

# Tocilizumab

## A Review of its Use in the Management of Rheumatoid Arthritis

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#### Data Selection

**Sources:** Medical literature published in any language since 1980 on 'tocilizumab', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

**Search strategy:** MEDLINE, EMBASE and AdisBase search terms were 'tocilizumab' or 'R 1569'. Searches were last updated 2 April 2009.

**Selection:** Studies in patients with rheumatoid arthritis who received tocilizumab. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Index terms:** Tocilizumab, rheumatoid arthritis, monoclonal antibody, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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## Summary

### Abstract

Tocilizumab (RoActemra® or Actemra®) is a recombinant humanized monoclonal antibody that acts as an interleukin (IL)-6 receptor antagonist. Intravenous tocilizumab 8 mg/kg (and no less than 480 mg), in combination with methotrexate, is approved in the EU for the treatment of moderate to severe active rheumatoid arthritis in adult patients with inadequate response to, or who are intolerant of, prior disease-modifying anti-rheumatic drug (DMARD) or tumour necrosis factor (TNF) antagonist therapy. It may also be administered as monotherapy in patients intolerant of methotrexate or in whom methotrexate therapy is inappropriate. Tocilizumab is also approved in Japan for the treatment of polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease.

Intravenous tocilizumab was effective and generally well tolerated when administered either as monotherapy or in combination with conventional DMARDs in several well designed clinical studies in adult patients with moderate to severe rheumatoid arthritis. Tocilizumab-based therapy was consistently more effective than placebo, methotrexate or other DMARDs in reducing disease activity, and some trials also showed significant benefits with tocilizumab in terms of reducing structural joint damage and improving health-related quality of life (HR-QOL). Notably, tocilizumab-based therapy was effective in patients with long-standing disease in whom anti-TNF therapy had previously failed. More data are required to determine the comparative efficacy and safety of tocilizumab versus other biological agents and to establish their relative cost effectiveness. However, the present data suggest that tocilizumab is an important emerging treatment option in adult patients with moderate to severe rheumatoid arthritis.

### Pharmacological Properties

Elevated levels of IL-6 in the serum and synovial fluid of rheumatoid arthritis patients contribute to the chronic inflammatory process characterizing this disease and correlate positively with disease activity. Tocilizumab binds selectively and competitively to soluble and membrane-expressed IL-6 receptors, blocking IL-6 signal transduction. *In vivo*, maximum (>90%) IL-6 receptor saturation was achieved when serum tocilizumab concentrations were >1 µg/mL. In dose-ranging studies, serum levels of inflammatory markers were normalized in rheumatoid arthritis patients who had detectable levels of tocilizumab in the serum. Tocilizumab displays dose-dependent, non-linear pharmacokinetics and has a long elimination half-life, allowing administration every 4 weeks.

### Therapeutic Efficacy

Several well designed studies in patients with early or long-standing rheumatoid arthritis, including those with treatment-refractory disease, demonstrated the efficacy of intravenous tocilizumab 8 mg/kg every 4 weeks in improving disease activity, structural joint damage and/or HR-QOL.

Monotherapy with tocilizumab 8 mg/kg was noninferior to methotrexate for achievement of a clinical response in patients who had not experienced any prior treatment failures in the AMBITION study; subsequent superiority analyses in the intent-to-treat population demonstrated that significantly more tocilizumab than methotrexate recipients achieved American College of Rheumatology (ACR) clinical responses at week 24. Tocilizumab recipients also demonstrated significant improvements at week 24 in HR-QOL measures.

Among patients with early (mean disease duration <3 years) rheumatoid arthritis whose previous treatment with conventional DMARDs had failed, monotherapy with tocilizumab 8 mg/kg for 1 year was significantly more effective than treatment with DMARDs for achieving an ACR20 response, preventing radiographic disease progression and improving HR-QOL.

Patients with long-standing treatment-refractory disease achieved significantly better clinical responses with tocilizumab 8 mg/kg monotherapy than with placebo or methotrexate. These beneficial effects were maintained for up to 5 years with tocilizumab in a noncomparative extension of a placebo-controlled trial. Five studies of tocilizumab-based combination therapy for up to 52 weeks in patients with long-standing, treatment-refractory disease demonstrated better clinical responses with tocilizumab 8 mg/kg plus methotrexate or other DMARDs than with methotrexate or other DMARDs alone. Improvements in the levels of inflammatory markers were also observed, including serum C-reactive protein levels, which reduced as early as week 2. The mean changes from baseline in HR-QOL outcomes also favoured patients receiving tocilizumab-based combination therapy. The RADIATE trial found that generally better clinical responses were achieved with tocilizumab 8 mg/kg plus methotrexate than methotrexate alone in patients whose therapy with at least one anti-TNF agent had failed. In LITHE, significantly less radiographic disease progression was seen with tocilizumab plus methotrexate than with methotrexate alone.

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## Tolerability

Intravenous tocilizumab was generally well tolerated in adult patients with early or long-standing rheumatoid arthritis. The rates of withdrawal because of treatment-emergent adverse events among patients receiving tocilizumab 8 mg/kg monotherapy or in combination with DMARDs were generally low ( $\leq 12\%$  of patients) and similar to those observed in active comparator groups. Most treatment-emergent adverse events were mild to moderate in intensity; upper respiratory tract infections, nasopharyngitis, headache, hypertension and ALT elevations were the most frequently reported adverse events in patients receiving tocilizumab monotherapy or combination therapy for up to 52 weeks. Mild infusion reactions were also common, but were generally transient.

Serious adverse events generally occurred with similar incidence among patients receiving tocilizumab, alone or in combination (with methotrexate or other DMARDs), and patients receiving methotrexate or other DMARDs alone. The incidence of serious treatment-emergent infections was generally low with tocilizumab (1–8% of patients) and similar to the incidence observed with methotrexate or other DMARDs.

Moderate, reversible increases in mean serum levels of total cholesterol, low- and high-density lipoprotein cholesterol and triglycerides occurred in tocilizumab recipients. No corresponding increases in vascular adverse events were observed with tocilizumab plus methotrexate versus methotrexate alone during 24 weeks of therapy and few changes were observed in the atherogenic index in patients

receiving tocilizumab for up to 1 year. Dose-dependent increases in serum ALT and AST levels were also frequently observed in patients receiving tocilizumab, with elevations in ALT and AST generally occurring more frequently with tocilizumab monotherapy than combination therapy (with methotrexate or other DMARDs). Hypersensitivity reactions and the development of antibodies are uncommon with tocilizumab.

## 1. Introduction

Rheumatoid arthritis is a chronic autoimmune disease that affects up to 1% of the population worldwide and is approximately 2.5 times more common in women than men.<sup>[1,2]</sup> The precise aetiology is unknown, but it is characterized by joint synovitis and a fluctuating, progressive disease course that results in progressive joint destruction, deformity, disability and premature death.<sup>[2]</sup>

Conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, have traditionally formed the mainstay of rheumatoid arthritis therapy.<sup>[3,4]</sup> However, although these agents may slow disease progression, conventional DMARDs are not effective in all patients and even those who experience an initial response are unlikely to achieve complete remission.<sup>[5]</sup>

More recently, biological drugs have been developed to target the cytokine mediators, such as tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6, involved in the inflammatory cascade.<sup>[6]</sup> Patients with rheumatoid arthritis have elevated serum levels of IL-6 and this cytokine represents a logical target for drug therapy.<sup>[7]</sup>

Tocilizumab (RoActemra® in the EU and Mexico and Actemra in other countries) is an intravenously administered humanized monoclonal antibody that acts as an IL-6 receptor antagonist.<sup>[8]</sup> It is approved in Europe for the treatment of moderate to severe rheumatoid arthritis<sup>[9]</sup> and in Japan for the treatment of rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease.<sup>[10,11]</sup> This article reviews the use of tocilizumab in

adult DMARD-naive or -resistant patients with active rheumatoid arthritis.

## 2. Pharmacodynamic Properties

This section summarizes the pharmacodynamic properties of tocilizumab; some studies discussed are only available as abstracts and/or posters.<sup>[12-17]</sup>

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits IL-6 signal transduction.<sup>[8]</sup> Because it is humanized, tocilizumab confers a low risk of antibody production compared with murine or chimeric mouse-human antibodies.<sup>[8]</sup>

IL-6 is implicated in the pathogenesis of both acute and chronic inflammatory responses; it stimulates hepatocyte production of acute phase proteins such as C-reactive protein (CRP) and amyloid A,<sup>[18]</sup> and IL-6 overproduction increases bone resorption via osteoclast activation.<sup>[19]</sup> Murine models demonstrated that IL-6 deficiency prevented the development of collagen-induced arthritis in DBA/1J mice and T-cell-mediated chronic autoimmune arthritis in SKG mice.<sup>[20]</sup> In patients with rheumatoid arthritis or other inflammatory arthritides, levels of IL-6 and soluble IL-6 receptors (sIL-6R) in the synovial fluid and serum are elevated versus controls.<sup>[21]</sup> IL-6 serum levels also correlate positively with rheumatoid arthritis disease activity<sup>[21]</sup> and the formation of osteoclast-like cells that contribute to the radiological joint damage that is characteristic of rheumatoid arthritis.<sup>[22]</sup>

Tocilizumab binds selectively and competitively to sIL-6R and membrane IL-6 receptors (mIL-6R), preventing dimerization of glycoprotein (gp)130 molecules on the cell membrane and

blocking IL-6 signal transmission into cells.<sup>[23]</sup> *In vitro*, tocilizumab inhibited proliferation of the mL-6R-expressing KPMM2 human myeloma cell line, and inhibited sIL-6R-mediated IL-6 signal transduction in BAR-h10, a human gp130-transfected mouse pro-B-cell line.<sup>[23]</sup>

*In vivo*, maximum (>90%) sIL-6R saturation was achieved when serum tocilizumab concentrations were >1 µg/mL.<sup>[24]</sup> Pooled data from over 2000 rheumatoid arthritis patients in four clinical studies of tocilizumab 4 or 8 mg/kg every 4 weeks (AMBITION, OPTION, RADIATE and TOWARD; see table I and section 4) found that serum IL-6 levels increased after the first infusion of tocilizumab 4 or 8 mg/kg, then decreased steadily over the 24-week study periods.<sup>[12]</sup> Among 1703 rheumatoid arthritis patients who received intravenous tocilizumab 4 or 8 mg/kg every 4 weeks for 24 weeks in the OPTION and TOWARD trials, a serum tocilizumab concentration of 3.72 µg/mL produced 50% of the maximal effect on disease activity score (DAS) 28 (see table II).<sup>[13]</sup> Similar effects of tocilizumab on IL-6 have been observed in Japanese patients; serum IL-6 levels were normalized to <35 pg/mL in 23 (52%) of 44 patients with detectable serum tocilizumab concentrations during the 24-week SATORI study

of tocilizumab 8 mg/kg every 4 weeks.<sup>[17]</sup> Most (14 of 23; 61%) of these patients achieved DAS 28 remission, indicating an association between tocilizumab-mediated IL-6 normalization and clinical response.<sup>[17]</sup> In another study in 33 Japanese patients with rheumatoid arthritis, the inhibition of IL-6R by tocilizumab resulted in an ≈10-fold increase in the serum level of sIL-6R (probably because its elimination half-life [ $t_{1/2}$ ] was prolonged by the formation of tocilizumab-sIL-6R complex) and an ≈1.5-fold increase in the serum level of IL-6 (probably because IL-6R-mediated consumption of IL-6 was inhibited as no tocilizumab-free IL-6R was available).<sup>[25]</sup> However, IL-6 signalling was inhibited as long as free tocilizumab was detectable in serum,<sup>[26]</sup> as indicated by the normalization of markers of inflammation,<sup>[14,26,27]</sup> and bone and cartilage turnover.<sup>[15]</sup>

In a repeat-dose study in 15 Japanese rheumatoid arthritis patients, treatment with tocilizumab 2, 4 or 8 mg/kg every 2 weeks normalized the erythrocyte sedimentation rate (ESR) and serum CRP and amyloid A levels at week 6.<sup>[26]</sup> Among patients who received tocilizumab 4 or 8 mg/kg every 4 weeks for 24 weeks in the OPTION study, normalized CRP levels were maintained in patients with serum tocilizumab concentrations of >1 µg/mL.<sup>[14]</sup> These data were supported by those from the pooled analysis of the OPTION, TOWARD, RADIATE and AMBITION studies, which showed that higher tocilizumab exposure was associated with decreased levels of the main biomarkers of inflammation (no statistical data available), particularly CRP levels.<sup>[28]</sup> Moreover, a more persistent reduction in the levels of biomarkers was observed with tocilizumab 8 mg/kg compared with the 4 mg/kg dosage, owing to higher exposure to the drug with the former dosage (no statistical data available). Sustained improvements ( $p < 0.05$  vs placebo) in markers of bone resorption (e.g. C-terminal cross-linking telopeptide of type I collagen) and cartilage turnover (e.g. N-terminal propeptide of type IIA collagen and type II collagen helical peptide) were seen in patients who received tocilizumab 8 mg/kg for 24 weeks in the OPTION trial, suggesting a beneficial effect on bone metabolism.<sup>[15]</sup>

**Table I.** Trial acronyms for clinical studies of tocilizumab

Acronym	Definition
AMBITION <sup>[32]</sup>	Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy
CHARISMA <sup>[34]</sup>	Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody
LITHE <sup>[38]</sup>	toCiLizumab safety and THE prevention of structural joint damage
OPTION <sup>[35]</sup>	tOcilizumab Pivotal Trial in methotrexate Inadequate respONders
RADIATE <sup>[37]</sup>	RheumAtoiD arthritis study in Anti-TNF-failurEs
SAMURAI <sup>[30]</sup>	Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor trial
SATORI <sup>[31]</sup>	Study of Active-controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with Inadequate response to methotrexate
STREAM <sup>[39]</sup>	Acronym not defined
TOWARD <sup>[36]</sup>	Tocilizumab in cOmbination With traditional DMARD therapy

**Table II.** Definitions and descriptions of key efficacy assessments used in clinical studies in patients with rheumatoid arthritis (RA)

Outcome measure	Definition (score range)	Clinical meaning
<b>Clinical response</b>		
ACR20, 50 or 70 response	Improvement of $\geq 20\%$ , $\geq 50\%$ or $\geq 70\%$ in TJC, SJC and 3 of 5 remaining ACR core components	ACR standard criteria for improvement in RA severity
ACR core components	TJC (0–68); SJC (0–66); PhGA; PtGA; patient's assessment of pain (0–100); HAQ DI; acute phase reactant value (ESR or CRP)	Higher scores indicate more active RA
DAS	44-joint DAS (1–9)	Higher scores indicate more active RA
DAS 28	28-joint DAS (2–10)	Higher scores indicate more active RA <sup>a</sup>
EULAR response	Improvement of $\leq 1.2$ (good), $>0.6$ to $\leq 1.2$ (moderate) and $\leq 0.6$ (none) in DAS or DAS 28 from baseline	Higher scores indicate more active RA
<b>Radiographic response</b>		
Erosion score	Assessed for 46 joints (0–5 per joint; 0–230 or 0–145)	In each measure, higher scores indicate more radiographic damage
JSN score	Assessed for 46 joints (0–4 per joint; 0–168 or 0–145)	
TSS	Sum of erosion and joint scores	
<b>Health-related quality of life (HR-QOL)</b>		
HAQ	Measure of general HR-QOL comprising four dimensions (disability, pain, drug toxicity and dollar costs)	Higher scores indicate worse HR-QOL
HAQ DI	Measure of functional disability (score 0–3)	Higher scores indicate disability
PhGA	Measure of functional disability (score 0–10)	Higher scores indicate disability
PtGA	Measure of functional disability (score 0–10)	Higher scores indicate disability
SF-36 score	Measure of physical and mental health in eight domains (score 0–100 VAS for each domain)	Higher scores indicate better health
FACIT-Fatigue score	Measure self-reported fatigue and its impact upon daily activities and function (score 0–52)	Higher scores indicate better health

a The ACR uses DAS 28 scores to define disease activity as low ( $\leq 3.2$ ), moderate (3.3–5.1) or high ( $>5.1$ ).<sup>[3]</sup>

**ACR** = American College of Rheumatology; **ACR20, 50 or 70** = improvement of  $\geq 20\%$ ,  $\geq 50\%$  or  $\geq 70\%$  in ACR standard criteria; **CRP** = C-reactive protein; **DAS** = disease activity score; **ESR** = erythrocyte sedimentation rate; **EULAR** = European League Against Rheumatism; **FACIT** = Functional Assessment of Chronic Illness Therapy; **HAQ** = Health Assessment Questionnaire; **HAQ DI** = HAQ-Disability Index; **JSN** = joint space narrowing; **PhGA** = physician's global assessment of disease activity; **PtGA** = patient's global assessment of disease activity; **SF-36** = Medical Outcomes Study 36-Item Short-Form General Health Survey; **SJC** = swollen joint count; **TJC** = tender joint count; **TSS** = van der Heijde- or Genant-modified total Sharp score; **VAS** = visual analogue scale.

### 3. Pharmacokinetic Properties

This section discusses the pharmacokinetic properties of intravenous tocilizumab, focusing on data from a population pharmacokinetic analysis of 1793 patients with rheumatoid arthritis who received a 1-hour infusion of tocilizumab 4 or 8 mg/kg every 4 weeks for 24 weeks (available from the European summary of product characteristics).<sup>[9]</sup> Also discussed is a dose-finding study of 15 Japanese rheumatoid arthritis patients who received tocilizumab 2, 4 or 8 mg/kg every 2 weeks for 6 weeks.<sup>[26]</sup>

In the population pharmacokinetic analysis, a dose proportional increase in maximum con-

centration ( $C_{\max}$ ) was observed after tocilizumab 4 and 8 mg/kg every 4 weeks; however, the increase in the mean area under the concentration-time curve (AUC) and the trough concentration ( $C_{\min}$ ) was more than dose proportional for these dosages.<sup>[9]</sup> The predicted steady-state AUC and  $C_{\max}$  values were 2.7- and 6.5-fold higher with tocilizumab 8 mg/kg than 4 mg/kg.<sup>[9]</sup>

After tocilizumab 8 mg/kg every 4 weeks, the predicted steady-state AUC,  $C_{\max}$  and  $C_{\min}$  values were 35.0 mg • h/mL, 183  $\mu\text{g/mL}$  and 9.7  $\mu\text{g/mL}$ , respectively.<sup>[9]</sup> Accumulation ratios for AUC,  $C_{\max}$  and  $C_{\min}$  were 1.22, 1.06 and 2.35.<sup>[9]</sup> Steady-state  $C_{\max}$  was reached after the first adminis-

tration, and steady-state AUC and  $C_{\min}$  after 8 and 20 weeks of tocilizumab 8 mg/kg; the steady-state volume of distribution of tocilizumab was 6.4 L (dosage not specified).<sup>[9]</sup>

In Japanese patients, mean AUC values after the first dose of tocilizumab 2, 4 or 8 mg/kg were 3.44, 4.66 and 10.66 mg • h/mL, respectively.<sup>[26]</sup>

Tocilizumab undergoes biphasic elimination; total clearance is concentration dependent and is the sum of linear and non-linear clearance.<sup>[9]</sup> Non-linear clearance, which plays a major role in clearance at low drug concentrations, was estimated to be 12.5 mL/h in the population pharmacokinetic analysis (dosage not specified).<sup>[9]</sup> Clearance of the drug is linear at higher tocilizumab concentrations when the non-linear pathway is saturated.<sup>[9]</sup>

Tocilizumab has a long  $t_{1/2}$ , allowing for administration every 4 weeks (section 6).<sup>[26]</sup> The  $t_{1/2}$  of tocilizumab is concentration dependant; the effective steady-state  $t_{1/2}$  decreased with decreasing concentrations of tocilizumab within a dosage interval from 14 days to 8 days after tocilizumab 8 mg/kg every 4 weeks.<sup>[9]</sup> Mean  $t_{1/2}$  values after the first dose of tocilizumab 2, 4 or 8 mg/kg in Japanese patients were 74.4, 96.9 and 160.2 hours, respectively.<sup>[26]</sup> After three doses of tocilizumab 8 mg/kg, mean  $t_{1/2}$  was prolonged to 242 hours, similar to the  $t_{1/2}$  of human immunoglobulin G.<sup>[26]</sup>

Tocilizumab clearance was not affected by concomitant administration of methotrexate, NSAIDs or corticosteroids.<sup>[9]</sup> Also, there was no significant effect on methotrexate exposure when a single dose of tocilizumab 10 mg/kg was coadministered with methotrexate 10–25 mg once weekly.<sup>[9]</sup>

Patients with rheumatoid arthritis may have reduced expression of the hepatic cytochrome P450 (CYP) isozymes CYP2C19 and CYP3A4 because of inflammation, resulting in increased serum concentrations of drugs metabolized by these isozymes, such as omeprazole and dextromethorphan. Tocilizumab normalized CYP2C19 and CYP3A4 expression in rheumatoid arthritis patients, thereby improving drug metabolism.<sup>[9,16]</sup> When discontinuing tocilizumab therapy, dosage adjustment of drugs metabolized by CYP3A4, CYP1A2,

CYP2C9 or CYP2C19 (eg. atorvastatin, calcium-channel blockers, warfarin and ciclosporin) may be required to maintain therapeutic effect of these drugs.<sup>[9]</sup> Tocilizumab may affect CYP isoenzyme activity for several weeks after discontinuation of therapy owing to its long  $t_{1/2}$ .<sup>[9]</sup>

Age, sex and ethnicity did not affect the pharmacokinetics of tocilizumab in the population pharmacokinetic analysis.<sup>[9]</sup> No study has been undertaken to assess the effect of renal or hepatic impairment on the pharmacokinetic parameters of tocilizumab. However, the population pharmacokinetic analysis showed that mild renal impairment (Cockcroft-Gault creatinine clearance  $\geq 50$  to  $< 80$  mL/min [ $\geq 3$  to  $< 4.8$  L/h]) did not affect the pharmacokinetics of tocilizumab.<sup>[9]</sup>

#### 4. Therapeutic Efficacy

Nine large ( $n > 100$ ), randomized, multicentre studies of up to 52 weeks' duration have investigated the effect of treatment with intravenous tocilizumab 2–8 mg/kg every 4 weeks in adult patients aged  $\geq 18$  years with active, moderate to severe rheumatoid arthritis.<sup>[29–38]</sup> This section focuses on the data for the approved dosage of tocilizumab 8 mg/kg every 4 weeks; data for the other dosages are presented in the tables but are not discussed further (see also section 7).

Studies evaluating the efficacy of tocilizumab were of double-blind design, except for the SAMURAI trial (table III),<sup>[30]</sup> which was x-ray reader-blinded. Three studies were performed in Japanese patients, including one placebo-controlled<sup>[29]</sup> and two active-controlled (SAMURAI<sup>[30]</sup> and SATORI<sup>[31]</sup>) studies. Six active-controlled trials have been conducted in other countries around the world. These include AMBITION,<sup>[32,33]</sup> CHARISMA,<sup>[34]</sup> LITHE,<sup>[38]</sup> OPTION,<sup>[35]</sup> TOWARD<sup>[36]</sup> and RADIATE.<sup>[37]</sup> Additionally, the long-term use of tocilizumab was evaluated in a 5-year noncomparative extension (STREAM study)<sup>[39]</sup> of the placebo-controlled Japanese study.<sup>[29]</sup> To date, CHARISMA,<sup>[34]</sup> OPTION,<sup>[35]</sup> RADIATE,<sup>[37]</sup> SAMURAI,<sup>[30]</sup> SATORI,<sup>[31]</sup> TOWARD,<sup>[36]</sup> the placebo-controlled Japanese study<sup>[29]</sup> and its extension (STREAM)<sup>[39]</sup> are fully published; additional data for these

**Table III.** Efficacy of intravenous tocilizumab (TCZ) 2, 4 or 8 mg/kg every 4 wk in adult patients (pts) aged  $\geq 18$  y with active rheumatoid arthritis (RA). Summary of randomized, multicentre trials of TCZ administered as monotherapy<sup>[29-32,34]</sup> or in combination with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs)<sup>[34-38]</sup> for up to 52 wk; studies were of double-blind design, except for SAMURAI,<sup>[30]</sup> which was x-ray reader-blinded. All studies except one (AMBITION<sup>[32]</sup>) included pts in whom previous therapy with MTX,<sup>[31,34,35]</sup>  $\geq 1$  conventional DMARD<sup>[29,30,36,38]</sup> or  $\geq 1$  anti-TNF agent had failed.<sup>[37]</sup> Unless otherwise specified, primary statistical analyses were conducted in the intent-to-treat (ITT) population using last-observation-carried-forward analysis

Study [duration; wk]	Mean duration of RA	Previous failed therapy [mean no. of prior treatments received]	Treatment (mg/kg)	No. of pts	Response rates (% of pts)			Remission rate (% of pts with DAS 28 <2.6)
					ACR20 <sup>a</sup>	ACR50	ACR70	
<b>In pts with no previous treatment failures</b>								
AMBITION <sup>[32]b</sup> [24]	$\approx 6$ y	Not failed MTX or anti- TNFs [1.2 DMARDs]	TCZ 8	286	70 <sup>+++ c</sup>	44 <sup>++ c</sup>	28 <sup>+++ c</sup>	34
			MTX <sup>d</sup>	284	53 <sup>c</sup>	34 <sup>c</sup>	15 <sup>c</sup>	12
<b>In treatment-refractory pts</b>								
<i>In pts with early RA</i>								
SAMURAI <sup>[30]</sup> [52]	$\approx 2$ y	DMARDs [2.8 DMARDs]	TCZ 8	157	78 <sup>+++</sup>	64 <sup>+++</sup>	44 <sup>+++</sup>	59 <sup>+++</sup>
			DMARDs <sup>f</sup>	145	34	13	6	3
<i>In pts with long-standing RA</i>								
CHARISMA <sup>[34]</sup> [16]	$\approx 10$ y	MTX [NR <sup>e</sup> ]	TCZ 2 <sup>d</sup>	53	31	6	2	NR
			TCZ 4 <sup>d</sup>	54	61 <sup>†</sup>	28	6	NR
			TCZ 8	52	63 <sup>†</sup>	41	16	17
			TCZ 2 + MTX <sup>d</sup>	52	64 <sup>+++</sup>	32	14	NR
			TCZ 4 + MTX <sup>d</sup>	49	63 <sup>+++</sup>	37	12	NR
			TCZ 8 + MTX <sup>d</sup>	50	74 <sup>+++</sup>	53 <sup>†</sup>	37 <sup>†</sup>	34
			MTX <sup>d</sup>	49	41	29	16	8
LITHE <sup>[38]</sup> [52]	NR	DMARDs (including MTX)	TCZ 4 + MTX <sup>d</sup>	399	47 <sup>g</sup>	29	16	30
			TCZ 8 + MTX <sup>d</sup>	398	56 <sup>+++ g</sup>	36 <sup>+++</sup>	20 <sup>+++</sup>	47 <sup>+++</sup>
			MTX <sup>d</sup>	393	25 <sup>g</sup>	10	4	8
Nishimoto et al. <sup>[29]</sup> [12]	7.6 y <sup>h</sup>	DMARDs [4-5 DMARDs <sup>h</sup> ]	TCZ 4	54	57 <sup>**</sup>	26 <sup>**</sup>	20 <sup>*</sup>	NR
			TCZ 8	55	78 <sup>**‡</sup>	40 <sup>**</sup>	14 <sup>*</sup>	NR
			PL	53	11	2	0	NR
OPTION <sup>[35]</sup> [24]	$\approx 8$ y	MTX [1.6 DMARDs]	TCZ 4 + MTX <sup>d</sup>	213	48 <sup>+++</sup>	31 <sup>+++</sup>	12 <sup>+++</sup>	13 <sup>+++</sup>
			TCZ 8 + MTX <sup>d</sup>	205	59 <sup>+++</sup>	44 <sup>+++</sup>	22 <sup>+++</sup>	27 <sup>+++</sup>
			PL + MTX <sup>d</sup>	204	26 <sup>a</sup>	11	2	1
RADIATE <sup>[37]</sup> [24]	$\approx 12$ y	anti-TNFs <sup>i</sup> [2.0 DMARDs]	TCZ 4 + MTX <sup>d</sup>	161	30 <sup>+++</sup>	17 <sup>+++</sup>	5	8
			TCZ 8 + MTX <sup>d</sup>	170	50 <sup>+++</sup>	29 <sup>+++</sup>	12 <sup>++</sup>	30 <sup>+++</sup>
			PL + MTX <sup>d</sup>	158	10	4	1	2
SATORI <sup>[31]</sup> [24]	$\approx 9$ y	MTX [3.5 DMARDs]	TCZ 8	61	80 <sup>+++</sup>	49 <sup>+++</sup>	30 <sup>+++</sup>	43 <sup>+++</sup>
			MTX <sup>d</sup>	64	25	11	6	2
TOWARD <sup>[36]</sup> [24]	$\approx 10$ y	DMARDs [1.6 DMARDs/anti- TNFs]	TCZ 8 + DMARDs <sup>j</sup>	803	61 <sup>+++</sup>	38 <sup>+++</sup>	21 <sup>+++</sup>	30 <sup>+++</sup>
			PL + DMARDs <sup>l</sup>	413	25	9	3	3

a Primary endpoint in all studies apart from SAMURAI<sup>[32]</sup> and LITHE.<sup>[38]</sup>

b Included pts who were MTX-naive or had not received MTX in the previous 6 mo.

c The primary analysis was for noninferiority (indicated if the lower limit of the 95% CI for the between-group difference in response rate was greater than or equal to  $-0.12$ ) in the per-protocol population (ACR20 at week 24 was 71% with TCZ vs 52% with MTX; weighted between-group difference was 0.21 [95% CI 0.13, 0.29]<sup>[32]</sup>). Results are reported for the secondary superiority analysis in the ITT population (weighted between-group difference was 0.19 [95% CI 0.11, 0.27] for ACR20, 0.12 (95% CI 0.04, 0.20) for ACR50 and 0.14 (95% CI 0.07, 0.22) for ACR70<sup>[32]</sup>).

Continued next page



Table III. Contd

- d Oral or parenteral MTX 7.5–20,<sup>[32]</sup> 8<sup>[31]</sup> or 10–25<sup>[34,35,37,38]</sup> mg/wk.
- e Most pts had received 1–3 different DMARDs, with some receiving more than five different DMARDs; 50% of pts had received anti-TNFs.
- f Pts received MTX (29% as monotherapy and 56% in combination with other DMARDs) or other DMARDs and/or immunosuppressants (14%).
- g Secondary endpoint.
- h Median value.
- i Across the three treatment groups, 42–50% of pts had received one anti-TNF, 32–44% had received two anti-TNFs and 12–18% had received more than three anti-TNFs.
- j Pts continued stable dosages of MTX, chloroquine, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine or parenteral gold.

ACR = American College of Rheumatology; **ACR20, 50 or 70** = improvement of  $\geq 20\%$ ,  $\geq 50\%$  or  $\geq 70\%$  in ACR standard criteria (see table II for ACR standard criteria); **DAS 28** = 28-joint disease activity score; **NR** = not reported; **PL** = placebo; **TNF** = tumour necrosis factor; \*  $p < 0.01$ , \*\*  $p < 0.001$  vs PL; †  $p < 0.05$ , ††  $p < 0.01$ , †††  $p < 0.001$  vs active comparator(s); ‡ vs TCZ 4 mg/kg.

trials and data from the other trials are available from abstracts, posters or oral presentations,<sup>[33,38,40–43]</sup> and from the assessment report by the European Medicines agency.<sup>[44]</sup>

In all studies except AMBITION,<sup>[32]</sup> which included patients whose therapy with methotrexate or anti-TNF agents had not previously failed, patients were required to have experienced an inadequate clinical response to previous therapy with methotrexate,<sup>[31,34,35,38]</sup> at least one conventional DMARD<sup>[29,30,36,38]</sup> or at least one anti-TNF agent.<sup>[37]</sup> The SAMURAI<sup>[30]</sup> trial included patients with early rheumatoid arthritis; patients in the other studies had long-standing disease.<sup>[29,31–38]</sup> Where specified, study inclusion criteria were: a diagnosis of rheumatoid arthritis according to American College of Rheumatology (ACR) criteria; disease duration of  $\geq 3$ <sup>[32]</sup> or  $\geq 6$ <sup>[29,30,34–37]</sup> months (and  $< 5$  years in the SAMURAI study<sup>[30]</sup>); active disease (swollen joint count  $\geq 6$ <sup>[29,30,32–37]</sup> and tender joint count  $\geq 6$ <sup>[29,30,34]</sup> or  $\geq 8$ <sup>[32,35–37]</sup>); ESR  $\geq 28$ <sup>[33–37]</sup> or  $\geq 30$ <sup>[29,30]</sup> mm/h and/or CRP  $\geq 1.0$ <sup>[29,33–37]</sup> or  $\geq 2.0$ <sup>[30]</sup> mg/dL.

Tocilizumab was administered by 1-hour intravenous infusion every 4 weeks. In studies of tocilizumab monotherapy,<sup>[29,30,32–34]</sup> patients randomized to tocilizumab were required to discontinue DMARDs or immunosuppressants before study initiation. Patients assigned to treatment with other DMARDs or immunosuppressants continued with stable pre-entry dosages. Where specified, oral or parenteral methotrexate

dosages were required to have been stable at 10–25 mg/week for at least 8<sup>[35,37]</sup> or 24<sup>[34]</sup> weeks prior to study initiation; folic acid was administered to minimize methotrexate-related toxicity. Concomitant therapy with stable-dose oral corticosteroids (prednisolone  $\leq 10$  mg/day) and/or NSAIDs was permitted.<sup>[29,30,34–37,39]</sup> Rescue therapy in patients who had not achieved at least 20% improvement in both swollen joint count and tender joint count by week 16 consisted of tocilizumab 8 mg/kg,<sup>[35,37]</sup> DMARDs and/or corticosteroids.<sup>[36]</sup>

Acronyms/abbreviations and definitions of clinical and radiographic efficacy and health-related quality of life (HR-QOL) measures used in these trials are listed in table II. Improvement of  $\geq 20\%$  in ACR standard criteria (ACR20) was the primary efficacy endpoint in all studies<sup>[29,32,34–37]</sup> except SAMURAI<sup>[30]</sup> and LITHE,<sup>[38]</sup> which evaluated radiographic disease progression from baseline using the van der Heijde<sup>[30]</sup> or Genant<sup>[38]</sup> -modified Sharp method. Where specified, between-group differences were evaluated using analyses of co-variance<sup>[30,34]</sup> or the Cochran-Mantel-Haenszel test.<sup>[35]</sup> Primary statistical analyses were conducted in the intent-to-treat (ITT) population with the last-observation-carried-forward in all studies except AMBITION,<sup>[32]</sup> in which the primary analysis was for noninferiority in the per-protocol population (noninferiority was demonstrated if the ACR20 response rate in the treatment group was 12 percentage points lower than the response rate with the comparator at week 24);

superiority was tested in the ITT population only if noninferiority was demonstrated. In AMBITION, analyses for secondary endpoints were also for superiority (indicated if the lower limit of the 95% confidence interval [CI] for the between-group difference was more than 0) in the ITT population (noninferiority limits were not predefined).<sup>[32]</sup>

Within individual studies, there were no statistically significant between-group differences in demographic and baseline characteristics, including disease activity.<sup>[30,32,34-37]</sup>

#### 4.1 In Patients with No Previous Treatment Failures

##### 4.1.1 Clinical Responses

Monotherapy with tocilizumab 8 mg/kg was noninferior to methotrexate for achievement of a clinical response in patients with rheumatoid arthritis in the AMBITION trial who had not experienced any prior treatment failures (table III).<sup>[32]</sup> The subsequent superiority analysis in the ITT population demonstrated that significantly more tocilizumab than methotrexate recipients achieved ACR20, ACR50 and ACR70 responses at week 24 ( $p < 0.01$  for all comparisons; table III). The superiority of tocilizumab relative to methotrexate therapy in terms of ACR20 response rates was apparent from as early as week 2, with between-group differences increasing over time.<sup>[32]</sup> Serum CRP levels were significantly lower, and below the upper limit of normal (ULN), with tocilizumab than methotrexate at week 24 (mean change from baseline to week 24  $-2.8$  vs  $-1.9$  mg/dL; adjusted mean between-group difference of  $-0.9$  [95% CI  $-1.5, -0.3$ ]). Clinical remission, defined as a DAS 28 score of  $< 2.6$ , was achieved in 34% of tocilizumab recipients and 12% of placebo recipients (table III), with 82% and 65% achieving a good or moderate European League Against Rheumatism (EULAR) response; between-group differences were not statistically significant.<sup>[32]</sup> By week 24, tocilizumab recipients were 5 times more likely to achieve DAS 28 remission (odds ratio [OR] 5.8 [95% CI 3.3, 10.4]), and approximately 4 times more likely to achieve at least a moderate EULAR response

(OR 4.2 [95% CI 2.9, 6.1]) than methotrexate recipients.

##### 4.1.2 Effects on Health-Related Quality of Life (HR-QOL)

HR-QOL was significantly improved with tocilizumab 8 mg/kg monotherapy versus methotrexate in patients with no previous treatment failures in the AMBITION trial.<sup>[32,33]</sup> Compared with methotrexate recipients, patients treated with tocilizumab reported significantly better mean changes from baseline at week 24 in Health Assessment Questionnaire Disability Index (HAQ DI) scores ( $-0.5$  vs  $-0.70$ ; difference  $-0.2$  [95% CI  $-0.3, -0.1$ ])<sup>[32]</sup> and Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) physical component summary scores (8.4 vs 10.0; difference 1.6 [95% CI 0.37, 3.65]); mean changes in the SF-36 mental component summary score did not significantly differ between tocilizumab and methotrexate (7.2 vs 5.5).<sup>[33]</sup>

#### 4.2 In Treatment-Refractory Patients with Early Rheumatoid Arthritis

##### 4.2.1 Clinical and Radiographic Responses

###### Monotherapy

Monotherapy with tocilizumab 8 mg/kg for 1 year was significantly more effective than DMARDs (including methotrexate) for reducing clinical and radiographic disease activity in patients with treatment-refractory early rheumatoid arthritis (disease duration of  $\approx 2$  years), regardless of previous therapy.<sup>[30]</sup> Seventy eight percent of patients receiving tocilizumab 8 mg/kg achieved ACR20, compared with 34% of patients receiving DMARDs ( $p < 0.001$ ; table III).<sup>[30]</sup> Significantly more tocilizumab recipients in SAMURAI also achieved ACR50 and ACR70 responses ( $p < 0.001$  vs DMARDs for both comparisons; table III).<sup>[30]</sup>

In SAMURAI, significantly less radiographic disease progression (the primary efficacy endpoint) was seen with tocilizumab 8 mg/kg monotherapy than with DMARDs after 52 weeks' therapy.<sup>[30]</sup> Significantly more patients receiving tocilizumab than DMARDs had no radiographic disease progression at week 52 (56% vs 39%;  $p < 0.01$ ).

Tocilizumab recipients had significantly smaller changes from baseline than DMARD recipients in mean total Sharp scores (2.3 vs 6.1;  $p < 0.01$ ), erosion scores (0.9 vs 3.2;  $p < 0.001$ ) and joint space narrowing scores (1.5 vs 2.9;  $p < 0.05$ ).<sup>[30]</sup>

Clinical remission was achieved by significantly more patients treated with tocilizumab 8 mg/kg monotherapy than patients receiving DMARDs in SAMURAI (table III).<sup>[30]</sup>

#### 4.2.2 Effects on HR-QOL

In SAMURAI, tocilizumab 8 mg/kg monotherapy produced significantly greater improvements in HR-QOL compared with DMARDs.<sup>[30]</sup> More tocilizumab recipients achieved a clinically significant decrease of  $>0.22$  units in the HAQ score at week 52 than patients treated with DMARDs (68% vs 40%;  $p < 0.001$ ).<sup>[30]</sup>

### 4.3 In Treatment-Refractory Patients with Long-Standing Disease

#### 4.3.1 Clinical and Radiographic Responses

##### Monotherapy

Tocilizumab 8 mg/kg monotherapy was significantly more effective than treatment with placebo<sup>[29]</sup> or methotrexate<sup>[31,34]</sup> in patients with long-standing, treatment-refractory rheumatoid arthritis (disease duration of 7.6<sup>[29]</sup> [median], or  $\approx 9$ <sup>[31]</sup> or  $\approx 10$ <sup>[34]</sup> [mean] years). More than 63% of tocilizumab 8 mg/kg recipients achieved ACR20 at study end, compared with 11% of placebo recipients and 25% or 41% of methotrexate recipients (table III).<sup>[29,31,34]</sup> ACR50 and ACR70 response rates and clinical remission rates, where reported, were also significantly higher with tocilizumab 8 mg/kg than with placebo or methotrexate in two studies (secondary endpoints; table III).<sup>[29,31]</sup>

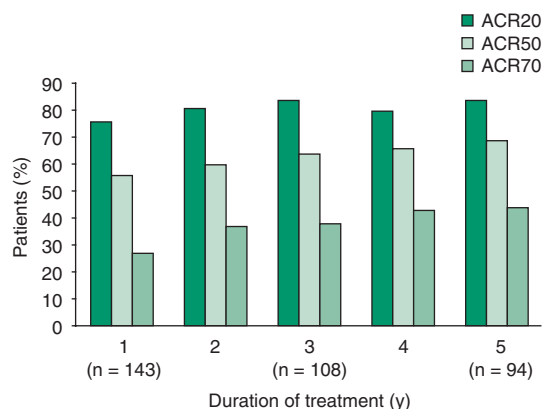
The efficacy of tocilizumab monotherapy was sustained during long-term therapy ( $\leq 5$  years) in patients with DMARD-resistant disease in the STREAM study,<sup>[39]</sup> an extension of the Japanese placebo-controlled study.<sup>[29]</sup> As shown in figure 1, at least 76% of patients maintained an ACR20 response over 5 years with tocilizumab monotherapy in this noncomparative study (value estimated from a graph). Of 163 patients who

completed the initial placebo-controlled Japanese study, 143 continued to receive tocilizumab 8 mg/kg plus oral prednisolone ( $\leq 10$  mg/day) or NSAIDs as required during the extension phase; at 5 years, 94 patients were receiving tocilizumab (median treatment duration  $\approx 5.6$  years).<sup>[39]</sup> Throughout the 5-year observation period, ACR50 and ACR70 responses were achieved by at least 56% and 27% of patients (values estimated from a graph); at 5 years, clinical remission (DAS 28  $< 2.6$ ) was achieved by 55% of patients. Of the 94 patients who received tocilizumab therapy for more than 5 years, 88 had received corticosteroids at baseline. Of these 88 patients, 78 (89%) had decreased their corticosteroid dosage and 28 (32%) had discontinued corticosteroids following 5 years of tocilizumab therapy.<sup>[39]</sup>

##### In Combination with Methotrexate or other DMARDs

Tocilizumab-based combination therapy was significantly more effective than methotrexate<sup>[34,35,37,38]</sup> or DMARDs (i.e. methotrexate, chloroquine, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, parenteral gold)<sup>[36]</sup> alone for reducing clinical<sup>[34-38]</sup> and radiographic<sup>[38]</sup> disease activity in patients with long-standing rheumatoid arthritis (mean disease duration ranged from  $\approx 8$  to  $\approx 12$  years, where reported) whose previous treatment with methotrexate,<sup>[34,35]</sup> at least one DMARD<sup>[36,38]</sup> or at least one anti-TNF agent had failed.<sup>[37]</sup> Tocilizumab plus methotrexate or DMARDs produced significantly higher ACR20, ACR50 and ACR70 response rates and significantly higher clinical remission rates, according to DAS 28 scores, than methotrexate or DMARDs alone at study end in OPTION, RADIATE and TOWARD (table III).<sup>[35-37]</sup> The ACR20, ACR50 and ACR70 response rates at study end were also significantly higher with tocilizumab plus methotrexate than methotrexate therapy alone in CHARISMA (table III).<sup>[34]</sup>

Similarly, in LITHE, the ACR20 response rate at week 24 (coprimary endpoint; 56% vs 27%;  $p < 0.0001$ ),<sup>[44]</sup> and the ACR20, ACR50, ACR70 and remission rates at week 52 (secondary endpoints; table III) were significantly higher with tocilizumab 8 mg/kg plus methotrexate than with



**Fig. 1.** Long-term efficacy of tocilizumab 8 mg/kg. Data are from a long-term, noncomparative extension (STREAM study)<sup>[39]</sup> of a randomized, double-blind, placebo-controlled study in Japanese patients with rheumatoid arthritis.<sup>[29]</sup> Patients completing the double-blind study received intravenous tocilizumab 8 mg/kg every 4 weeks for up to 5 years, plus oral prednisolone or NSAIDs as required. Patient numbers at 2 and 4 years were not reported. Shown are the proportions of patients achieving an ACR20, ACR50 or ACR70 response (values estimated from a graph). **ACR** = American College of Rheumatology; **ACR20, 50 or 70** = improvement of  $\geq 20\%$ ,  $\geq 50\%$  or  $\geq 70\%$  in ACR standard criteria (see table II for ACR standard criteria).

methotrexate alone.<sup>[38]</sup> Furthermore, radiographic disease progression was significantly less in patients receiving tocilizumab plus methotrexate therapy than methotrexate alone at week 52 (coprimary endpoint).<sup>[38]</sup> Significantly smaller increases from baseline to week 52 in the total Genant-modified Sharp (0.3 vs 1.1;  $p \leq 0.0001$ ), erosion (0.2 vs 0.7;  $p \leq 0.0001$ ) and joint space narrowing (0.1 vs 0.4;  $p < 0.01$ ) scores were observed with tocilizumab 8 mg/kg plus methotrexate compared with patients receiving methotrexate alone.<sup>[38]</sup>

Mean CRP levels had normalized at study end in patients treated with tocilizumab plus methotrexate or DMARDs in CHARISMA,<sup>[34]</sup> RADIATE,<sup>[37]</sup> OPTION<sup>[35]</sup> and TOWARD,<sup>[36]</sup> with reductions observed from week 2 onwards. Changes from baseline in mean haemoglobin levels were significantly greater with tocilizumab 8 mg/kg plus methotrexate than with methotrexate alone in OPTION (12.4 vs  $-0.3$  g/L;  $p < 0.0001$ )<sup>[35]</sup> and in RADIATE (1.2 vs  $-0.1$  g/dL [values estimated from a graph];  $p < 0.001$ ), and with tocilizumab 8 mg/kg plus DMARD than

with DMARD alone in TOWARD (mean 0.98 g/dL vs  $-0.13$  g/dL;  $p < 0.0001$ ).<sup>[36]</sup>

#### 4.3.2 Effects on HR-QOL

Significantly greater improvements in HR-QOL measures were observed with tocilizumab plus methotrexate or DMARD combination therapy in patients with moderate to severe rheumatoid arthritis in the LITHE,<sup>[38]</sup> OPTION,<sup>[35]</sup> TOWARD<sup>[36]</sup> and RADIATE<sup>[37]</sup> trials. In LITHE, the AUC of HAQ DI scores at week 52 reduced significantly with tocilizumab 8 mg/kg plus methotrexate compared with methotrexate alone, with a treatment difference of  $-86$  (95% CI  $-113, -59$ ).<sup>[38]</sup> In OPTION, patients receiving tocilizumab 8 mg/kg plus methotrexate achieved significantly greater improvements from baseline to week 24 versus methotrexate alone recipients in the HAQ DI ( $-0.55$  vs  $-0.34$ ), Physician's Global Assessment ( $-42$  vs  $-33$ ) and Patient's Global Assessment ( $-33$  vs  $-18$ ) scores ( $p < 0.05$  for all comparisons).<sup>[35]</sup> Similarly, in RADIATE, improvements from baseline to week 24 in HAQ ( $-0.39$  vs  $-0.05$ )<sup>[37]</sup> and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (8.8 vs 4.2)<sup>[42]</sup> scores were significantly ( $p \leq 0.05$ ) greater with tocilizumab 8 mg/kg plus methotrexate than methotrexate alone.

Tocilizumab 8 mg/kg plus DMARD therapy also produced significantly greater ( $p < 0.0001$ ) improvements from baseline to week 24 in HAQ ( $-0.5$  vs  $-0.2$ ), FACIT-Fatigue (8.0 vs 3.6), SF-36 physical (8.9 vs 4.1) and mental (5.3 vs 2.3) summary scores in TOWARD.<sup>[36]</sup>

In addition, a pooled analysis of data from OPTION and TOWARD showed that the improvement in HR-QOL measures was rapid and sustained during tocilizumab therapy; SF-36 individual component and physical and mental summary scores reduced significantly ( $p$ -Value not reported) from week 8 onwards until week 24 with tocilizumab 8 mg/kg plus DMARDs relative to DMARDs alone.<sup>[41]</sup> Another pooled analysis of these two studies showed that improvement from baseline to week 24 in HR-QOL measures with tocilizumab 8 mg/kg plus DMARD

relative to DMARD therapy generally occurred irrespective of age, i.e. in patients aged <65 years and in those aged  $\geq 65$  years.<sup>[43]</sup>

Improvements in HR-QOL were also observed with tocilizumab monotherapy. There was significant ( $p < 0.01$ ) improvement in modified HAQ scores from baseline to study end with tocilizumab 8 mg/kg relative to methotrexate in SATORI; a clinically significant improvement (a decrease of  $\geq 0.22$  units) in HAQ scores was observed in 67% of tocilizumab monotherapy recipients compared with 34% of methotrexate recipients.<sup>[31]</sup>

## 5. Tolerability

This section reports tolerability data from the fully published individual clinical trials discussed in section 4, with the focus on data for the 8 mg/kg approved dosage of tocilizumab, wherever possible.<sup>[29,30,34,35,37]</sup> Also discussed are data from 3778 patients who received at least one dose of tocilizumab 4 or 8 mg/kg and long-term data (including open-label extension studies) from 2562 patients who received tocilizumab 8 mg/kg with or without DMARDs (total exposure 3685 patient-years), available from the European summary of product characteristics.<sup>[9]</sup> In addition, tolerability data from the European assessment report are also presented.<sup>[44]</sup> In general, only descriptive analyses of tolerability data were reported.

### 5.1 General Tolerability Profile

Intravenous tocilizumab 8 mg/kg every 4 weeks was generally well tolerated when administered as monotherapy<sup>[29-32,34]</sup> or in combination with methotrexate<sup>[34,37]</sup> or DMARDs<sup>[36]</sup> for up to 52 weeks in patients with rheumatoid arthritis. The rates of withdrawal because of treatment-emergent adverse events were generally low in tocilizumab 8 mg/kg monotherapy recipients (10% [5 of 52],<sup>[34]</sup> 4% [11 of 288]<sup>[32]</sup>) and methotrexate monotherapy recipients (8% [4 of 49]<sup>[34]</sup> or 5% [15 of 284]<sup>[32]</sup>). Among patients receiving tocilizumab-based combination therapy in CHARISMA,<sup>[34]</sup> TOWARD<sup>[36]</sup> and RADIATE,<sup>[37]</sup> the rates of discontinuation be-

cause of adverse events were 4–12% with tocilizumab 8 mg/kg plus methotrexate or DMARDs and 2–5% with methotrexate or DMARDs alone.

Pooled data from 2644 patients participating in five controlled trials (AMBITION,<sup>[32]</sup> LITHE,<sup>[38]</sup> OPTION,<sup>[35]</sup> TOWARD<sup>[36]</sup> and RADIATE<sup>[37]</sup>) showed that the most common (incidence  $\geq 5\%$ ) treatment-emergent adverse events with tocilizumab plus methotrexate or DMARD therapy were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT (incidences not reported).<sup>[9]</sup> Patients in these trials had received tocilizumab 8 mg/kg in combination with methotrexate ( $n = 774$ ), tocilizumab 8 mg/kg in combination with methotrexate or other DMARDs ( $n = 1582$ ), or tocilizumab 8 mg/kg monotherapy ( $n = 288$ ).

Treatment-emergent adverse events were generally mild to moderate in nature, regardless of whether tocilizumab was administered alone or in combination with other DMARDs<sup>[29,30,34,35,37]</sup> The most commonly occurring adverse events with tocilizumab monotherapy in the placebo-controlled Japanese trial in patients with long-standing rheumatoid arthritis included common cold (9.1% of tocilizumab 8 mg/kg recipients vs 13.0% of placebo recipients), headache (5.5% vs 1.9%), pruritus (3.6% vs 5.6%), skin eruption (5.5% vs 1.9%), stomatitis (7.3% vs 3.7%) and fever (5.5% vs 1.9%).<sup>[29]</sup>

Adverse events occurring in  $\geq 5\%$  of patients with early rheumatoid arthritis receiving tocilizumab 8 mg/kg monotherapy or DMARDs in SAMURAI,<sup>[30]</sup> and in patients with long-standing rheumatoid arthritis receiving tocilizumab 8 mg/kg plus methotrexate or methotrexate alone in OPTION<sup>[35]</sup> are shown in figure 2. The most frequent adverse events in the two studies were nasopharyngitis,<sup>[30]</sup> and dyspepsia and abdominal pain,<sup>[35]</sup> respectively (figure 2).

Serious adverse events occurred in 2.8% of tocilizumab 4 or 8 mg/kg monotherapy recipients and 3.8% of placebo recipients in the placebo-controlled Japanese trial;<sup>[29]</sup> the incidence of serious adverse events during a 5-year extension of this study (STREAM) was 27.5 events/100 patient-years.<sup>[38]</sup> In active comparator-controlled trials, serious adverse events occurred in 4–18%

of patients receiving tocilizumab 8 mg/kg monotherapy,<sup>[30,32,34]</sup> 6–14% of patients receiving tocilizumab 8 mg/kg in combination with methotrexate<sup>[34,35,37]</sup> and 3–13% of patients receiving methotrexate or other DMARDs alone.<sup>[30,32,34,35,37]</sup>

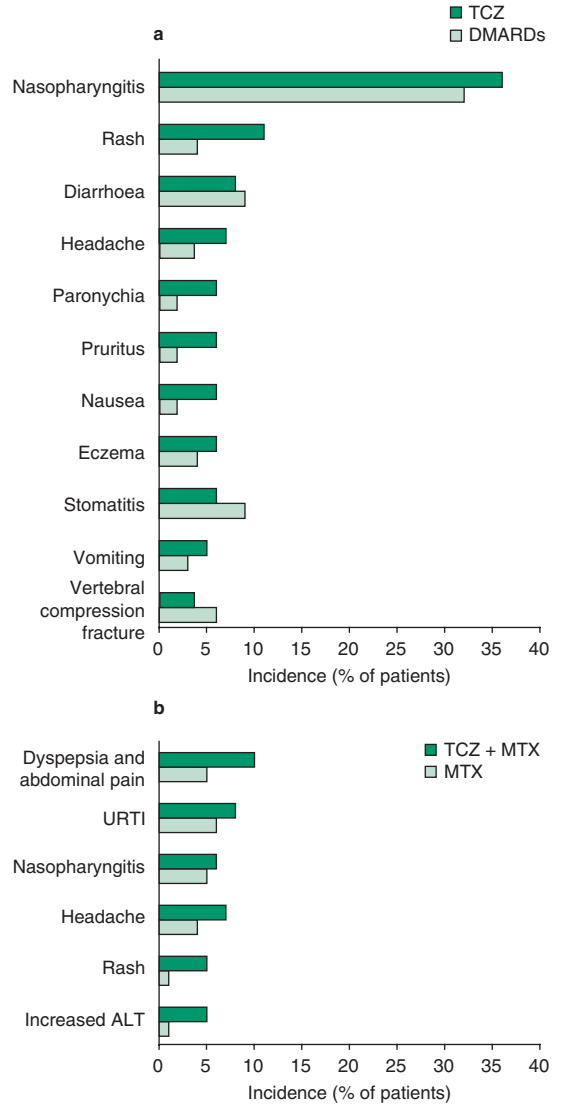
Rates of death were generally similar in patients receiving tocilizumab 4 or 8 mg/kg, DMARD or methotrexate therapy in 6-month trials (0.41/100 patient-years, 0.8/100 patient-years and 0.75/100 patient-years, respectively); the rate of death in tocilizumab recipients did not increase in long-term extension studies (0.42/100 patient-years).<sup>[44]</sup> Of the deaths reported in patients receiving tocilizumab, five occurred in the 6-month controlled studies, 12 during the long-term extension studies and one occurred prior to enrolling in a long-term study. Causes of death included myocardial ischaemia, cardiopulmonary arrest, stroke and infections.<sup>[44]</sup>

5.2 Infections

In clinical trials of up to 52 weeks' duration, the incidence of infections in tocilizumab recipients was 127 events/100 patient-years compared with 112 events/100 patient-years in placebo plus DMARD recipients.<sup>[9]</sup> The rate of infection during long-term extension studies (total exposure 3685 patient-years) was 116 events/100 patient-years.<sup>[9]</sup>

The incidence of serious treatment-emergent infections was generally low with tocilizumab; the proportions of tocilizumab recipients and methotrexate or other DMARD recipients experiencing serious infections are shown in table IV.<sup>[32,34-37]</sup> Similarly, in pooled data from controlled clinical trials the incidence of serious treatment-emergent infections in patients receiving tocilizumab plus methotrexate or DMARD was 5.3 events/100 patient-years compared with 3.9 events/100 patient-years in those receiving methotrexate or DMARDs alone.<sup>[9]</sup>

The incidence of treatment-emergent serious infections, including pneumonia, cellulitis and diverticulitis, in the long term (core and extension studies) was also generally low (3.9 events/100 patient-years).<sup>[9]</sup> For example, in STREAM, the



**Fig. 2.** Tolerability of intravenous tocilizumab (TCZ) 8 mg/kg administered every 4 wk in patients with rheumatoid arthritis (RA) in the (a) SAMURAI and (b) OPTION trials. Shown are the most frequent (≥5%) adverse events occurring in patients who received TCZ or conventional disease-modifying antirheumatic drugs (DMARDs) in two randomized, multicentre trials of double-blind<sup>[35]</sup> or x-ray reader-blinded<sup>[30]</sup> design. (a) Patients in SAMURAI with early RA received TCZ 8 mg/kg monotherapy or conventional DMARDs for 52 wk.<sup>[30]</sup> (b) Patients in OPTION with long-standing RA received TCZ 8 mg/kg plus methotrexate (MTX) or MTX alone for 24 wk.<sup>[35]</sup> URTI = upper respiratory tract infection.

5-year Japanese extension study, the incidence of serious infections was 5.7 events/100 patient-years in

**Table IV.** Incidence of serious treatment-emergent infections in patients (pts) receiving intravenous tocilizumab (TCZ) 2, 4 or 8 mg/kg every 4 wk. Data are from randomized, multicentre studies of TCZ in adult pts with rheumatoid arthritis reporting the incidence of serious treatment-emergent infection.<sup>[32,34-37]</sup> studies were of double-blind design, except for SAMURAI,<sup>[30]</sup> which was x-ray reader-blinded. TCZ was administered either as monotherapy or in combination with methotrexate (MTX) or disease-modifying antirheumatic drugs (DMARDs). Trial acronyms are defined in table I and study details are described in table III

Study	Treatment (mg/kg)	Pts with serious infection [%]	Infection type (no. of pts)
AMBITION <sup>[32]</sup>	TCZ 8	4 of 288 [1.4]	NR
	MTX	2 of 284 [0.7]	NR
CHARISMA <sup>[34]</sup>	TCZ 2	4 of 53 [7.6]	RTI (2); limb abscess (1); osteomyelitis (1)
	TCZ 4	0	
	TCZ 8	0	
	TCZ 2+MTX	0	
	TCZ 4+MTX	0	
	TCZ 8+MTX	3 of 50 [6]	Sepsis (2); infective arthritis (1)
	MTX	0	
OPTION <sup>[35]</sup>	TCZ 4+MTX	3 of 212 [1]	NR
	TCZ 8+MTX	6 of 206 [3]	NR
	MTX	2 of 204 [1]	NR
RADIATE <sup>[37]</sup>	TCZ 4+MTX	3 of 163 [1.8]	Necrotising pneumonia <sup>a</sup>
	TCZ 8+MTX	8 of 175 [4.6]	Staphylococcal polyarthritis <sup>a</sup>
	MTX	5 of 160 [3.1]	Urosepsis; osteomyelitis/cellulitis <sup>a</sup>
SAMURAI <sup>[30]</sup>	TCZ 8	12 of 157 [7.6]	Pneumonia (3); upper RTI (2); cellulitis (2); gastroenteritis (1); herpes zoster (1); herpes simplex (1); perianal abscess (1); unidentified infection (1)
	DMARDs <sup>b</sup>	8 of 145 [5.6]	Gastroenteritis (3); pneumonia (2); upper RTI (1); herpes zoster (1); sepsis (1)
TOWARD <sup>[36]</sup>	TCZ 8+DMARDs	22 of 802 [2.7]	Cellulitis (5); pneumonia (3); herpes zoster (3) <sup>c</sup>
	DMARDs <sup>b</sup>	8 of 414 [1.9]	Pneumonia (2) <sup>c</sup>

a Only serious infections leading to treatment discontinuation were specified.

b In SAMURAI,<sup>[30]</sup> pts received MTX (either as monotherapy or in combination with other DMARDs), other DMARDs and/or immunosuppressants. In TOWARD,<sup>[36]</sup> pts continued stable dosages of MTX, chloroquine, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine or parenteral gold.

c Not all serious infections were specified.

**NR** = not reported; **RTI** = respiratory tract infection.

patients receiving tocilizumab 8 mg/kg monotherapy, with the most frequent infections being pneumonia (1.5 events/100 patient years), herpes zoster (1.1 events/100 patient years), acute bronchitis (0.8 events/100 patient years) and pyelonephritis (0.5 events/100 patient years).<sup>[38]</sup>

Tocilizumab did not affect the humoral response of rheumatoid arthritis patients to influenza vaccination, eliciting a similar response to that observed in patients receiving DMARDs.<sup>[45]</sup> There were no cases of tuberculosis in OPTION,<sup>[35]</sup> RADIATE,<sup>[37]</sup> CHARISMA<sup>[34]</sup> or SATORI.<sup>[31]</sup>

Fatal reactivation of Epstein-Barr virus infection occurred in one patient in the placebo-controlled Japanese study,<sup>[29]</sup> although it is not

known whether this was related to tocilizumab; Epstein-Barr virus DNA was found in the patient's plasma and in blood samples taken prior to study initiation. Retrospective screening found no evidence of Epstein-Barr virus DNA positivity in blood samples from other patients.<sup>[29]</sup>

### 5.3 Effects on Lipid Levels

Moderate, reversible increases in mean serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides occurred in tocilizumab recipients.<sup>[29-32,34-37]</sup> Sustained elevations in total cholesterol of  $\geq 6.2$  mmol/L and low-density lipoprotein cholesterol (LDL-C)

of  $\geq 4.1$  mmol/L occurred in  $\approx 24\%$  and  $15\%$  of patients in clinical trials.<sup>[9]</sup>

However, the atherogenic index ([total cholesterol – HDL-C]/HDL-C) was generally unchanged among patients receiving tocilizumab monotherapy for 1 year in patients with early rheumatoid arthritis in SAMURAI; 27 patients received lipid-lowering therapy during the study and their cholesterol levels improved.<sup>[30]</sup>

The artherogenic index was also generally unchanged in patients with long-standing rheumatoid arthritis in CHARISMA, though there were some increases and decreases between infusions in patients receiving tocilizumab 8 mg/kg (monotherapy or combination therapy).<sup>[34]</sup> In OPTION, there was no corresponding increase in vascular adverse events with tocilizumab 8 mg/kg plus methotrexate compared with methotrexate alone (6% vs 5%).<sup>[35]</sup> In RADIATE, a  $>30\%$  increase in the LDL-C/HDL-C index occurred in 22% of patients receiving tocilizumab 8 mg/kg and in 10% of methotrexate recipients; no ischaemic cardiac disorders were reported in tocilizumab recipients.<sup>[37]</sup>

In TOWARD in patients receiving tocilizumab 8 mg/kg plus DMARD combination therapy, 1.4% of tocilizumab compared with  $<1\%$  of DMARD alone recipients experienced an increase in triglyceride levels from  $<500$  mg/dL to  $\geq 500$  mg/dL, but the increase was not associated with clinical symptoms (particularly pancreatitis).<sup>[36]</sup> A  $>30\%$  increase in total cholesterol:HDL-C ratio was reported in 12% of tocilizumab 8 mg/kg plus DMARD and 7% of DMARD alone recipients; a  $>30\%$  increase in LDL-C:HDL-C ratio occurred in 20% and 12% of patients in the corresponding treatment groups.<sup>[36]</sup>

Generally similar increases in lipid levels, which stabilized during long-term therapy (STREAM study), were also seen in Japanese patients with long-standing rheumatoid arthritis receiving tocilizumab 8 mg/kg monotherapy for up to 5 years;<sup>[29,38]</sup> mean total blood cholesterol in these patients was 185 mg/dL at baseline, 220 mg/dL at 1 year and 214 mg/dL at 5 years.<sup>[38]</sup> However, apart from ischaemic heart disease in one patient, there were no treatment-related cardiovascular serious adverse events.<sup>[38]</sup>

## 5.4 Effects on Liver Enzymes

Transient or intermittent mild and moderate elevations of hepatic transaminases, which were not associated with hepatic injury, have been commonly reported in patients receiving tocilizumab in clinical trials.<sup>[9]</sup> In clinical trials, transient elevations in ALT or AST of more than 3 times the ULN occurred in 2% of tocilizumab 8 mg/kg compared with 5% of methotrexate recipients, and in 7% of tocilizumab 8 mg/kg plus DMARDs compared with 2% of DMARD recipients.<sup>[9]</sup>

Combination therapy with methotrexate (a potentially hepatotoxic agent) generally resulted in an increase in the incidence of AST and ALT elevations relative to monotherapy, with elevations in ALT and AST of  $>5$  times the ULN reported in 0.7% of tocilizumab monotherapy compared with 1.4% of tocilizumab plus DMARD recipients, the majority of whom discontinued therapy.<sup>[9]</sup> However, no clinically relevant increases in direct bilirubin or clinical evidence of hepatitis or hepatic impairment was observed in these patients.<sup>[9]</sup> For example, liver enzyme elevations were dose dependent and larger (no p-value reported) with tocilizumab plus methotrexate than with tocilizumab alone in CHARISMA in patients with long-standing rheumatoid arthritis; the maximum increase in ALT from baseline to week 2 was 88% with tocilizumab 8 mg/kg plus methotrexate versus 45% with tocilizumab alone vs 0% with methotrexate alone.<sup>[34]</sup> A total of 127 tocilizumab (4 or 8 mg/kg monotherapy or combination therapy) recipients had ALT levels above the ULN; all mean liver enzyme levels returned to near-baseline levels within 8 weeks of the final infusion of tocilizumab.<sup>[34]</sup> Bilirubin levels increased gradually throughout the study; the total bilirubin elevation was  $<3$  times greater than the ULN and there was no relationship between ALT and total bilirubin increases.<sup>[34]</sup>

Similarly, in OPTION in patients with long-standing rheumatoid arthritis, combination therapy with tocilizumab 4 or 8 mg/kg plus methotrexate was associated with 11 withdrawals owing to elevations in ALT levels; of these, seven patients had increases  $>5$  times above



the ULN and four patients had levels 3–5 times above the ULN.<sup>[35]</sup> None of these patients developed signs or symptoms associated with hepatitis.<sup>[35]</sup> Two patients receiving tocilizumab 4 mg/kg in this study discontinued treatment because of elevated total bilirubin levels (1.8 and 2.8 times the ULN); no concomitant increases in ALT or AST levels were observed.<sup>[35]</sup> In RADIATE,<sup>[37]</sup> increases in ALT levels of more than 3-fold greater than the ULN occurred in 2.5% of tocilizumab 8 mg/kg plus methotrexate recipients (compared with <1% in methotrexate alone recipients); there were two cases of mild to moderate hepatic steatosis, but no evidence of clinical hepatic dysfunction or hepatitis.<sup>[37]</sup>

Transient increases in ALT and AST levels were also observed during long-term tocilizumab 8 mg/kg monotherapy. In the STREAM 5-year extension study, increases in AST and ALT of grade 2 or higher severity occurred in 9 (6%) and 14 (10%) of 143 patients (most of the increases were transient and resolved without treatment); no serious liver disorders were observed during this study.<sup>[38]</sup>

### 5.5 Effects on Haematological Parameters

Tocilizumab therapy was associated with transient, dose-dependent decreases in neutrophils.<sup>[34,36,37]</sup> Neutrophil counts of  $<1 \times 10^9/L$  were reported in 3% of tocilizumab 8 mg/kg recipients compared with <0.1% of DMARD recipients in clinical trials, with approximately half of these patients developing the condition within 8 weeks of initiating therapy.<sup>[9]</sup> Decreases in neutrophil counts of  $<0.5 \times 10^9/L$  occurred in 0.3% of patients.<sup>[9]</sup> No associations were observed between reduced neutrophil counts and the incidence of infection.<sup>[9,34,36,37]</sup>

Four tocilizumab 8 mg/kg recipients had Common Toxicity Criteria (CTC) grade 4 neutropenia in RADIATE, necessitating withdrawal from the study, and there were four tocilizumab 8 mg/kg recipients with transient CTC grade 3 neutropenia.<sup>[37]</sup> In the STREAM 5-year extension study, transient grade 2 and 3 neutropenia occurred in 17 (12%) and 9 (6%) of 143 patients receiving tocilizumab 8 mg/kg mono-

therapy; no patient experienced febrile neutropenia or withdrew from the study because of neutropenia.<sup>[38]</sup>

Decreases in platelet counts resulting in values of  $<100 \times 10^3/\mu L$  were reported in 1.7% of tocilizumab 8 mg/kg recipients compared with <1% of DMARD recipients; however, these decreases were not associated with bleeding events.<sup>[9]</sup>

### 5.6 Other Adverse Events

Infusion reactions (selected reactions occurring during or within 24 hours of infusion) occurred in 7% versus 5% of tocilizumab 8 mg/kg and DMARD plus placebo recipients.<sup>[9]</sup> Events occurring primarily during infusion were episodes of hypertension, whereas headache and skin reactions (rash and urticaria) occurred within 24 hours of the infusion.<sup>[9]</sup> These events were not treatment limiting<sup>[9]</sup> and were generally transient and mild in severity.<sup>[29,30,37]</sup>

Anaphylactic reactions occurred in 0.2% (6 of 3778 patients) of tocilizumab recipients and were generally higher (several fold) with the 4 mg/kg than with the 8 mg/kg dosage of the drug.<sup>[9]</sup> Clinically significant hypersensitivity reactions (generally observed during the second to fifth infusions) requiring treatment discontinuation occurred in 0.3% (13 of 3778 patients) of tocilizumab recipients in the controlled and open-label extension trials. Anti-tocilizumab antibodies were reported in 1.6% (46 of 2876) of patients; six of these patients developed clinically significant hypersensitivity reactions, of which five discontinued therapy. Neutralizing antibodies were reported in 1.1% (30 of 2876 patients), but these appeared not to be associated with any clinical response.<sup>[9]</sup>

Complications of diverticulitis, including generalized purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess, occurred uncommonly during 6 months of controlled tocilizumab therapy.<sup>[9]</sup>

Clinical data are insufficient to assess the incidence of malignancies following tocilizumab therapy. However, three malignancies were reported in SAMURAI among tocilizumab recipients and none among DMARD recipients;<sup>[30]</sup> the incidence of malignancies in Japanese rheu-

matoid arthritis patients receiving tocilizumab appeared to be similar to the incidence observed in an observational cohort of Japanese rheumatoid arthritis patients.<sup>[46]</sup>

## 6. Dosage and Administration

Tocilizumab, in combination with methotrexate, is approved in the EU for the treatment of moderate to severe active rheumatoid arthritis in adult patients with inadequate response to, or who are intolerant of, prior DMARD or TNF antagonist therapy; it may also be administered as monotherapy in patients intolerant of methotrexate or in whom methotrexate therapy is inappropriate.<sup>[9]</sup> The drug is not recommended for use in paediatric patients in the EU.<sup>[9]</sup> Tocilizumab is also approved in Japan for the treatment of rheumatoid arthritis (including the inhibition of structural joint damage progression), polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease in patients who do not show a sufficient response to existing therapies.<sup>[10,11]</sup>

The recommended dosage for use in adult rheumatoid arthritis patients is tocilizumab 8 mg/kg (and no less than 480 mg<sup>[9]</sup>), administered every 4 weeks as an intravenous infusion over 1 hour.<sup>[9,10]</sup> As part of the approval, the manufacturer is required to gather post-marketing safety data.<sup>[9,10]</sup>

Tocilizumab should not be initiated in patients with active infections and patients should be screened for latent tuberculosis infections prior to initiating therapy.<sup>[9]</sup> Regular monitoring of ALT and AST levels, lipid parameters, and neutrophil and platelet counts is recommended. Caution is advised and/or drug dosage should be reduced, interrupted or discontinued in patients with liver enzyme abnormalities (ALT or AST persistently elevated >ULN), low absolute neutrophil count (absolute neutrophil count <2×10<sup>9</sup>/L) or low platelet count (count <100×10<sup>3</sup>/μL) [see summary of product characteristics for full dosage recommendations<sup>[9]</sup>].

Local prescribing information should be consulted for additional information on use in special patient populations, precautions and contraindications.

## 7. Place of Tocilizumab in the Management of Rheumatoid Arthritis

The chronic inflammation and progressive joint destruction that characterize rheumatoid arthritis have serious consequences for patients, causing functional disability that reduces work capacity and substantially impairs quality of life.<sup>[2]</sup> Moreover, major organ damage resulting from chronic inflammation can reduce life expectancy.<sup>[47]</sup> The aims of rheumatoid arthritis management are to prevent or control joint damage, prevent functional impairment and minimize pain.<sup>[3]</sup> Typically, treatment comprises initial pain relief with NSAIDs and/or analgesics, followed by the initiation of DMARDs as soon as possible (preferably within 3 months of diagnosis) to reduce disease activity and joint destruction.<sup>[3,4,48,49]</sup>

DMARD selection is individualized according to patient characteristics, including comorbidities, disease severity and prognosis, and drug characteristics, such as relative efficacy and tolerability, convenience of administration, cost and monitoring requirements.<sup>[3]</sup> The most commonly used conventional DMARDs are methotrexate, hydroxychloroquine and sulfasalazine, administered either alone or with low-dose oral corticosteroids. Methotrexate is considered the gold standard of DMARDs because of its low cost and well established efficacy and tolerability.<sup>[3,48]</sup> However, many patients do not achieve long-term remission of rheumatoid arthritis with methotrexate monotherapy; approximately 44% of patients receiving monotherapy with oral or subcutaneous methotrexate 15–30 mg/week did not sustain clinical remission (DAS ≤2.4) after 6–9 months in one study.<sup>[50]</sup> Strategies such as switching to other conventional DMARDs, intensive therapy with combinations of conventional DMARDs or additional therapy with NSAIDs, oral corticosteroids or analgesics may be useful,<sup>[48]</sup> although patients do not achieve a clinical response to methotrexate monotherapy are estimated to have only a 10% likelihood of response to other conventional DMARDs.<sup>[50]</sup> Thus, a substantial proportion of patients experience progressive, treatment-refractory

disease despite extensive therapy with conventional DMARDs.<sup>[51]</sup>

Clinical outcomes can be improved by the addition of biological response modifiers that target specific molecules in the inflammatory cascade.<sup>[48]</sup> These include the anti-TNF agents (e.g. etanercept, infliximab and adalimumab), rituximab (an anti-CD20 monoclonal antibody that selectively depletes B cells) and abatacept (a T-cell co-stimulator modulator).<sup>[52]</sup> Combination therapy with biological agents plus methotrexate or other conventional DMARDs has been shown to be more effective than monotherapy or sequential therapy with conventional DMARDs for preventing radiographic disease progression, even in patients who do not achieve a complete clinical response.<sup>[5]</sup> Of the currently available biological agents, anti-TNF agents are the most commonly used.

Treatment guidelines issued by the ACR<sup>[3]</sup> and EULAR,<sup>[48]</sup> and the 2007 consensus statement on biological agents<sup>[49]</sup> recommend that anti-TNF therapy be considered instead of, or in addition to, treatment with conventional DMARDs in patients who do not achieve a satisfactory clinical response to one conventional DMARD (usually methotrexate, which EULAR considers an 'anchor' drug for rheumatoid arthritis therapy<sup>[48]</sup>). The recent ACR recommendations suggest that biological agents be considered based on the duration of disease and disease activity.<sup>[3]</sup> Anti-TNF agents are recommended for patients with early disease (<6 months) and high disease activity, and for patients with intermediate (6–24 months) or long-term ( $\geq 24$  months) disease and at least moderate disease activity.<sup>[3]</sup> A similar approach is advocated by the British Society for Rheumatology, although these guidelines require patients to have not responded to two previous DMARDs before starting anti-TNF therapy.<sup>[53]</sup> Furthermore, both the British<sup>[53]</sup> and EULAR<sup>[48]</sup> guidelines suggest that anti-TNF agents may be appropriate first-line therapy in patients with severe disease or those in whom conventional DMARDs are contraindicated. Nonetheless, anti-TNF agents are not efficacious in all patients; up to 50% of patients receiving anti-TNF-based therapy fail to achieve significant improvements

in disease status.<sup>[54]</sup> These agents may also be associated with serious adverse effects, such as tuberculosis.<sup>[5,55]</sup> Thus, there remains a need for effective therapies that confer clinical improvement and prevent disease progression.

IL-6, which has been shown to have a critical role in the pathogenesis of rheumatoid arthritis, is an attractive target for biological therapy and tocilizumab is the first agent developed to specifically target this molecule.<sup>[7]</sup> Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits IL-6 signal transduction, and has been shown to normalize serum IL-6 levels in rheumatoid arthritis patients (section 2). It is administered intravenously and has a favourable pharmacokinetic profile with a long  $t_{1/2}$  that allows administration every 4 weeks (section 3).

Well designed studies of up to 52 weeks' duration have demonstrated that tocilizumab 8 mg/kg is generally efficacious and well tolerated in patients with moderate to severe rheumatoid arthritis, including those whose previous therapy with methotrexate, other conventional DMARDs or anti-TNF agents had failed (section 4). Although lower dosages of tocilizumab were evaluated in some clinical trials (table III), consistently better efficacy in terms of ACR20, ACR50 and ACR70 responses, individual ACR components, DAS 28 and patient reported outcomes, was observed with the 8 mg/kg dosage, which is the approved dosage.<sup>[44]</sup> In addition, logistic regression analyses of data from two pivotal studies showed that the odds of achieving an ACR20 response was higher with tocilizumab 8 mg/kg relative to comparator than with the 4 mg/kg dosage relative to comparator.<sup>[44]</sup> Furthermore, across all studies that evaluated the 4 and 8 mg/kg dosages (table III), clinical responses with tocilizumab 8 mg/kg were generally higher than with the 4 mg/kg dosage (statistical data available only for one study<sup>[29]</sup>).

In patients who had not experienced any prior treatment failures, tocilizumab 8 mg/kg monotherapy was noninferior to methotrexate in terms of reducing disease activity (section 4.1). Additional analyses demonstrated that at week 24,

ACR20, ACR50 and ACR70 response rates were significantly higher and HR-QOL scores were improved to a significantly greater extent with tocilizumab than with methotrexate.

In patients with an inadequate response to previous therapy, monotherapy with tocilizumab 8 mg/kg reduced clinical disease activity more effectively than conventional DMARDs in patients with early rheumatoid arthritis (section 4.2), or than placebo, methotrexate or other DMARDs in patients with long-standing disease (section 4.3). At least 63% of tocilizumab 8 mg/kg monotherapy recipients achieved ACR20 at study end (vs 11% of placebo and 25–41% of patients treated with methotrexate or other DMARDs). These benefits were maintained during long-term therapy with tocilizumab 8 mg/kg for up to 5 years in a noncomparative extension study in patients with long-standing rheumatoid arthritis (section 4.3.1). In addition, significantly less radiographic disease progression was seen with tocilizumab 8 mg/kg monotherapy than with DMARDs in patients with early rheumatoid arthritis (section 4.2.1).

Combination therapy with a biological agent plus conventional DMARDs is likely to produce better disease control than therapy with a single DMARD, especially in patients with severe rheumatoid arthritis.<sup>[48]</sup> Tocilizumab 8 mg/kg administered in combination with methotrexate or other conventional DMARDs was more effective than methotrexate or DMARDs alone in terms of improving clinical outcomes and/or HR-QOL in patients with early or long-standing rheumatoid arthritis whose treatment with methotrexate or other conventional DMARDs had failed (section 4.3). In addition, significantly less radiographic disease progression was seen with tocilizumab 8 mg/kg plus methotrexate combination therapy than with DMARDs alone in one study in patients with long-standing rheumatoid arthritis (section 4.3.1).

Notably, tocilizumab may represent an effective treatment option in patients who have previously not responded to anti-TNF therapy. Recent results from RADIATE<sup>[37]</sup> demonstrate that tocilizumab plus methotrexate is efficacious and generally well tolerated in patients

with long-standing rheumatoid arthritis who did not achieve a satisfactory response to anti-TNF therapy. Significantly better ACR20, ACR50 and ACR70 responses were achieved with tocilizumab 8 mg/kg plus methotrexate than with methotrexate alone in patients whose previous therapy with at least one anti-TNF agent had failed (section 4.3.1). In addition, significantly greater improvements in HR-QOL measures were observed with tocilizumab-based combination therapy in these patients (section 4.3.2). Although more data are required from patients switching from anti-TNF therapy to tocilizumab, it is encouraging that there may be a new treatment option available to patients who have experienced an inadequate response to anti-TNF therapy and for whom other therapy options have been exhausted.

To date, there have been no head-to-head, randomized, controlled studies comparing the efficacy of tocilizumab with that of other biological agents, such as the anti-TNF agents (e.g. etanercept, infliximab and adalimumab), rituximab or abatacept. It appears that the rate of ACR20 response is similar (up to 80%) in treatment-refractory patients treated with tocilizumab (as monotherapy or in combination with methotrexate or other DMARDs; sections 4.2 and 4.3) to that reported in patients receiving anti-TNF agents plus methotrexate (approximately 80%).<sup>[56]</sup> Studies directly comparing the efficacy and safety of these therapies are awaited with interest. It would also be of interest to investigate the effects of starting therapy with tocilizumab early, within 1 year of the onset of rheumatoid arthritis, to determine whether there are any advantages to aggressive initial treatment.

The tolerability profile of tocilizumab is generally acceptable and consistent with its mechanism of action. Infections are a cause of concern with anti-TNF agents<sup>[51]</sup> and, as expected with agents that affect the humoral immune response, they are common with tocilizumab. However, the rates of serious treatment-emergent infection were generally low with tocilizumab-based therapy (1–8%) and similar to rates observed in the comparator groups (0.7–5.6%; table IV). There is no evidence from clinical trials that tocilizumab

increases the risk of latent tuberculosis or an increase in the incidence of malignancies. Fatal reactivation of Epstein-Barr virus infection was reported in one patient in the placebo-controlled Japanese study,<sup>[29]</sup> although it is not known whether this was related to tocilizumab.

Increased serum lipid levels have been observed in patients receiving tocilizumab therapy and are of particular concern because of the increased risk of cardiovascular disease among patients with rheumatoid arthritis.<sup>[57]</sup> However, the clinical relevance of these abnormal lipid profiles is unclear, as there were no corresponding increases in cardiovascular events in tocilizumab recipients in the studies reporting these outcomes (section 5.3). Recently, it has been suggested that these changes, in particular the increases in cholesterol and triglycerides, may be a predictable response to the attenuation of inflammation and may not represent increased cardiovascular risk.<sup>[58]</sup> Severe rheumatoid arthritis is often associated with reductions in HDL-C and total cholesterol levels, which may be because of the cytokine-induced activation of the reticuloendothelial system, and treatment with biological agents (e.g. tocilizumab) may dampen inflammation, thereby increasing the levels of HDL-C, LDL-C, total cholesterol and, perhaps, triglycerides.<sup>[58]</sup>

Adherence to treatment is a major issue affecting the outcome of long-term therapy. Tocilizumab has a long  $t_{1/2}$  (section 3) that allows a 4-weekly dose administration schedule, which is convenient compared with some other biological agents such as etanercept and adalimumab that must be administered once weekly or every other week.<sup>[52]</sup> However, it should be noted that tocilizumab is administered intravenously, whereas etanercept and adalimumab are administered subcutaneously.

Cost is another important consideration when comparing biological therapies. Anti-TNF therapy is expensive and the cost prevents the early initiation of therapy with these agents in many eligible patients in the UK.<sup>[59]</sup> No data on the cost of tocilizumab therapy are available at present and pharmacoeconomic studies are required.

In conclusion, intravenous tocilizumab was effective and generally well tolerated when administered either as monotherapy or in combination with conventional DMARDs in adult patients with rheumatoid arthritis, regardless of disease duration or prior therapy. It is the first commercially available agent to target IL-6 as a mediator of inflammation. Tocilizumab-based therapy was consistently more effective than placebo, methotrexate or other DMARDs in reducing disease activity, and some trials also showed significant benefits with tocilizumab in terms of reducing structural joint damage and improving HR-QOL. Notably, tocilizumab-based therapy was effective in patients with long-standing disease who had previously not responded to anti-TNF therapy. More data are required to determine the comparative efficacy and safety of tocilizumab versus other biological agents and to establish their relative cost effectiveness. However, the present data suggest that tocilizumab is an important emerging treatment option in adult patients with rheumatoid arthritis, especially in patients with long-standing, treatment-refractory disease.

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