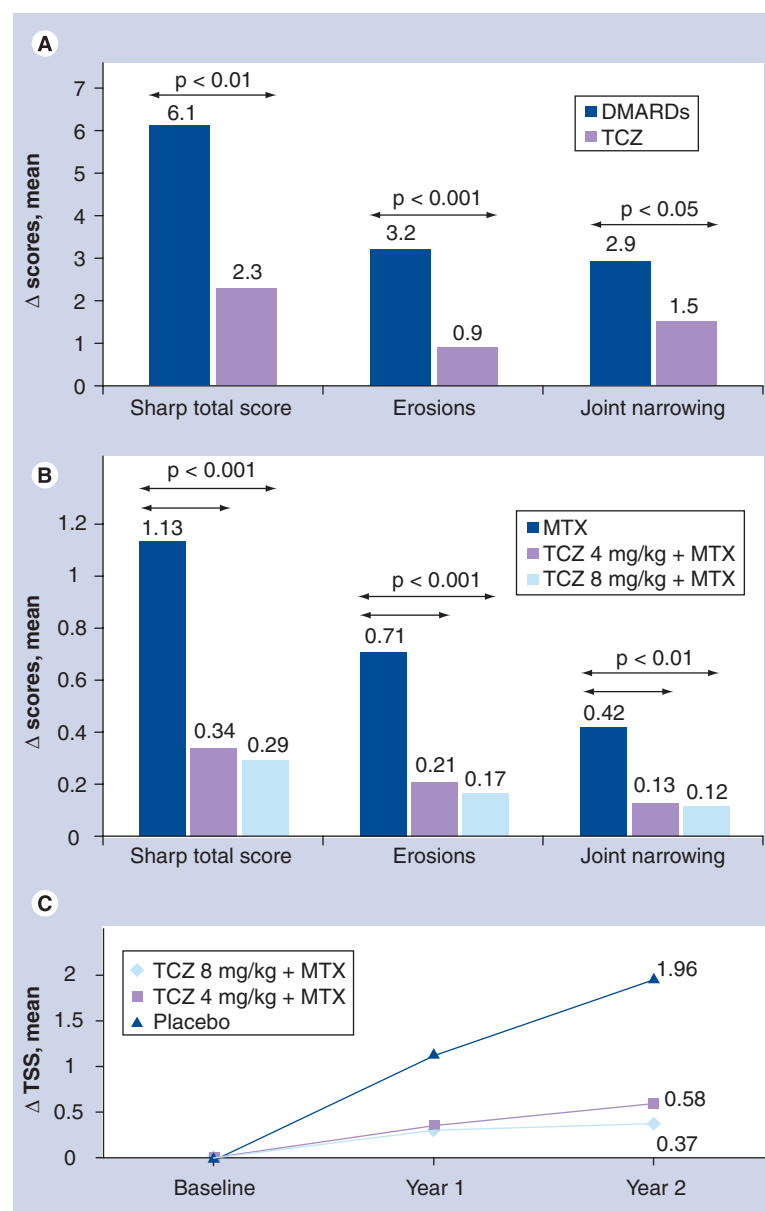


Figure 5. Radiological progression with tocilizumab. (A) Increase in the Sharp score modified by van der Heijde in the SAMURAI trial at week 52. TCZ at a dose of 8 mg/kg in monotherapy is compared with traditional disease-modifying drugs [31]. (B) Increase in the Sharp score modified by Genant in the LITHE trial at week 52 [28]. (C) Progression from baseline in TSS. TCZ at a dose of 4 mg/kg and 8 mg/kg combined with MTX is compared to placebo (MTX alone) [45]. DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; TCZ: Tocilizumab; TSS: Total Sharp–Genant score.

Infections

Serious infection is the most common SAE of TCZ (Table 2). Its frequency is relatively low in all the therapeutic groups with no significant differences compared with placebo [46]. Patients receiving TCZ combined with DMARDs during 24 weeks presented an increase of serious infections compared with TCZ in monotherapy or DMARDs, although such an increase was not statistically significant [46]. These serious infection rate are very similar to those seen with anti-TNF drugs [48]. Also, recent published data have shown that the number of serious infections remained stable over time (4.5/100 patients-years) [47].

Similar data were obtained in the STREAM trial (5-year extension Japanese study that included TCZ-treated patients in monotherapy [49]) with a serious infection rate of 5.7/100 patient-years. The most frequently reported serious infections have been pneumonia, herpes zoster, cellulitis, gastroenteritis and diverticulitis [47,50].

Infections by opportunistic agents, even mycobacteria, were rare (0.3/100 patient-years) [47]. TCZ did not affect the response to influenza vaccination, being similar to that observed in patients receiving DMARDs [51]. The only factors that predispose to the development of serious infection were diabetes mellitus, an age of 65 years or older, the use of steroids and a history of previous infection [52].

Malignancies

Although there are limited data on this issue, combined analyses of the different studies did not show an increase in the incidence of malignancies in patients treated with TCZ, with a rate of malignancies after 2.6 years of treatment of 1.16/100 patient-years [47].

Infusion reactions

Infusion reactions (occurring within 24 h of the infusion) were reported in 6% of patients receiving TCZ 8 mg/kg plus DMARDs compared with 0% in the placebo plus DMARD group (Table 2). Most of them were mild and they did not require discontinuation of treatment. The most common infusion reactions were nausea, exanthema, hypertension, headache and pruritus and severe infusion reactions (e.g., anaphylactic reactions) occurred in 0.2% [101].

In addition, TCZ was associated with a low production of autoantibodies and immunogenicity [53].

Neutropenia

Treatment with TCZ was often associated with the development of neutropenia, which was generally mild (grade 1 or 2), transient and not associated with infection. In this regard, grades 3/4 neutropenia were reported in 4% of patients [50,52].

Table 2. Main adverse events of the different clinical trials of tocilizumab in rheumatoid arthritis. The combined data of five clinical trials in Phase III after 24 weeks are shown: OPTION, TOWARD, RADIATE, AMBITION and LITHE.

Treatment groups	Combined treatment		Monotherapy groups	
	TCZ 8 mg/kg + DMARDs (n = 1582)	Placebo + DMARDs (n = 1170)	TCZ 8 mg/kg (n = 288)	MTX (n = 284)
Total patients per year	754	507	140	134
1000 patient-years index (95% CI)				
Total AEs	462 (447–478)	377 (361–395)	492 (456–530)	450 (414–487)
Severe AEs	15 (13–18)	15 (12–18)	9 (4–15)	11 (6–19)
Infections	118 (110–126)	104 (95–113)	106 (90–125)	109 (92–128)
Severe infections	5.2 (3.7–7.1)	3.8 (2.3–5.9)	2.9 (0.8–7.3)	1.5 (0.2–5.4)
Neoplasms	1.3	1.4	1.4	2.2
Incidence, n (%)				
Infusion reactions	6 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
AEs that led to drug discontinuation	74 (4.7)	28 (2.4)	11 (3.8)	15 (5.3)
AEs related to the drug	756 (47.8)	401 (34.3)	163 (56.6)	141 (49.6)

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

Data taken from [46].

Neutropenia was found to be related to TCZ dose [24]. IL-6 physiologically increases the number of circulating neutrophils and its inhibition with TCZ can lead to the opposite effect [54].

■ Elevation of liver enzymes

Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin have often been reported. However, most of the ALT and AST increases were mild (less than three-times above the upper limit of normal), transient, unrelated to bilirubin increases, and normalized either spontaneously or following discontinuation of TCZ therapy [55]. In addition, no cases of hepatitis or liver dysfunction were seen. The frequency of ALT and AST elevations greater than three times the upper limit of normal in the pooled data of the five Phase III trials at week 24 were 3.6 and 1.4%, respectively, and this frequency did not increase after 2.6 years of treatment [47]. Elevations of ALT and AST were observed more frequently in the high dose TCZ group, especially when combined with MTX. In this regard, elevation of liver enzymes following TCZ monotherapy was similar to that observed with MTX monotherapy [55]. 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 with TCZ is still unknown [56].

■ Alteration of the lipid profile

Increases in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and apolipoprotein A1 and B have been reported in clinical

trials [27,46,50,57]. This increase is observed as early as at week 6 [27], with no further elevation over time [46,47]. Unlike dyslipidemia, serum levels of high-density lipoprotein cholesterol are increased in patients receiving TCZ, which contributes to the correction of the atherogenic index. Lipid-lowering therapy was initiated in 7.8% of patients during long-term TCZ treatment [47] leading to improvement of the lipid profile [58]. Interestingly, TCZ drastically decreased the inflammation markers. 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 [59,60]. Therefore, the overall cardiovascular effect of both effects (lipid alteration and improvement on inflammatory parameters) remains unclear and somehow contradictory, although the evidence shows that patients receiving TCZ during 2.5 years do not have increased rates of cardiovascular complications (myocardial infarction: 0.25/100 patient-years and stroke: 0.19/100 patient-years) [47].

Similar alterations in the lipid profile and in the inflammatory parameters have also been described in RA patients undergoing anti-TNF therapy [61–63]. However, in these patients an important reduction in the incidence of cardiovascular events has been observed, in particular in those who experienced good therapeutic response following the use of TNF- α antagonists [64,65].

Future perspective

Tocilizumab is a therapeutic option different from other biologic agents, such as anti-TNF- α agents, RTX or abatacept. However, its efficacy and safety

needs to be confirmed in further long-term studies in clinical practice.

It is necessary to develop patient profiles with the purpose of selecting the most adequate biological agent to each patient. In this regard, patients with RA and high inflammatory response as well as those with severe anemia seem to be good candidates for TCZ.

It is also important to confirm the potential efficacy of TCZ in several special situations related to RA, such as amyloidosis [66] or interstitial lung disease. Finally, it is possible that TCZ might also be useful in other diseases

different from RA such as adult Still's disease [67] and some cases of refractory polymyalgia rheumatic [68].

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Executive summary

- The results shown in this article support the use of tocilizumab (TCZ) in the management of patients with rheumatoid arthritis.
- 8 mg/kg i.v. infusions every 4 weeks combined with methotrexate or with another disease-modifying antirheumatic drug or even in monotherapy seem to be the most adequate way of TCZ administration.
- TCZ administration has also been associated with an adequate safety profile. It is as effective in traditional disease-modifying antirheumatic drug rheumatoid arthritis resistant patients as well as in those resistant to anti-TNF- α inhibitors, with clinical remission scores at 6 months of approximately 30%.

Bibliography

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 Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* 370, 1861–1874 (2007).
- 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.* 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 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).
- 13 Lotz M, Jirik F, Kabouridis P, Tsoukas C *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).
- 14 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, 7251–7255 (1987).
- 15 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).
- 16 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).
- 17 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).
- 18 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).
- 19 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).
- 20 Choy EH, Isenberg DA, Garrood T *et al.* Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. *Arthritis Rheum.* 46, 3143–3150 (2002).

- 21 Nishimoto N, Yoshizaki K, Miyasaka N *et al.* Long-term safety and efficacy of anti-interleukin 6 receptor antibody (MRA) in patients with rheumatoid arthritis. *Arthritis Rheum.* 48(Suppl. 9), 126 (2003).
- 22 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).
- 23 Nishimoto N, Yoshizaki K, Maeda K *et al.* Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. *J. Rheumatol.* 30, 1426–1435 (2003).
- 24 Maini RN, Taylor PC, Szechinski J *et al.* 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).
- 25 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).
- **Demonstrates the efficacy of tocilizumab (TCZ) in monotherapy versus methotrexate (MTX) outside Japan.**
- 26 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).
- 27 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).
- 28 Kremer JM, Fleischmann RM, Halland AM *et al.* Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with an inadequate response to methotrexate: the LITHE study. *Arthritis Rheum.* 58(9 Suppl. 2), L11 (2008).
- **Demonstrates that treatment with TCZ plus MTX resulted in inhibition of joint damage progression compared with MTX alone.**
- 29 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).
- **The first study to prove the additive effect of TCZ on any disease-modifying antirheumatic drugs.**
- 30 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).
- **Demonstrates the efficacy of TCZ in rheumatoid arthritis patients with an inadequate response to anti-TNF- α agents.**
- 31 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).
- 32 Yazici Y, Curtis JR, Ince A *et al.* Tocilizumab is effective as early as 4 weeks with continued and increased response at 6 months: a randomized, doubled-blind study in patients with moderate to severe active RA: the ROSE study. *Ann. Rheum. Dis.* 69(Suppl. 3), 547 (2010).
- 33 Bykerk V, Östör A, Álvaro-Gracia J *et al.* tocilizumab in patients with rheumatoid arthritis and an inadequate response to DMARDs and/or TNF inhibitor therapy: ACT-SURE preliminary results. *Ann. Rheum. Dis.* 69(Suppl. 3), 379 (2010).
- 34 Rubbert-Roth A, Braun J, Feist E *et al.* Interim results of the TAMARA Study effectiveness and safety of the interleukin-6 (IL-6) receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis (RA). *Arthritis Rheum.* 60(Suppl. 10), 412 (2009).
- 35 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).
- 36 Ito S, Gross WL, Reinhold-Keller E *et al.* Rheumatology in Japan, Germany, and Egypt: a comparison of medical practices. *Acta Med. Biol.* 54(2), 51–58 (2006).
- 37 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).
- 38 Genovese M, Becker J-C, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N. Engl. J. Med.* 353, 1114–1123 (2005).
- 39 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).
- 40 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).
- 41 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).
- 42 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).
- 43 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).
- 44 Nishimoto N, Hashimoto J, Miyasaka 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).
- 45 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).

- 46 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(Suppl. 9), 1669 (2008).
- ■ This analysis demonstrated the safety of TCZ from pooled data from several clinical trials.
- 47 van Vollenhoven RF, Scali J, Curtis JR *et al.* Safety of tocilizumab in patients with rheumatoid arthritis: analysis of median of 2.6 years of treatment in long-term extension studies. *Ann. Rheum. Dis.* 69(Suppl. 3), 544 (2010).
- 48 Dixon WG, Watson K, Lunt M *et al.* 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).
- 49 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).
- 50 van Vollenhoven RF, Smolen J, Tony HPT *et al.* Safety of tocilizumab in patients with rheumatoid arthritis: an interim analysis of long-term extension trials with a mean treatment duration of 1.5 years. *Arthritis Rheum.* 58(Suppl. 9), 1670 (2008).
- 51 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(Suppl. 9), 1495 (2008).
- 52 Kremer JM, Vollenhoven RF, Ridley DJ *et al.* Relationship between patient characteristics and the development of serious infections in patients receiving tocilizumab: Results from long-term extension studies with a follow-up duration of 1.5 years. *Arthritis Rheum.* 58(Suppl. 9), 1668 (2008).
- 53 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(Suppl. 9), 993 (2008).
- 54 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).
- 55 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(Suppl. 9), 1667 (2008).
- 56 Taub R. Liver regeneration: From myth to mechanism. *Nat. Rev. Mol. Cell Biol.* 5, 836–847 (2004).
- 57 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 (Suppl. 9), 987 (2008).
- 58 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(Suppl. 9), 1672 (2008).
- 59 Gonzalez-Gay MA, Gonzalez-Juanatey C, Piñeiro A, Garcia-Porrúa C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. *J. Rheumatol.* 32, 1219–1223 (2005).
- 60 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).
- 61 Seriola B, Paolino S, Sulli A, Fasciolo D, Cutolo M. Effects of anti-TNF- α treatment on lipid profile in patients with active rheumatoid arthritis. *Ann. NY Acad. Sci.* 1069, 414–419 (2006).
- 62 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).
- 63 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).
- 64 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).
- 65 Dixon WG, Watson KD, Lunt M *et al.* 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).
- 66 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).
- 67 Perdan-Pirkmajer K, Praprotnik S, Tomšić M. A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature. *Clin. Rheumatol.* 29(12), 1465–1467 (2010).
- 68 Hagihara K, Kawase I, Tanaka T, Kishimoto T. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. *J. Rheumatol.* 37(5), 1075–1076 (2010).

■ Website

- 101 European Medicines Agency. RoActemra (tocilizumab): EPAR – Product Information www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf