

Tocilizumab for the treatment of rheumatoid arthritis

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Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody, which binds to circulating soluble IL-6 receptor and membrane-expressed IL-6 receptor, inhibiting IL-6 binding to both forms of IL-6 receptor. Several Phase III clinical trials demonstrate the clinical efficacy of tocilizumab as monotherapy or with disease-modifying anti-rheumatic drugs for adult patients with moderately to severely active rheumatoid arthritis. Tocilizumab in combination with methotrexate after 24 weeks of treatment could induce disease remission in 30% of patients with rheumatoid arthritis refractory to anti-TNF antagonist therapy. The most common adverse reactions reported in clinical studies are upper respiratory tract infection, nasopharyngitis, headache, hypertension and mild, reversible increases in alanine aminotransferase enzymes. Serious adverse reactions include infections, gastrointestinal perforations and hypersensitivity reactions, including anaphylaxis. The clinical efficacy and safety of tocilizumab has led to the approval of this innovative drug for the treatment of rheumatoid arthritis in more than 70 countries worldwide.

KEYWORDS: anti-IL-6 receptor monoclonal antibody • IL-6 • rheumatoid arthritis • tocilizumab

IL-6 is a multifunctional cytokine. It was first recognized as a T-cell-derived factor, which induces B-cell differentiation into antibody-producing cells. This cytokine was variously known as B-cell differentiation factor, B-cell-stimulating factor-2, IFN- β 2, 26-kDa protein, hybridoma growth factor and hepatocyte-stimulating factor before it was recognized that all these entities were identical and the name was unified as IL-6. Subsequent *in vitro* studies and analysis of IL-6 transgenic mice have shown that IL-6 acts not only on B cells but also on T cells, hepatocytes, hematopoietic progenitor cells and neuronal cells, and performs various functions (FIGURE 1) [1–3]. Despite a wide range of biological activities, IL-6-deficient mice grow well except for a lower immune response, which indicates that IL-6 is induced by injury or infection and acts as an SOS signal [4].

Human IL-6 is a secreted 21-kDa glycoprotein containing 185 amino acids with two intramolecular disulphide bridges in the mature protein. The IL-6 receptor system consists of two chains, the 80-kDa IL-6-binding subunit, IL-6 receptor (IL-6R), with a short cytoplasmic domain, and the signal transducer 130-kDa membrane glycoprotein gp130 (FIGURE 2). IL-6R and gp130 constitute a high-affinity binding site for IL-6 by means of the

following mechanism. After binding of IL-6 to IL-6R, the resultant IL-6/IL-6R complex associates with gp130 and induces homodimerization of gp130, which triggers activation of Janus kinase family tyrosine kinases [5,6]. Tyrosine-phosphorylated gp130 then recruits and activates signal transducer and activator of transcription (STAT)3 and SH2-domain containing protein tyrosine phosphatase-2. Next, activated STAT3 forms homodimers, translocates into the nucleus and regulates transcription for various sets of genes [7]. SH2-domain-containing protein tyrosine phosphatase-2 associates with adaptor molecule growth factor receptor-bound protein 2, activates son of sevenless (SOS)/Ras and then the downstream Raf–MEK–MAP kinase pathway. After a series of IL-6 signal transductions, the activated STAT3 induces suppressor of cytokine signaling, which attenuates the IL-6 signal as a negative feedback molecule [8]. Soluble forms of IL-6R (sIL-6R) and gp130 (sgp130) are both present in human serum and modify the functions of IL-6 [9]. sIL-6R binds to IL-6 and transduces the IL-6 signal onto the IL-6R-negative/gp130-positive cells, while sgp130 inhibits binding of the IL-6/sIL-6R complex to cell-surface gp130. IL-6R is a unique binding receptor for IL-6, whereas gp130 is shared

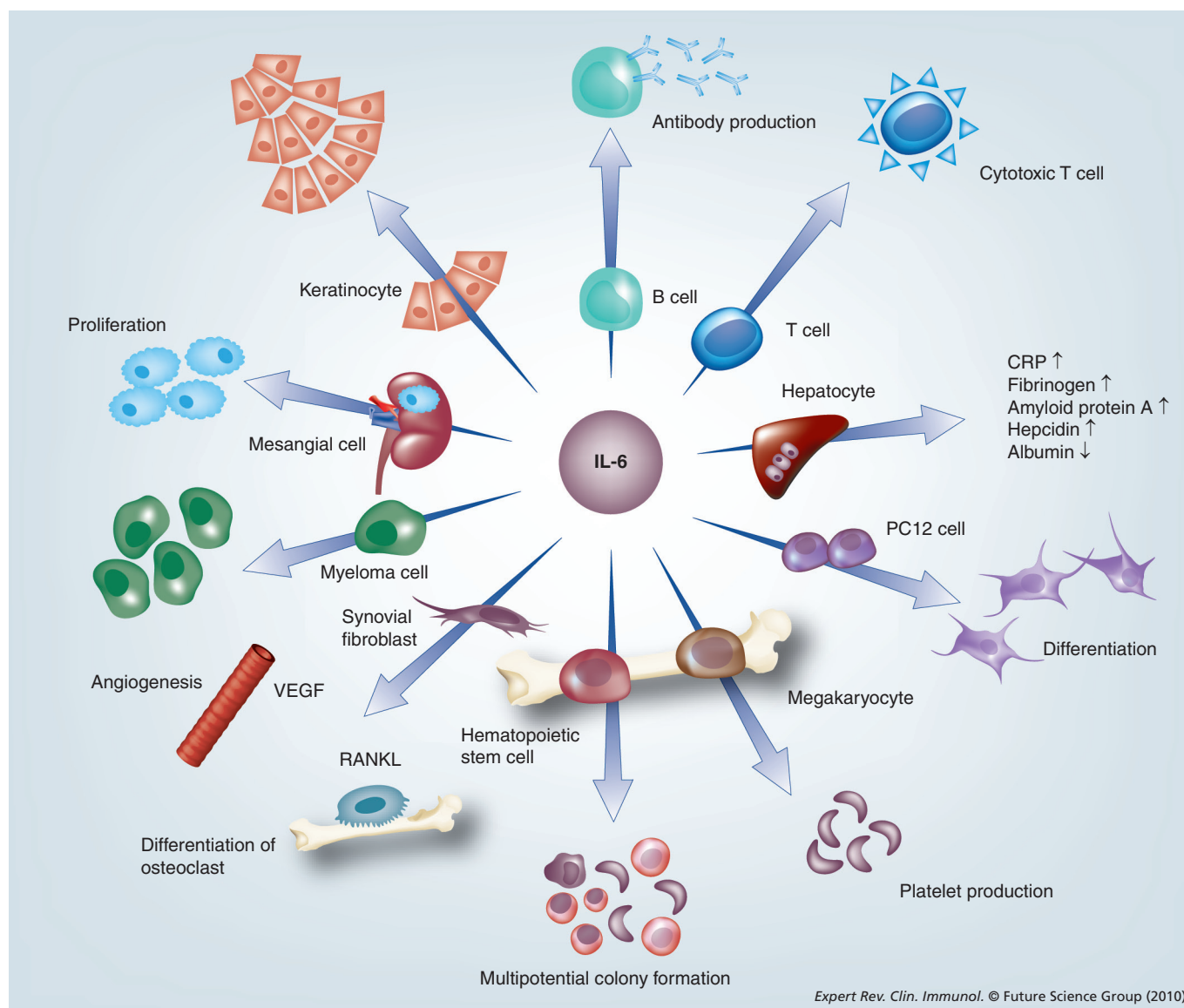


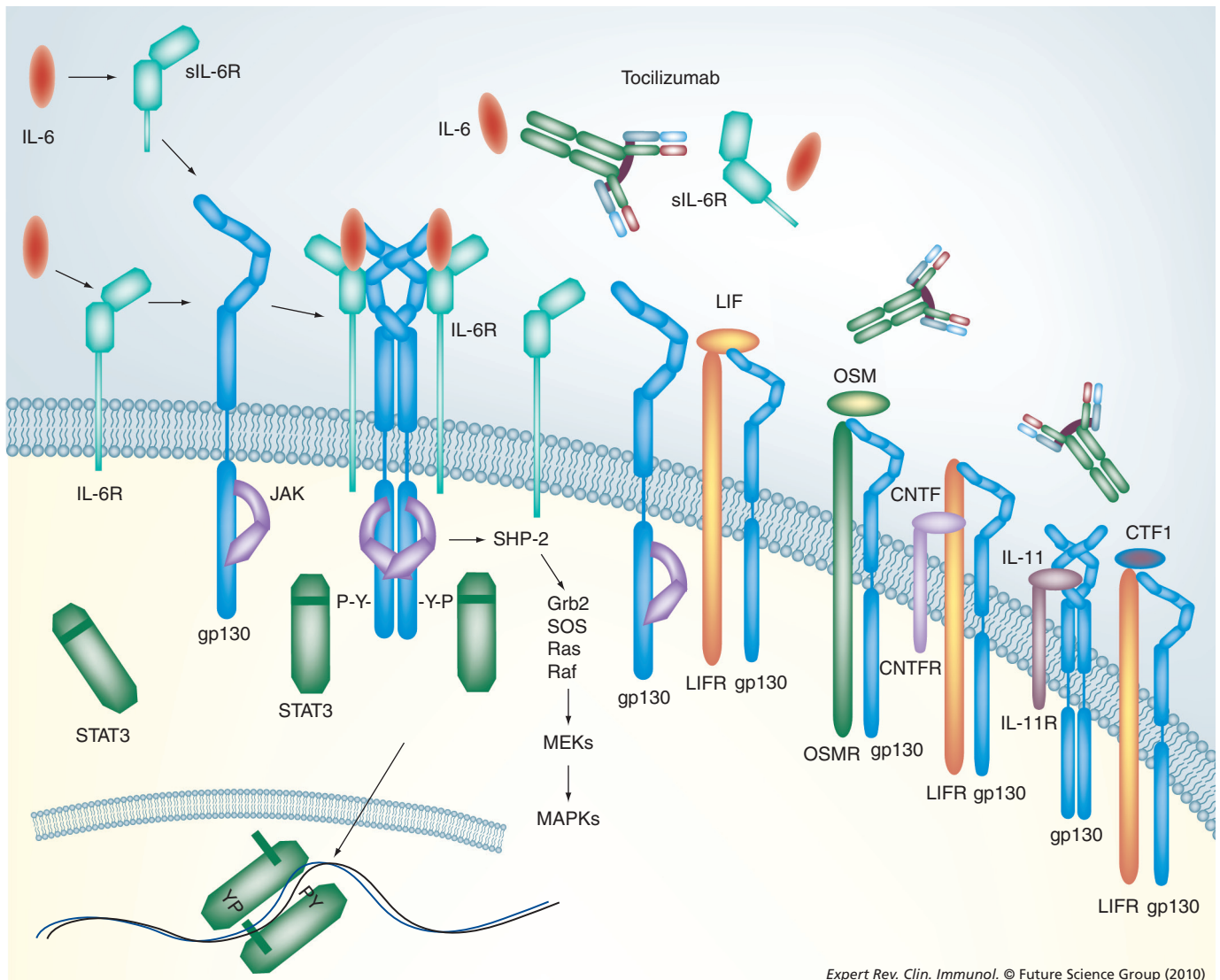
Figure 1. Multifunctional cytokine IL-6. IL-6 induces cell differentiation or specific gene expression, immunoglobulin induction in B cells, cytotoxic T-cell differentiation, production of acute-phase proteins in hepatocytes, neuronal cell differentiation, maturation of megakaryocytes to platelets and activation of hematopoietic stem cells. IL-6 acts on synovial fibroblast cells to produce VEGF and RANKL to promote angiogenesis and differentiation of osteoclasts. Furthermore, IL-6 stimulates the growth of cells such as myeloma/plasmacytoma cells, mesangial cells and keratinocytes.

CRP: C-reactive protein; RANKL: Receptor activator of nuclear factor- κ B ligand.

by IL-6 family cytokines including leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, IL-11 and cardiotrophin 1. These cytokines often show overlapping functions with those of IL-6. The model in which various cytokines use the common signal transducer gp130 explains why various cytokines show functional redundancy [10].

While basic studies have focused on identification of the IL-6 signaling pathway from cell surface receptors to the IL-6-induced transcriptional regulation in the nucleus, clinical studies have identified the effects of IL-6 on various inflammatory diseases such as cardiac myxoma, Castleman's disease and rheumatoid arthritis (RA) [11–13]. These diseases show fever, increased level of

acute-phase proteins, hypergammaglobulinemia, elevated erythrocyte sedimentation rate, thrombocytosis and anemia. Evidence from several studies has clarified the relationship between IL-6 and inflammatory symptoms. For example, inflammation disappeared after the surgical removal of myxoma, and production of IL-6 was observed in an *in vitro* culture of myxoma cells [11]. Moreover, IL-6 was identified in hyperplastic lymph nodes of Castleman's disease patients, and reduction of serum IL-6 and clinical improvement was observed after surgical removal of the hyperplastic lymph node [12]. High levels of IL-6 were detected in synovial fluids from RA patients, but not from osteoarthritis patients [13].



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Figure 2. IL-6 receptor system and common signal transducer gp130. IL-6 induces homodimerization of gp130 and activates JAK family tyrosine kinases, while JAKs induce tyrosine phosphorylation of gp130 and recruitment of STAT3 via the SH2 domain, followed by phosphorylation of STAT3 by JAKs and translocation into the nucleus to regulate gene activation. Recruitment of SHP-2 to gp130 leads via Grb2 to activation of SOS/Ras, followed by activation of the Raf–MEK–MAP kinase pathway. An anti-IL-6R antibody, tocilizumab, binds to soluble and membranous IL-6R and competitively blocks binding of IL-6 to IL-6R or sIL-6R. Gp130 is shared with IL-6 family cytokines including LIF, OSM, CNTF, IL-11 and CTF1.

CNTF: Ciliary neurotrophic factor; CTF1: Cardiotrophin 1; IL-6R: IL-6 receptor; JAK: Janus kinase; LIF: Leukemia inhibitory factor; LIFR: Leukemia inhibitory factor receptor; OSM: Oncostatin M; OSMR: Oncostatin M receptor; sIL-6R: Soluble IL-6 receptor; SOS: Son of sevenless; STAT: Signal transducer and activator of transcription.

Rheumatoid arthritis is a chronic, progressive inflammatory disease of the joints and surrounding tissues that is associated with intense pain, irreversible joint destruction and systemic complications [14]. The biological activities of IL-6 and its elevation in serum as well as synovial fluids in patients with RA indicate that IL-6 is one of the key cytokines involved in the development of RA. Indeed, the significant role of IL-6 in the development of arthritis was confirmed by analysis of a mouse model. Compared with severe arthritis and extensive damage to articular cartilage in wild-type mice, IL-6-deficient mice showed mild arthritis and well-preserved articular cartilage after the induction of antigen-induced arthritis [15]. These

findings have led to the notion that IL-6 blockade could be a novel treatment approach for RA and, for this purpose, tocilizumab, a humanized anti-IL-6R monoclonal antibody, was developed.

Introduction to the drug

Tocilizumab is a humanized anti-human IL-6R monoclonal antibody of the IgG1 class that was generated by grafting the complementarity-determining regions of a mouse anti-human IL-6 antibody onto human IgG1. Tocilizumab blocks IL-6-mediated signal transduction through inhibition of IL-6 binding to membrane and sIL-6R (FIGURE 2).

The pharmacokinetic properties of tocilizumab were determined by treatment of RA patients with tocilizumab using a 1-h infusion of 4 or 8 mg/kg every 4 weeks for 24 weeks [101]. The following estimated parameters (predicted mean + standard deviation) were obtained for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state AUC of 35000 ± 15500 h $\mu\text{g/ml}$, trough concentration ($C_{\min}$) of 9.74 ± 10.5 $\mu\text{g/ml}$ and maximum concentration ($C_{\max}$) of 183 ± 85.6 $\mu\text{g/ml}$, while the accumulation ratios for AUC and $C_{\max}$ were low: 1.22 and 1.06, respectively. The accumulation ratio was higher for $C_{\min}$ (2.35), which was expected based on the non-linear clearance contribution at lower concentrations. Steady state for $C_{\max}$ was reached following the first administration and for AUC and $C_{\min}$ after 8 and 20 weeks, respectively. Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab is concentration dependent and constitutes the sum of the linear and non-linear clearance. The linear clearance, estimated as a parameter in the population pharmacokinetic analysis, was 12.5 ml/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, clearance at higher tocilizumab concentrations is mainly determined by the linear clearance. The half-life of tocilizumab was found to be concentration dependent. Once steady state had been reached following a dose of 8 mg/kg

every 4 weeks, the effective half-life decreased, with a decrease in concentrations within a dosing interval from 14 to 8 days. Pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and $C_{\min}$ was observed for doses of 4 and 8 mg/kg every 4 weeks, while $C_{\max}$ increased dose-proportionally. At steady state, predicted AUC and $C_{\min}$ were, respectively, 2.7- and 6.5-fold higher at 8 mg/kg than at 4 mg/kg.

Clinical studies

The summaries of Phase I/II and Phase III clinical studies are shown in TABLES 1, 2 & 3.

A randomized double-blind placebo-controlled dose-escalation Phase I trial was performed in the UK [16]. Patients were sequentially allocated to receive a single intravenous dose of 0.1, 1, 5 or 10 mg/kg of tocilizumab or placebo. At week 2, a significant difference was observed between the patients treated with 5 mg/kg of tocilizumab and with placebo, with five patients (55.6%) in the tocilizumab cohort and none in the placebo cohort achieving American College of Rheumatology (ACR)20 improvement.

An open-label Phase I/II clinical study was performed in Japan [17]. Patients with active RA were intravenously infused with three doses (2, 4 or 8 mg/kg) of tocilizumab biweekly for 6 weeks, after which a pharmacokinetic assessment was performed. After continuation of the tocilizumab treatment for

Table 1. Phase I and II clinical trials for rheumatoid arthritis patients.

Study	Year reported	Population studied	Design & country	Objective	Duration	Patients (n)	Treatment	Conclusion	Ref.
	2002	DMARDs IR	Phase I UK	Efficacy and safety of a single injection of TCZ	2 weeks	45	0.1, 1, 5 and 10 mg/kg TCZ or placebo	Well tolerated and efficacious in 5 and 10 mg/kg TCZ	[16]
MRA002JP MRA003JP	2003		Phase I/II Japan	Efficacy (ACR20), tolerability and long-term safety of TCZ	6 weeks	15	2, 4 and 8 mg/kg TCZ biweekly for 6 weeks and maintained by 8 mg/kg TCZ every 4 weeks	Well tolerated and efficacious	[17]
MRA004JP	2004		Phase II Japan	Efficacy (ACR20) of TCZ versus placebo	12 weeks	162	4 and 8 mg/kg TCZ or placebo at weeks 0, 4 and 8	8 mg/kg TCZ is better than placebo. TCZ at 8 mg/kg is better than at 4 mg/kg	[18]
CHARISMA	2006	MTX IR	Phase II Europe	Efficacy (DAS28, ACR20) and safety of TCZ	16 weeks	359	2, 4 and 8 mg/kg TCZ with or without MTX, and placebo	Well tolerated. 4 and 8 mg/kg TCZ is better than placebo	[19]
MRA010JP (STREAM)	2009		Phase II Japan	Long-term efficacy (ACR20) and safety of TCZ	5-year extension	143	8 mg/kg TCZ every 4 weeks	Well tolerated and efficacious	[20]

ACR: American College of Rheumatology; DMARD: Disease-modifying antirheumatic drug; IR: Inadequate response; MTX: Methotrexate; TCZ: Tocilizumab.

24 weeks, the patients were assessed for safety and efficacy of the drug. The findings were that treatment was well tolerated at all doses with no severe adverse events (AEs). Although there was no statistically significant difference in efficacy among the three dose groups, nine out of 15 patients achieved ACR20 at week 6, and 86 and 33% of patients achieved ACR20 and ACR50, respectively, at week 24.

A 12-week, double-blind multicenter placebo-controlled late Phase II trial was also performed in Japan [18]. Patients were randomized to either tocilizumab administration of 8 or 4 mg/kg every 4 weeks or placebo. At week 12, ACR20 response was observed in 78, 57 and 11% of RA patients treated with tocilizumab 8 mg/kg, 4 mg/kg and in the control groups, respectively, and ACR50 response in 50% of patients treated with tocilizumab

Table 2. Phase III clinical trials for rheumatoid arthritis.

Study	Year reported	Population studied	Design & country	Objective	Duration	Patients (n)	Treatment	Conclusion	Ref.
NCT00144508 (SAMURAI)	2007	DMARDs IR	Phase III Japan	Efficacy (modified Sharp score) and safety of TCZ	52 weeks	302	8 mg/kg TCZ or placebo every 4 weeks versus conventional DMARDs	TCZ is better than DMARDs	[21]
NCT00106574 (TOWARD)	2008	DMARDs IR	Phase III International	Efficacy (ACR20/50/70, DAS remission) of TCZ plus DMARDs versus DMARDs	24 weeks	1216	8 mg/kg TCZ plus DMARDs every 4 weeks or traditional DMARDs	TCZ plus DMARDs is better than traditional DMARDs alone	[22]
NCT00106522 (RADIATE)	2008	Anti-TNF IR	Phase III International	Efficacy (ACR20, DAS28) of TCZ plus MTX versus MTX in TNF antagonists failure	24 weeks	489	4 mg/kg TCZ plus MTX, 8 mg/kg TCZ plus MTX, or MTX every 4 weeks	Both doses of TCZ plus MTX are better than MTX	[23]
NCT00106548 (OPTION)	2008 2010	MTX IR	Phase III International	Efficacy (ACR20) of TCZ plus MTX versus MTX	24 weeks	623	4 mg/kg TCZ plus MTX, 8 mg/kg TCZ plus MTX, or MTX every 4 weeks	Both doses of TCZ plus MTX are better than MTX	[24] [25]
MRA213JP (SATORI)	2009	MTX IR	Phase III Japan	Efficacy (ACR20, DAS28) of TCZ versus MTX	24 weeks	125	8 mg/kg TCZ every 4 weeks versus 8 mg/week MTX	TCZ is better than MTX	[26]
WA1823 (LITHE)	2009	MTX IR	Phase III International	Efficacy (ACR20, modified Sharp score, HAQ) or TCZ plus MTX versus MTX	2 years	1186	4 mg/kg TCZ plus MTX, 8 mg/kg TCZ plus MTX, or MTX	Both doses of TCZ plus MTX are better than MTX	[27]
NCT00109408 (AMBITION)	2010	MTX, anti-TNF naive	Phase III International	Efficacy (ACR20, DAS28) of TCZ monotherapy versus MTX monotherapy	24 weeks	570	8 mg/kg TCZ every 4 weeks or MTX (7.5–20 mg/week)	TCZ is better than MTX	[28]

ACR: American College of Rheumatology; Anti-TNF: Anti-tumor necrosis factor; DAS: Disease activity score; DMARD: Disease-modifying antirheumatic drug; IR: Inadequate response; MTX: Methotrexate; TCZ: Tocilizumab; TNF: Tumor necrosis factor.

Table 3. Summary of the efficacy of tocilizumab in Phase III trials.

Study	Day at evaluation	Treatment arms	Patients (n)	Response rates (%)			Remission rate (%)	Radiological progression from baseline		
				ACR20	ACR50	ACR70	DAS28 < 2.6	Total Sharp score	Erosion score	Joint space narrowing score
SAMURAI	52 weeks	TCZ (8 mg/kg) DMARDs	157	78	64	44	59	2.3	0.9	1.5
			145	34	13	6	3	6.1	3.2	2.9
TOWARD	24 weeks	TCZ (8 mg/kg) + DMARDs	803	61	38	21	30			
			413	25	9	3	3			
RADIATE	24 weeks	TCZ (4 mg/kg) + MTX	161	30	17	5	8			
		TCZ (8 mg/kg) + MTX	170	50	29	12	30			
		Placebo + MTX	158	10	4	1	2			
OPTION	24 weeks	TCZ (4 mg/kg) + MTX	214	48	31	12	13			
		TCZ (8 mg/kg) + MTX	205	59	44	22	27			
		Placebo + MTX	204	26	11	2	1			
SATORI	24 weeks	TCZ (8 mg/kg) MTX	61	80	49	30	43			
			64	25	11	6	2			
LITHE	52 weeks	TCZ (4 mg/kg) + MTX	395	47	29	16	30	0.34	0.21	0.13
		TCZ (8 mg/kg) + MTX	398	56	36	20	47	0.29	0.17	0.12
		MTX	393	25	10	4	8	1.13	0.71	0.42
AMBITION	24 weeks	TCZ (8 mg/kg)	286	70	44	28	34			
		MTX	284	53	34	15	12			

ACR: American College of Rheumatology; DAS28: Disease activity score using 28 joint counts; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; TCZ: Tocilizumab.

8 mg/kg. The respective overall incidences of AEs were 56, 59 and 51% for the placebo, 4 and 8 mg/kg groups. These findings confirmed the safety and tolerability of tocilizumab.

The Chugai Humanized Antirheumatic Interleukin Six Monoclonal Antibody (CHARISMA) study was a Phase II, double-blind placebo-controlled multicenter trial of tocilizumab [19]. Active RA patients with an inadequate response to methotrexate (MTX) were randomized to one of the following seven treatment arms: tocilizumab at doses of 2, 4 or 8 mg/kg either as monotherapy or in combination with MTX, or MTX plus placebo. ACR20 response at week 16 was achieved by 61 and 63% of patients receiving 4 and 8 mg/kg of tocilizumab as monotherapy, respectively, and by 63 and 74% of patients receiving the same doses of tocilizumab plus MTX, respectively, compared with 41% of patients receiving placebo plus MTX. Statistically significant ACR50 and ACR70 responses were observed in patients receiving combination therapy with either 4 or 8 mg/kg of tocilizumab plus MTX ($p < 0.05$) [19]. Tocilizumab was mostly well tolerated. However, anti-tocilizumab antibodies were produced in approximately 25% of the tocilizumab 2-mg/kg monotherapy group.

The Long-term Safety and Efficacy of Tocilizumab, an Anti-IL-6 Receptor Monoclonal Antibody, in Patients with Rheumatoid Arthritis (STREAM) study was an open-label, long-term extension trial following an initial 3-month randomized Phase II trial [20]. This study investigated the safety and efficacy of tocilizumab monotherapy (8 mg/kg) administered every 4 weeks over a 5-year period. Concomitant therapy with NSAIDs and/or oral prednisolone (10 mg daily maximum) was permitted. Of the 143 patients enrolled in this trial, 94 (66%) patients completed the 5-year study and were analyzed. Overall, 32 patients (22%) withdrew from the study due to AEs. The serious AE rate was 27.5 events per 100 patient-years (pt-yr), with 5.7 serious infections per 100 pt-yr, based on a total tocilizumab exposure of 612 pt-yr. After 5 years, 84.0, 69.1 and 43.6% of the patients met improvement criteria for ACR20, ACR50 and ACR70, respectively. The disease activity score using 28 joint counts (DAS28) remission rate was 55.3%. These findings proved the sustained long-term efficacy and generally good safety profile of tocilizumab monotherapy.

The Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI) study was

the first Phase III double-blind placebo-controlled multicenter trial of tocilizumab [21]. Patients were allocated to receive either tocilizumab monotherapy at 8 mg/kg intravenously every 4 weeks or conventional disease-modifying antirheumatic drugs (DMARDs) for 52 weeks. At week 52, the tocilizumab group showed statistically significantly less radiographic change in total van der Heijde's modified Sharp score (mean 2.3; 95% CI: 1.5–3.2) than the DMARD group (mean 6.1; 95% CI: 4.2–8.0; $p < 0.01$). Signs and symptoms also improved with tocilizumab monotherapy. The respective overall incidences of AEs were 89 and 82%, of serious AEs were 18 and 13%, and of serious infections were 7.6 and 4.1% for the tocilizumab and DMARD groups, respectively. These findings indicate that tocilizumab monotherapy was generally well tolerated and provided radiographic benefit for patients with RA.

The Phase III, double-blind, placebo-controlled, multicenter Tocilizumab in Combination With Traditional DMARD Therapy (TOWARD) study was conducted to observe the effects of tocilizumab added to a stable dosage of conventional DMARDs for moderate-to-severe RA in patients with an inadequate response to DMARDs [22]. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks. At week 24, the proportion of patients achieving ACR20 was significantly greater in the tocilizumab plus DMARD group than in the control group (61 vs 25%; $p < 0.0001$), while AEs leading to withdrawal from the study were infrequent. Tocilizumab combined with any of the DMARDs in this study was found to be safe and effective for reducing articular and systemic symptoms in patients with an inadequate response to these DMARDs alone.

The Research on Actemra Determining Efficacy after Anti-TNF Failures (RADIATE) study examined the efficacy and safety of tocilizumab for patients with RA refractory to tumor necrosis factor (TNF) antagonist therapy [23]. ACR20 was achieved at 24 weeks by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively. DAS28 remission rates at week 24 were clearly dose related, being achieved by 30.1, 7.6 and 1.6% of the 8 mg/kg, 4 mg/kg and control groups, respectively. Most AEs were mild or moderate.

The multicenter double-blind randomized placebo-controlled parallel-group Phase III Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders (OPTION) study was conducted to observe the effects of tocilizumab added to a stable dosage of MTX in moderate-to-severe RA in patients with an inadequate response to MTX [24]. Patients were randomized to receive tocilizumab (4 or 8 mg/kg) or placebo intravenously every 4 weeks, with MTX continued at stable pre-study doses (10–25 mg/week). Rescue therapy with tocilizumab (8 mg/kg) was offered at week 16 to patients with a less than 20% improvement in both swollen and tender joint counts. The primary end point was the proportion of patients with ACR20 response at week 24, which was achieved by 59, 48 and 26% of the patients in the tocilizumab 8 mg/kg, 4 mg/kg and control groups, respectively. Biochemical markers of bone and cartilage metabolism showed that tocilizumab induced marked dose-dependent reductions in bone resorption, cartilage

turnover and proteolytic enzyme matrix metalloproteinase-3 levels at week 4. These reductions were maintained until week 24, and were associated with increased levels of bone formation markers observed at week 4 [25]. Tocilizumab-treated patients who achieved ACR50 response or DAS28 clinical remission at week 24 showed greater reductions in these markers than did ACR50 nonresponders.

The Study of Active-controlled Tocilizumab Monotherapy for Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate (SATORI) study investigated the clinical efficacy and safety of tocilizumab monotherapy for active RA patients with an inadequate response to low-dose MTX [26]. This study was conducted to observe the effects of tocilizumab for moderate-to-severe RA in patients with an inadequate response to MTX. Patients were allocated to receive either tocilizumab 8 mg/kg every 4 weeks plus MTX placebo, or tocilizumab placebo plus MTX 8 mg/week for 24 weeks. At week 24, the ACR20 response rate was 80.3 and 25.0%, respectively, for the tocilizumab and MTX groups. In fact, the ACR response of the tocilizumab group was superior to that of the MTX group at all time points. In addition, serum VEGF levels were significantly reduced by tocilizumab. The overall respective AE incidences for the tocilizumab and MTX groups were 92 and 72% (serious AEs: 6.6 and 4.7%; serious infections: 3.3 and 1.6%).

The Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE) trial was a three-arm, randomized double-blind placebo-controlled first-year study [27]. Patients were randomized to receive tocilizumab (4 or 8 mg/kg, once every 4 weeks) plus MTX, or placebo plus MTX (control). Stepwise rescue therapy starting at week 16 was allowed if patients did not respond. At week 52, ACR20, ACR50 and ACR70 were achieved by 56, 36 and 20%, respectively, of RA patients treated with tocilizumab 8 mg/kg plus MTX. All patients were offered to initiate open-label tocilizumab 8 mg/kg for year 2, unless they had achieved 70% or greater improvement, which allowed for continuation until week 104 of the blinded therapy they were receiving at the end of year 1. At week 52, radiographic progression evaluated by Genant's modified Sharp score method was significantly less with 4 and 8 mg/kg tocilizumab ($p \leq 0.0001$) and the change of health assessment questionnaire of disability index (HAQ-DI) showed significant improvement in physical function of patients treated with tocilizumab 4 and 8 mg/kg. The DAS28 remission rates of tocilizumab 8 mg/kg-treated patients were 47% at week 52 and continued to increase (65%) until week 104.

The 24-week, double-blind, double-dummy, parallel-group Actemra versus Methotrexate Double-blind Investigative Trial in Monotherapy (AMBITION) study was conducted to determine the efficacy and safety of tocilizumab monotherapy as compared with MTX for patients with active RA who had not failed previous treatments with MTX/biological agents [28]. Patients were randomized to receive tocilizumab 8 mg/kg every 4 weeks, or MTX starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. Results for tocilizumab were better than for MTX treatment with a higher ACR20 response (69.9 vs 52.5%; $p < 0.001$), and

DAS28 remission rate (33.6 vs 12.1%) at week 24. The incidence of serious AEs with tocilizumab was 3.8 versus 2.8% with MTX ($p = 0.50$), and 1.4 versus 0.7% for serious infections.

The aforementioned trial data demonstrate the therapeutic efficacy of tocilizumab in adult patients with moderate-to-severe RA. The summary of the efficacy of tocilizumab in Phase III clinical trials is shown in TABLE 3.

Safety & tolerability

The overall safety profile of tocilizumab is consistent across all global clinical studies and with the Japanese study program. Serious AEs associated with tocilizumab include serious infections that may lead to hospitalization or death, gastrointestinal perforations and hypersensitivity reactions including anaphylaxis. The most common AEs reported in clinical studies were upper respiratory tract infection, nasopharyngitis, headache, high blood pressure and increased liver enzymes. The latter increases were generally mild and reversible and did not lead to apparent permanent or clinically evident hepatic injury. Changes in laboratory findings, including increases in total cholesterol and triglycerides in the blood, and decreases in neutrophils and platelets, were also reported.

The safety profiles of tocilizumab monotherapy for Japanese RA patients obtained from six initial trials and five long-term extensions were reported [29]. For these studies, 601 patients with moderate-to-severe RA and with a total exposure of 2188 pt-yr were enrolled. The median treatment duration was 3.8 years. The incidence of AEs, including abnormal laboratory test results, was calculated as 465.1 per 100 pt-yr, with infections being the most common serious AEs (6.22 per 100 pt-yr). Abnormalities in the laboratory test results, such as increases in lipid and liver function parameters, were common but most were mild. Of the patients treated for longer than 5 years, 91.3, 73.0 and 51.3% met the respective ACR20, ACR50 and ACR70 response criteria, while 59.7% met the DAS28 remission criterion at 5 years, thus demonstrating the good tolerability and high efficacy of tocilizumab.

Post-marketing surveillance

Since tocilizumab was approved for the treatment of RA in April 2008, all patients receiving tocilizumab treatment in Japan have been enrolled in post-marketing surveillance studies to obtain more information about the efficacy and safety of tocilizumab for RA patients. At the end of May 2010, 10,670 patients with RA were enrolled in the surveillance. In 2072 patients, DAS28 had decreased from 5.53 to 3.00 at week 28 [30], while the percentage of patients whose DAS28 became less than 2.6 (DAS28 remission rate) reached 45%. Regarding safety, 5109 adverse drug reactions were reported for 2944 RA cases, and a list of adverse drug reactions for tocilizumab injection can be accessed at the Chugai Pharmaceutical Co. website [102].

Regulatory affairs

In April 2005, tocilizumab (Actemra®, Chugai Pharmaceutical Co., Tokyo, Japan) was approved as an orphan drug for Castleman's disease in Japan, and it was launched in June 2005. The recommended posology is 8 mg/kg bodyweight administered

once every 2 weeks. Subsequently, tocilizumab was approved in April 2008 for the treatment of RA (8 mg/kg every 4 weeks), systemic-onset juvenile idiopathic arthritis (8 mg/kg every 2 weeks) and polyarticular-course juvenile idiopathic arthritis (8 mg/kg every 4 weeks). The therapeutic indication of tocilizumab in Japan is for RA patients who show inadequate response to treatment for at least 3 months with the maximum permissible dose of one of the DMARDs or inadequate response to the biologics approved in Japan (infliximab, etanercept and adalimumab) [31]. Tocilizumab can be administered as monotherapy or in combination with DMARDs. In the EU, tocilizumab (RoACTEMRA®, F Hoffmann-La Roche, Basel, Switzerland), in combination with MTX, was approved in January 2009 for the treatment of moderately to severely active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF antagonists. Tocilizumab can be administered as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. The recommended posology is 8 mg/kg once every 4 weeks. In January 2010, the US FDA approved tocilizumab (ACTEMRA®, Genentech Co., South San Francisco, CA, USA) for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies. In the USA, tocilizumab may be used alone or in combination with MTX or other DMARDs. Whether used in combination with DMARDs or as monotherapy, the recommended starting dose is 4 mg/kg once every 4 weeks, followed by an increase to 8 mg/kg, depending on clinical response. In March 2010, Genentech submitted a supplemental biologics license application for tocilizumab for the prevention of structural joint damage (radiographically assessed) and improvement in physical function of adults with moderately to severely active RA to the FDA. There is therefore a substantial difference in posology of tocilizumab for the treatment of RA between Japan, the EU and the USA. Tocilizumab is currently approved worldwide as a biological drug for RA in more than 70 countries.

Expert commentary

A number of biologics are available for the treatment of RA. These include anti-TNF blockers (infliximab, etanercept, adalimumab, golimumab and certolizumab), an IL-1 antagonist (anakinra), a B-cell depletor (rituximab), an IL-6R inhibitor (tocilizumab) and a T-cell-activation blocker (abatacept) [14]. These biological modifiers target different molecules and B cells, leading to different clinical effects and causing different adverse effects. Since no head-to-head comparative studies have been made of the efficacy of these various agents, it has not yet been determined which of these biologics should be selected for a given patient. Currently, one of the anti-TNF drugs is chosen as a first-line biologic, but between 14 and 38% of patients show no or little response to anti-TNF treatment, with as many as 40% of patients discontinuing these drugs within 1 year and 50% within 2 years. The findings of the RADIATE trial showed that RA patients who had previously discontinued TNF inhibitors, mainly due

to their inefficacy, achieved ACR20/50/70 responses of 50, 28.8 and 12.4%, respectively, when tocilizumab was administered at 8 mg/kg every 4 weeks [23]. After the approval of tocilizumab for the treatment of RA, several guidelines for the use of tocilizumab have been issued in Japan and some European countries [31–34]. At the present time, tocilizumab is likely to be prescribed as a second-line biologic therapy, but will have to overcome significant competition from established anti-TNF therapies [35–38]. In Japan, tocilizumab is recommended for RA patients who show inadequate response despite treatment for at least 3 months with one of the DMARDs, and a post-marketing surveillance study disclosed that for 31.9% (1089 out of 3418) of RA patients, tocilizumab was selected before anti-TNFs for treatment [30]. The reason(s) why physicians, upon receiving informed consent, opted for tocilizumab as the first-use biologic, remains to be determined. The ultimate decision as to which biologic is selected for a given patient's care may be determined by the properties and safety of the biologics as well as the patient's status (compliance, complications and so on). For a better understanding of the involvement of these factors, further post-marketing surveillance studies, clinical trials and basic experiments are required.

It is anticipated that tocilizumab will be selected as a first-line biologic for moderately to severely active RA patients with certain complications. For instance, reactivation of TB is one of the major infectious side effects encountered during anti-TNF therapies and patients should therefore be screened for latent TB infection. Those patients with latent TB should be treated with a standard anti-mycobacterial therapy prior to the start of anti-TNF treatment [39]. To date, reactivation of TB has occurred in seven out of 11,856 RA patients who received tocilizumab treatment in Japan. This frequency of TB reactivation during tocilizumab treatment appears below that during anti-TNF treatment (although screening for latent TB is actually required as per the label in most countries). Indeed, IFN- γ synthesis by peripheral blood mononuclear cells in response to TB antigens was found to be significantly inhibited by anti-TNFs (infliximab and etanercept) but not by tocilizumab [40]. An immunocompromised status to TB or perhaps even to intracellular pathogens is, thus, evoked to a greater extent by a TNF blockade than by an IL-6 blockade. By contrast, since IL-6 determines the direction of naive T-cell differentiation into Th17 cells, tocilizumab treatment may induce an immunocompromised status to extracellular bacteria or fungus, whereas this treatment may cause reduction of autoreactive Th17 cells and induce regulatory T cells [41].

Another example that differentiates tocilizumab from other biologics is its powerful inhibitory effect on serum amyloid A (SAA), an acute-phase protein produced in the liver. Reactive AA amyloidosis is a serious complication of RA and amyloid fibril deposition causes progressive deterioration in various organs. Since the activation of the SAA gene depends primarily on IL-6 [42,43], tocilizumab injection promptly decreases serum concentrations of SAA, just as in the case of C-reactive protein (CRP) [44]. Three case studies recently reported the clinical ameliorative effect of tocilizumab on gastrointestinal symptoms due to intestinal amyloidosis [45–47] and amyloid A fibril deposits were

found to have disappeared in two cases after three injections of tocilizumab. This suggests that tocilizumab may be suitable as a first-line drug for RA patients who are complicated with, or are at high risk of developing, reactive AA amyloidosis. A comprehensive understanding of the effect of biological modifiers on immunological responses to autoantigens and environmental pathogens, as well as of their effects on other host systems, is thus a matter of major importance.

Five-year view

Tocilizumab, a first-in-class monoclonal antibody targeting IL-6R, has been shown to be effective for moderately to severely active RA, either as monotherapy or in combination with DMARDs, and is now approved as a biological drug for RA in over 70 countries. Analyst estimates for tocilizumab sales are relatively modest, with sales in Japan reaching US\$16 million in 2008 and a 2013 sales potential of US\$460 million [37]. Further clinical trials and post-marketing surveillance will undoubtedly clarify the position of tocilizumab in the treatment of RA.

C-reactive protein normalizes within a few days after infusion of tocilizumab 8 mg/kg in over 90% of patients. In some patients, there is then a gradual increase to levels around the upper limit of normal, due to pharmacokinetic reasons. The trough concentration of tocilizumab in such patients is less than 1 $\mu\text{g/ml}$, since it is clearly shown that CRP is normalized as long as the free tocilizumab concentration is above 1 $\mu\text{g/ml}$ [48]. The factor(s) that affect the degradation rate of tocilizumab remains to be determined, but in patients with a fairly low exposure to tocilizumab, an incomplete response can be observed. The efficacy of tocilizumab will possibly improve if the administration dose or interval is varied from individual to individual on the basis of CRP values and, if possible, on serum tocilizumab concentration rates.

So far, tocilizumab has been approved for the treatment of Castleman's disease, RA and juvenile idiopathic arthritis in Japan and for RA in more than 70 countries. Since IL-6 has been demonstrated to play a role in the development of autoimmune inflammatory diseases and neoplasms [2,3], tocilizumab, as an IL-6R antagonist, may also function as a novel drug for these diseases. According to reports of pilot and case studies, tocilizumab treatment ameliorated clinical symptoms and laboratory findings for Crohn's disease [49], adult-onset Still's disease [50–54], Takayasu arteritis [55], systemic lupus erythematosus [56], relapsing polychondritis [57], reactive arthritis [58], ankylosing spondylitis [59], remitting seronegative symmetrical synovitis with pitting edema [60], polymyalgia rheumatica [61] and systemic sclerosis [62]. Tocilizumab is likely to become a novel drug for these diseases, although further clinical evaluations will be essential.

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Key issues

- Tocilizumab, an IL-6 receptor antagonist, is a first-in-class biologic response modifier.
- Tocilizumab is effective for the treatment of moderately to severely active rheumatoid arthritis, either as monotherapy or in combination with disease-modifying anti-rheumatic drugs.
- Tocilizumab improves treatment outcomes in rheumatoid arthritis patients refractory to anti-tumor necrosis factor biologics.
- Patients treated with tocilizumab are at an increased risk of infections.

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