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Tocilizumab: a new form of biological therapy for rheumatoid arthritis

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Overactivity of IL-6 plays a very important role in both the exsudative and proliferative phase of rheumatoid inflammation, joint destruction and osteoporosis. Blocking of IL-6 activity is a rational goal in the treatment of rheumatoid arthritis (RA). Tocilizumab (TCZ) is a humanized antibody against the soluble IL-6 receptor (sIL-6R) and membrane-bound IL-6 receptor (mIL-6R), blocking these receptor complexes and preventing IL-6 transmembrane signaling. Phase I–II, II and III trials with TCZ in RA patients demonstrated clinical efficacy mirrored by ACR responses and disease activity score, normalized C-reactive protein and serum amyloid A levels, improved functional capacity and the slowing down of radiological progression of the disease. To date, the only long-term study has demonstrated good clinical efficacy and a low rate of severe adverse events. Health-related quality of life as measured by health assessment questionnaire, and the physical and mental component of the Medical Outcomes Study Short Form-36 were significantly improved with TCZ.
TCZ 8 mg/kg administered by intravenous infusion every 4 weeks seems to be an ideal dosage, and concomitant administration of methotrexate may improve the clinical results. The safety of TCZ seems to be satisfactory, but one patient has died due to reactivation of Epstein-Barr virus infection. Other bacterial and viral infections were usually mild, and no tuberculosis have been reported. An increase in total cholesterol, high-density lipoprotein cholesterol and triglyceride levels was regularly seen. Although the values usually stabilized at the upper level of normal, even in the long-term study, and the atherogenic index did not change, the clinical significance of elevated lipid levels should be studied further.

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing irreversible joint destruction and functional impairment. Although its etiology is still obscure, the course and outcome of RA has been favorably changed in the last two decades [1] owing to early effective treatment with conventional DMARDs [2] and TNF-α blockers [3]. The improved understanding of its pathomechanism [4–6] has contributed to the development of new drugs and more successful treatments [7,8].

Need for new treatment modalities for rheumatoid arthritis

Although DMARD treatment, including combination therapies, can lead to ACR remission rates in up to 88–94% of patients [9], the average improvement is usually less. TNF-α-blocking treatment is also successful, especially in combination with methotrexate (MTX), and satisfactory remission can be achieved in approximately 70% of patients [10]. However, high IgA rheumatoid levels may be associated with poor clinical response to TNF-α-blocking treatment [11]. TNF-α-blocking may also cause severe side effects, such as activating tuberculosis [12]. Therefore, development of further and more effective treatments for this severe disease are still required [7,8,13,14].

Rationale of anti-IL-6 treatment

IL-6 was initially identified as B-cell stimulatory factor (BSF)-2; a T-cell factor inducing B cells to differentiate into immunoglobulin-producing cells [15]. BSF-2 was later found to be identical to the 26 kDa IFN-α-2 protein, the hepatocyte stimulating factor and the hybridoma/plasmocytoma growth factor. These names were then unified as IL-6 [16].

From the history of IL-6 it is clear that this molecule is a pleiotropic cytokine with various essential biological activities [17,18], including involvement in specific and nonspecific immune response and inflammation [19,20]. IL-6 is produced by T-cells, B-cells, macrophages, monocytes, fibroblasts, synovial fibrocytes, endothelial cells, mesangial cells, keratinocytes, some tumor cells and many other cell types [21]. IL-6 induces activated B-cell differentiation, which induces antibody and immunoglobulin production [22]. It also induces T-cell differentiation to cytolytic T cells in cooperation with IL-2 [23] and activates natural killer cells [24].

Keywords: clinical trials, IL-6, rheumatoid arthritis, tocilizumab, treatment

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The role of IL-6 in the inflammatory process is also manifold whereby it induces fever and the production of acute-phase proteins, that is C-reactive protein (CRP), serum amyloid α (SAA) protein, fibrinogen, complement and α1-antitrypsin [25]. IL-6 also induces secretion of the liver hormone hepcidin, an iron-metabolism-regulating peptide, which diminishes iron absorption from the intestine and increases iron recycling by macrophages [26]. IL-6 suppresses albumin production [27], stimulates synoviocyte proliferation [28], promotes the production of VEGF [29], and induces osteoclast differentiation and maturation in the presence of soluble IL-6 receptor (sIL-6R) [30].

Signal transduction mechanism of IL-6

IL-6 has a unique receptor system. It binds to the IL-6-binding receptor (IL-6R) α chain, (CD126), and the 130 kDA non-IL-6-binding but signal-transducing IL-6R β chain (gp130) [31,32]. sIL-6R lacks the intracytoplasmic part of membranous IL-6R (mIL-6R), but can also bind IL-6 and form a complex with gp130 [33]. These complexes bring together the intracellular regions of gp130 to initiate a signal-transduction cascade through JAKs, STAT-3 and transcription factors. As a result, STAT-3 accumulates and the signal is transmitted to the nucleus [19].

IL-6 in arthritis

IL-6 is expressed in cells of rheumatoid synovial tissue [34], and the synovium is a source of IL-6 [35]. High IL-6 levels are found in the synovial fluid of RA patients, and correlate with both disease activity [36,37] and histological characteristics of chronic synovitis [38]. Serum IL-6 levels are also closely associated with the activity of RA [39] and strongly correlate with sedimentation rate, rheumatoid factors and to a lesser degree with platelet counts [40]. Overproduction of IL-6 may explain several systemic features of RA: raised levels of acute-phase reactants, low iron levels and inflammatory anaemia, rheumatoid factor and antinuclear factor production, thrombocytosis and increased osteoclast activity [41].

It is well known that increased angiogenesis is an important pathologic feature of RA, and VEGF plays an important role in this process [42]. Serum VEGF levels in RA patients correlate with disease activity scores (DAS) and radiologic progression [43]. IL-6-receptor blockade suppresses VEGF production of synovial fibroblasts and reduces serum levels in RA patients [44].

Animal models

There is an elevated production of IL-6 in both collagen induced and adjuvant arthritis [45]. IL-6 is required for the development of collagen-induced arthritis (CIA) [46]. Moreover, anti-IL-6R antibodies ameliorate CIA [47], and IL-6-deficient mice have a delayed onset and reduced severity of CIA [48]. Arthritic SKG mice are rheumatoid-factor positive, but genetic deficiency of IL-6 suppresses the development of arthritis [49]. A deficiency of TNF-α and IL-1 has a similar effect, but not as a profound as the lack of IL-6 [49].

Recently, further autoimmune animal arthritis models have been developed. Mice with a point mutation of tyrosine 759 in gp130 develop autoimmune arthritis through insufficient clonal selection of T cells in the thymus, and an increase in the number of autoreactive antibodies [50]. These facts clearly indicate that IL-6 plays an important role in the pathogenesis of animal models and human RA.

IL-6-receptor-blocking treatment

A rat-antimouse IL-6R monoclonal antibody (MR16–1) was used to treat mice with CIA. MR16–1 significantly reduced the incidence and severity of CIA, and reduced the development of antibodies against type II collagen and the proliferative response of splenic lymphocytes to type II collagen [47]. MR16–1, however, had to be administrated on the first or third day of immunizing the mice with type II collagen, before arthritis developed. By contrast, anti-TNF and anti-IL-1 antibodies are effective even in established arthritis [51,52]. Humanized mouse-antihuman IL-6-receptor antibodies inhibit CIA in cynomolgus monkeys [53]. In a very interesting study, joint tissue of RA patients was grafted subcutaneously into severe combined immunodeficiency mice [54]. The implanted tissues were similar to those in human RA even 2 months after implantation. Intraperitoneal administration of IL-6-receptor antibodies reduced the volume of inflammatory tissue and the number of inflammatory cells, reduced synovial inflammation and prevented joint destruction, thereby decreasing matrix metalloproteinase production and the number of osteoclasts.

First human studies with IL-6-receptor blockade

During the last decade of the 20th century, a mouse monoclonal anti-IL-6-neutralizing monoclonal antibody (Mab anti-IL-6/BE8 Mab) was used to treat five patients with severe RA. BE8

Mab 10mg administered by daily infusion for 10 days resulted in significant clinical improvement and a reduction in CRP levels. Improvement seen in these patients lasted for 2 months [55].

Targeting IL-6 itself appears to be the appropriate method of IL-6 blockade, but it was observed that monomeric immune complexes of IL-6 formed when an antibody against the cytokine itself was used [56].

Tocilizumab

Chemistry

Tocilizumab (TCZ; previously known as MRA) is a humanized mouse-antihuman IL-6-receptor antibody of the κ-IgG1 subclass. It was humanized by grafting the complement-determining regions of mouse antihuman IL-6R Mab onto human IgG1 by recombinant DNA technology, thereby creating a functioning antigen-binding site in a reshaped human antibody [57]. The dissociation constant (kd value) of TCZ determined by Scatchand analysis using iodine (I^{125})-labelled TCZ was 2.54 ± 0.12 nmol (mean ± standard deviation) [20].

Pharmacology & pharmacokinetics

Nishimoto *et al.*, studied the pharmacology of TCZ in their dose-finding study. TCZ 2, 4 and 8 mg/kg was administered by intravenous infusion biweekly. Serum concentration of TCZ could be detected in all periods and all patients in only those cases treated with TCZ 8 mg/kg [58]. TCZ levels of 125 mg/ml were measured after the third infusion, which decreased to 40 mg/ml after 2 weeks. The area under the curve (AUC) and $T_{½}$ value increased after the first infusions and a $T_{½}$ of 241.8 ± 71.4 h was observed in the 8 mg/kg group after the third infusion.

First clinical studies with tocilizumab

In the first clinical trial in Japan, 11 patients with refractory RA were treated on a compassionate basis [59]. The patients received TCZ 50–100 mg once or twice a week. Three patients were withdrawn, one for developing anti-idiotypic antibodies. The remaining eight patients were treated for 8 weeks or longer. A total of 88% of patients had an ACR20 response and 50% had an ACR50 response. No major adverse events were associated with the treatment but a transient decrease of the neutrophil counts – mostly within the normal range – was observed in the majority of patients.

Phase I–II trials

In an open-label, Phase I–II, dose-escalation study in Japan, 15 RA patients with active disease were treated. TCZ was administered intravenously in 2, 4 and 8 mg/kg doses, biweekly for 6 months [58]. By week 24, 87% of patients achieved an ACR20 response, 33% ACR50 and 13% ACR70. SAA was normalized within weeks and the results were not dose dependent. A total of 70 adverse events occurred mainly in the TCZ group (14 out of 15 patients).

In the UK, a randomized double-blind, placebo-controlled, Phase I–II, dose-finding study was conducted [60]. Patients (n = 45) with active RA received either a single dose of 0.1 (n = 9), 1.0 (n = 9), 5.0 (n = 9) or 10.0 mg/kg (n = 7) of TCZ or placebo (n = 11). Erythrocyte sedimentation rate (ESR) and CRP levels normalized within 1 week in the 5 and 10 mg/kg dose groups. Patients were followed for 8 weeks. ACR20 response at 2 weeks following the single intravenous injection was the primary end point. Five patients in the 5 mg/kg dose group achieved this end point compared with none of the control group. This difference was maintained throughout 8 weeks. In the 10 mg/kg group, significant difference in ACR20 response was achieved only at week 6 compared with placebo.

Phase II trials

In the Japanese study, 164 RA patients with refractory disease were randomized to placebo (n = 53), TCZ 4 mg/kg (n = 54) or 8 mg/kg (n = 55) administered every 4 weeks for 3 months [61].

The primary outcome end point was an improvement of ACR20 response at week 12. Secondary end points were: DAS-28 score and ACR50 and -70 response. By week 12, 78 and 57% of patients in the 8 and 4 mg/kg groups, respectively, reached the ACR20 response level compared with 11% of patients on placebo. ACR50 response was observed in 40% of patients in the 8 mg/kg group, and 26% of patients in the 4 mg/kg group. ACR70 response was observed in 16% of the 8 mg/kg group, and in 20% of patients in the 4 mg/kg group. In the placebo group ACR50 and ACR70 responses. were 2% and 0%, respectively.

Moderate or good reduction of DAS-28 occurred in 91% of the TCZ 8 mg/kg group and 72% of the 4 mg/kg group, compared with 19% of patients who received placebo. CRP levels were normalized in 76 and 28% of patients in the 8 mg

and 4 mg/kg group, respectively, versus 19% of patients in the placebo group. Hemoglobin, platelet count, fibrinogen, SAA, rheumatoid factor and albumin levels also improved markedly, together with bone formation (osteocalcin and carboxy-terminal propeptide of type-1-procollagen) and bone resorption markers (urinary pyridinoline and deoxypyridinoline output).

In the European CHARISMA study, 356 RA patients with active disease and an inadequate response to MTX (≥10 mg/kg for 6 months) were randomly allocated to either MTX (≥10 mg/week) only, or 2 , 4 or 8 mg/kg TCZ, with or without the previous MTX dose [62]. Patients on TCZ received appropriate MTX placebo doses, while patients on MTX were given placebo infusions. Infusions were administered every 4 weeks for 12 weeks [62]. The primary end point, ACR20, was achieved at week 16 by 61 and 63% of the patients receiving monotherapy with 4 and 8 mg/kg of TCZ, respectively, compared with 41% of patients received placebo.

The improvements observed in of the 2 mg/kg group were no better than that of the placebo plus MTX-treated group. The ACR20 responses among patients receiving combination therapy with TCZ 2, 4 and 8 mg/kg plus MTX were 64, 63 and 74%, respectively. The secondary end points included ACR50 and -70 responses, individual disease-activity parameters, such as swollen and tender joint count, health assessment questionnaire (HAQ), EULAR remission rate (DAS-28 < 2.6), ESR, CRP levels and so on. At week 16, only combination treatment with TCZ 8 mg/kg plus MTX was better than placebo plus MTX, measured by ACR50 and -70 responses ($p < 0.05$). With the exception of the TCZ group on 2 mg/kg, all groups receiving TCZ alone or combined with MTX showed greater improvement than placebo plus MTX. In the 8 mg/kg TCZ plus MTX group, the mean DAS-28 decreased to 2.9 at week 16. The EULAR remission rate was achieved in 34% of patients assigned to TCZ 8 mg plus MTX, 17% in the group receiving TCZ 8 mg/kg monotherapy, and 8% in the placebo plus MTX group. Each of the individual clinical components of ACR response, as well as the duration of morning stiffness, showed an improvement in all doses of TCZ greater than or equal to 4 mg/kg.

The results of the Phase II trials are summarized in **Table 1**.

Phase III Trials

In one of the Japanese studies, 125 RA patients with inadequate response to MTX 8 mg/week (the recommended dose in Japan) were randomly allocated to TCZ 8 mg/kg infusion every 4 weeks plus MTX placebo (n = 61) [63], or TCZ 8 mg/kg infusion every 4 weeks plus MTX 8 mg/week [60]. Outcome end point at week 24 were DAS-28, EULAR response and ACR20, -50 and -70 responses, with

Table 1. Clinical efficacy of tocilizumab in Phase II clinical trials.

Trial	Dosage & administration (every 4 weeks for 3 months)	Efficacy (%)				C-reactive protein‡ (%)	Ref.
		ACR20	*ACR50*	*ACR70*	*DAS-28**		
Nishimoto *et al.* Randomized, placebo controlled trial, 164 patients with refractory RA	TCZ 4 mg/kg (n = 54)	57	26	20	72	26	[61]
	TCZ 8 mg/kg (n = 55)	78	40	16	91	76	
	placebo (n = 53)	11	2	0	19	1.9	
		Increase in bone formation and decrease in bone absorption markers					
Maini *et al.* Randomized double-blind, placebo-controlled trial, 359 active RA patients with inadequate response to MTX	TCZ 2 mg/kg (n = 54)	31	6	2	–		[62]
	TCZ 4 mg/kg (n = 54)	61	28	6	–		
	TCZ 8 mg/kg (n = 52)	63	41	16	17		
	Plus MTX 2 mg/kg (n = 52)	64	32	14	–		
	4 mg/kg (n = 49)	63	37	12	–		
	8 mg/kg (n = 49)	74	53	37	34		
	placebo +MTX (n = 49)	41	29	16	8		
		Significant reduction of erythrocyte sedimentation rate and CRP in all patient groups with the exception of TCZ 2 mg/kg monotherapy and placebo plus MTX					

**DAS-28 moderate or good improvement in percentage of patients.*

‡CRP normalized in percentage of patients.

CRP: C-reactive protein; DAS: Disease activity score; MTX: Methotrexate; RA: Rheumatoid arthritis; TCZ: Tocilizumab.

the primary end point being ACR20. Patients in the TCZ groups had an ACR20 or better response rate in 80.3% of patients compared with the 25.0% in the MTX group ($p < 0.001$). The patients on TCZ also demonstrated significantly higher ACR50 and 70 responses than patients on MTX alone: 49.2 versus 10.9% ($p < 0.001$) and 29.5 versus 6.3% ($p < 0.01$), respectively. DAS-28 scores decreased significantly (-3.95) in the TCZ groups, than in the MTX group (-1.069), and 43% of patients on TCZ went into remission (DAS-28 < 2.6) compared with 2% on MTX ($p < 0.001$). An overwhelming majority of patients (96.6%) on TCZ demonstrated moderate to good EULAR response compared with 39.7% of patient on MTX ($p < 0.001$).

In the SAMURAI study patients with relatively early (<5 years) active RA were evaluated [64].

Patients (n = 302) were randomly allocated to either TCZ 8 mg/kg four weekly or DMARDs. In the DMARD group, 67% of patients were on MTX and 37% on a combination of MTX and other DMARDs at the entry of the study. Anti-TNF-α blockers and leflunomide treatment were not allowed. The efficacy end points at week 52 included the change of modified total Sharp score (TSS) from baseline, (evaluated by two blinded readers) and ACR response rates. Laboratory values and adverse events were monitored for safety.

The two groups were similar at entry regarding duration of disease (2.4 ± 1.3 to 2.2 ± 1.4 years), DAS-28 score (6.5 ± 0.8 to 6.4 ± 0.9), CRP (47 ± 29 to 49 ± 29 mg/l) and modified TSS (28.3 ± 43.9 to 30.6 ± 42). At week 52, patients on TCZ showed significantly less radiological progression measured by TTS than those on DMARDs 2.3 (95% confidence interval [CI]: 1.5, 3.2) versus 6.1 (95% CI: 4.2, 8.0), $p = 0.01$). TCZ was also superior to DMARDs in preventing both joint erosion and joint-space narrowing ($p < 0.001$ and $p = 0.05$, respectively) ACR20, -50 and -70 response rates were 78, 64 and 44% in the TCZ group, respectively, and 34, 13 and 6% in the DMARD group ($p < 0.001$,) respectively. TCZ monotherapy significantly improved modified HAQ scores compared with conventional DMARDs ($p < 0.001$).

In the Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders (OPTION) study, Smolen *et al.* included 623 patients with moderate and severe RA patients with inadequate responds to MTX [65]. The primary end point was ACR20, but ACR50, -70, DAS-28 and EULAR responses were also assessed. All patients received MTX at their prestudy dose throughout the study (10–25mg weekly) while other DMARDs were discontinued at entry. The patients were randomly allocated to three groups: TCZ 8 mg/kg plus MTX, TCZ 4 mg/kg plus MTX and placebo plus MTX. ACR20 response at 24 weeks was observed in a significantly higher proportion of patients on TCZ 8 mg/kg (58.5%) and 4 mg/kg (47.9%) compared with patients receiving placebo plus MTX (26.5%; $p < 0.0001$). The number of patients with ACR50 and -70 responses was significantly higher in both the TCZ-treated groups compared with the placebo plus MTX group (0.15%; $p < 0.0001$). EULAR response was also significantly better in both TCZ groups compared with patients receiving only placebo plus MTX ($p < 0.0001$). TCZ was well tolerated, with an adverse event profile consistent with data previously reported. The improvement of health-related quality of life from the same study was reported separately [66]. HAQ scores, both the physical and mental components of Short Form-36, and the Functional Assessement of Chronic Illness Therapy – fatigue scale (FACIT – fatigue scale), was improved in both TCZ-treated groups compared with the placebo plus MTX-treated group.

The clinical results of Phase III trials, with the exception of radiological progression and health-related quality of life studies are shown in **Table 2**.

Long-term study

In an open-label, long-term extension [67] of the Phase II trial completed by Nishimoto *et al.* [61], 143 RA patients were treated with TCZ 8 mg/kg every 4 weeks. A total of 96 (67%) of these patients continued TCZ treatment until January 2007. A total of 86 patients received TCZ for 5 years or more and concomitant treatment with NSAIDs and prednisolone (≤10 mg) was allowed. Mean duration of treatment was 62.8 months. A total of 32 patients (22%) were withdrawn owing to side effects, one for lack of efficacy and 14 patients (10%) for other reasons. At the 5-year assessment, 84.2% of patients met ACR20 criteria for improvement, 63.4% met ACR50 and 44.7% met ACR70. The baseline DAS-28 (6.7) was reduced to 3.1 at 12 months and 2.6 at 5 years. Out of the 84 patients receiving corticosteroids, 74 (88.1%) decreased their corticosteroid dose and 34 (40.5%) discontinued corticosteroid treatment.

Table 2. Clinical efficacy of tocilizumab in Phase III clinical trials.

Trial	Dosage & administration	Efficacy				Ref.
		ACR20 (%)	*ACR50 (%)*	*ACR70 (%)*	*DAS-28 decrease*	
Nishimoto *et al.* Randomized, double-blind with 125 active RA patients. Inadequate response to MTX comparing TCZ 8 mg/kg with MTX 8 mg/week (TCZ every 4 weeks for 24 weeks)	TCZ 8 mg/kg (n = 61)	80.3	40	29.5	-3.215	[63]
	8 mg/week MTX (n = 64)	25	10.9	6.3	-1.069	
Nishimoto *et al.* Randomized controlled trial 302 RA patients comparing TCZ with DMARDs (TCZ every 4 weeks for 52 weeks)	TCZ 8 mg/kg (n = 157)	78	64	44		[64]
	DMARDs (n = 145)	34	13	6		
Smolen *et al.* Randomized, double-blind trial 623 patients with moderate and severe RA. Inadequate response to MTX (TCZ every 4 weeks for 24 weeks)	TCZ 4 mg/kg plus MTX (n = 214)	47.9	31.5	12.2	-2.6	[65]
	TCZ 8 mg/kg plus MTX (n = 205)	58.5	43.9	22.0	-3.43	
	Placebo plus MTX (n = 204)	26.5	10.8	2.0	-1.55	

DAS: Disease activity score; MTX: Methotrexate; RA: Rheumatoid arthritis; TCZ: Tocilizumab.

Summary of clinical efficacy of toculizumab

- Good clinical effects were measured by ACR20, -50 and -70 responses, EULAR remission criteria and a decrease of DAS-28 comparable with that of TNF-α blockers;
- Excellent results were seen regarding acute-phase reactants: CRP and ESR normalization were seen to occur in a very short time. Normalizing of SAA may prevent amyloidosis;
- TCZ decreased radiological progression as measured by modified Sharp score;
- HAQ, physical and mental components of Short Form-36 and FACIT – fatigue scores, significantly improved;
- TCZ improves both bone formation and resorption markers, which raises the possibility that TCZ can be used for the prevention and/or treatment of osteoporosis accompanying RA;
- Combination with MTX may improve efficacy.

Unfortunately, there are no trials comparing TCZ with TNF-α-blocking treatment or studies of TCZ in nonresponders with TNF-α-blocking treatment.

Safety & tolerability

Reactivation of Epstein–Barr virus infection

Although TCZ was generally well tolerated – withdrawal rate was low and few side effects occurred – in the first dose-finding, open-label trial, a lethal side effect was registered: reactivation of Epstein–Barr virus (EBV) infection-associated with haemophagocytosis syndrome [58,68]. Retrospectively, EBV-DNA positivity was found in this patient's plasma and in samples taken before entering the trial. EBV-DNA positivity was not found in any other cases through the retrospective screening of patients' blood samples. EBV DNA, however, was found in the blood cells of several patients, but these patients exhibited no corresponding side effects during the trial. Furthermore, EBV-DNA positivity disappeared from the blood of some patients during the course of treatment. EBV positivity is common in the normal population and also in RA patients. This issue therefore requires further thorough research. Screening for latent EBV infection seems to be important before treatment with TCZ.

Other infections

Seven cases of severe infections were observed in the CHARISMA study, four in the TCZ 2 mg/kg group and three in the TCZ 8 mg/kg plus MTX group [62]. In the OPTION study, 11 serious infections were reported, two of them in the placebo group [65]. In the SAMURAI study, 12 serious infections occurred in the TCZ group and eight in the DMARD group [64].

In the only long-term study, 0.06 serious infections/patients/year have been reported in a total of 588 patients/year. No lethal outcome was reported. Other mild, mixed viral and bacterial infections of the upper respiratory tract were observed in several studies. No cases of tuberculosis were observed.

Hypersensitivity & development of antibodies

Hypersensitivity reactions were only reported in the CHARISMA study [62]. Anaphylaxis occurred in five out of the 102 patients. With

one exception, all were in the TCZ 2 or 4 mg/kg monotherapy groups. Smaller doses administered without MTX seem to be more dangerous regarding the risk of hypersensitivity. During the CHARISMA study, anti-TCZ antibodies developed in 25 patients. All those were in the TCZ 2 and 4 mg/kg monotherapy groups, clearly demonstrating a protective effect of MTX. In the other Phase II Japanese study [61], only two patients, and in the SAMURAI study only four patients, developed anti-TCZ antibodies [64]. There was no increase in autonuclear antibodies (ANA) or anti-DNA antibodies; this seems to be an advantage compared with TNF-α-blocking treatment, which induced anti-dsDNA antibodies in 16% of patients [69]. It is of practical importance that TCZ did not affect the success of influenza vaccination [70].

Neutropenia, liver enzyme & lipid-level elevations

Transient neutropenia and a rise in liver enzymes frequently occurred, but both abnormalities normalized in the course of the studies. Raised serum bilirubin levels were also noticed [62], but this was not associated with amino alaninetransferase and aspartate aminotransferase elevation.

Certainly the most intriguing laboratory abnormality shown in all studies was the rise of total cholesterol, high-density lipoprotein-cholesterol and triglyceride levels. These levels were stabilized during the course of the treatment and did not tend to rise further even in the long-term trial [67]. The atherogenic index did not change either in the CHARISMA or in the SAMURAI studies, and no cardiovascular effects were observed. IL-6 certainly decreases serum cholesterol in cancer patients [71,72] and increases inflammation of chronic disease. Cholesterol level elevation may be related to the suppression of inflammation [73] and has also been observed as a side effect of infliximab treatment for RA [74]. The change in cholesterol and lipid levels requires further research, especially because it is well known that the risk of cardiovascular disease is increased in RA [75].

Malignancies

In the SAMURAI study three cases of malignancies were reported in the TCZ group, but non in the DMARD group. Incidence of malignancies in Japanese patients receiving TCZ has been found to be almost equivalent to those in an observational cohort of Japanese RA patients and Japanese population data [76].

Effect of tocilizumab on amyloid A amyloidosis

Amyloid A (AA) amyloidosis occurs in 5% of adults with RA in Europe [77] and is responsible for half of the deaths caused by juvenile rheumatoid arthritis (JIA) [78]. AA amyloidosis is the deposition of AA amyloid fibrils in different organs – especially in the kidneys – disrupting their structure. AA amyloid fibrils derive from circulating acute-phase reactant SAA proteins [79]. The outcome of AA amyloidosis is favorable when SAA concentration is maintained below 10 mg/l by rigorous treatment of underlying disease, specifically, RA. TNF-α blocking may improve AA amyloidosis complicating inflammatory arthritides [80,81].

IL-6 has been demonstrated to be the key cytokine for SAA production [82]. As we have seen, IL-6R blockage causes rapid reduction of serum SAA concentrations in RA patients. Animal experiments show that anti-IL-6R antibody inhibits murine AA amyloidosis [83]. In children with JIA complicated by severe AA amyloidosis, TCZ treatment normalized SAA levels, eliminated all clinical symptoms, and marked regression of amyloid deposition was observed [84].

Further long-term controlled trials are necessary for obtaining appropriate information concerning long-term efficacy and safety.

Conclusion

It can be concluded that TCZ treatment of RA significantly reduces inflammatory activity and modified Sharp score, moreover, it quickly normalizes CRP and SAA levels. Concomitant treatment with MTX further increases clinical efficacy. Future studies concerning the long-term effect on disease activity, joint destruction and quality of life measurement are clearly required.

TCZ safety seems satisfactory. The lethal outcome of the treatment caused by the reactivation of EBV infection in one patient indicates that patients may require screening for chronically activated EBV infection before and during treatment.

The clinical significance of elevation of some lipid levels requires further study. The other side effects that occured were usually mild and transient. TCZ treatment of RA is a promising treatment opportunity, especially long-term, trials are clearly needed.

Future perspective

IL-6 plays an important role in the pathogenesis of RA. Full-dose TCZ treatment normalizes CRP and SAA, as well as VEGF levels,

indicating that this treatment controls both the exsudative and proliferative phase of rheumatoid inflammation. Should the side-effect profile prove satisfactory, TCZ treatment may be used even in early RA, presumably combined with MTX treatment. TCZ also appears promising in the prevention and treatment of osteoporosis and amyloidosis complicating RA.

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Executive summary

Mechanism of action

- Tocilizumab (TCZ) binds both to the soluble and membrane bound IL-6 receptors, blocking IL-6 signaling to the cells.
- By this mechanism it inhibits IL-6 induced T- and B-cell differentiation, production of acute-phase proteins, immunoglobulins and rheumatoid factors, normalizes VEGF levels, increases bone formation and decreases bone absorption markers.

Clinical efficacy

- Short-term clinical efficacy of TCZ has been demonstrated in rheumatoid arthritis (RA), reflected by ACR and EULAR remission criteria, and a decrease in the disease activity score (DAS)-28.
- C-reative protein (CRP) and serum amyloid A (SAA) levels normalized during full dose (8 mg/kg) TCZ treatment.
- Methotrexate (MTX) cotreatment seems to improve the clinical efficacy of TCZ.
- In the only study assessing x-ray damage, radiological progression was significantly decreased.
- TCZ improves joint function in RA and the health-related quality of life.

Safety

- TCZ seems to be well tolerated. Severe adverse effects, including severe infections, occurred rarely. Nonsevere infections, first and foremost nasopharyngitis, were frequently seen.
- Reactivation of Epstein–Barr virus (EBV) infection was lethal in one patient. TCZ treatment should be avoided in cases of chronically active EBV infection.
- Anti-TCZ antibodies developed rarely; in 25 patients of the CHARISMA study on TCZ 2–4 mg/kg, two patients in the Japanese Phase I–II study and in four patients in the SAMURAI study.
- No occurrence of anti-DNA antibodies or development of autoimmune disease has been observed until now.
- No cases of tuberculosis reactivation have occurred to date.
- Anaphylaxis was seen in a few cases, mostly on low dose.
- Increased total cholesterol, high-density lipoprotein-cholesterol and triglyceride levels were frequently seen, but the levels were stabilized at the upper limit of normal, even in the long-term trial. The atherogenic index did not change and no cardiac side-effects were observed.
- Neutropenia and raised liver enzyme serum levels were frequently seen, but usually returned to the normal level during treatment.

Dosage & administration

- TCZ 8 mg/kg administered in slow intravenous infusions every 4 weeks seems to be the effective dose.
- Cotreatment with MTX may improve the results.

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