Tocilizumab: a novel humanized anti-interleukin 6 receptor antibody for the treatment of patients with rheumatoid arthritis

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Abstract: Tocilizumab (TCZ; RoActemra® or Actemra®) is a recombinant humanized monoclonal antibody that acts as an interleukin 6 (IL-6) receptor antagonist. For rheumatoid arthritis (RA), intravenous (IV) TCZ 8 mg/kg every 4 weeks has been approved since 2008 in Japan (where it is also approved for polyarticular juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease), and since 2009 in Europe in combination with methotrexate (MTX) for the treatment of moderate to severe active RA in adult patients with inadequate response to, or intolerance of, disease-modifying antirheumatic drug (DMARD) or tumor necrosis factor (TNF) antagonist therapy. It may also be administered as monotherapy in the same dose regimen in patients with methotrexate intolerance or with inadequate response to MTX. Since January 2011 in the United States, the indication for treatment with TCZ for RA patients with an inadequate response to one or more TNF antagonists was extended to patients with moderately to severely active RA, and the recommended starting dose is 4 mg/kg every 4 weeks, with an increase to 8 mg/kg based on clinical response. All of these approvals are based on the effectiveness and safety of the 8 mg/kg dose regimen when administered either as monotherapy or in combination with conventional DMARDs in well-designed clinical studies in adult patients with moderate to severe RA. TCZ at this dose is more effective than placebo, MTX or other DMARDs in reducing disease activity and improving health-related quality of life (HR-QoL). Although there were fewer responses with the 4 mg/kg dose, this dose every 4 weeks was not statistically different to 8 mg/kg when administered in combination with MTX, and this dose is the recommended starting dose in the US. Both doses have also been shown to inhibit structural joint damage in patients with an inadequate response to MTX. Thus, TCZ is an important new treatment option in patients with moderate to severe RA.

Keywords: interleukin 6, monoclonal antibody, rheumatoid arthritis, tocilizumab

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting up to 1% of the population [Silman, 1993]. The disease is characterized by fluctuating, progressive synovitis and systemic and extra-articular manifestations, resulting in joint destruction and severe disability, even premature death [Kvien, 2009]. Current treatment recommendations are designed to assure rapid complete control of signs and symptoms and to assure limitation of structural joint

damage, which markedly decreases the likelihood of loss of function and disability. Disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) alone and in combination [Saag *et al.* 2008] are effective in a majority of patients, but in approximately 30% of cases RA is not effectively controlled by conventional DMARDs. There is thus a need for more effective treatments for RA based on a better understanding of the underlying pathophysiology of the disease process [Furst *et al.* 2010].

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Recently the development of the new class of biological drugs has led to the approval of five biological groups with different mechanisms of action:

- (i) tumor necrosis factor (TNF) blockers [Maini *et al.* 1998];
- (ii) interleukin 1 (IL-1) monoclonal antibody and receptor antagonists [Alten *et al.* 2008];
- (iii) a selective T-cell costimulatory modulator [Moreland *et al.* 2002];
- (iv) a monoclonal antibody, that inhibits B cells [Dorner and Burmester, 2003]; and
- (v) a receptor monoclonal antibody that inhibits IL-6 receptor signaling [Nishimoto *et al.* 2004, 2003].

The anti-IL-6 receptor monoclonal antibody tocilizumab (TCZ) is the focus of this review.

IL-6 is a pleiotropic pro-inflammatory, multi-functional cytokine produced by a variety of cell types including lymphocytes, monocytes and fibroblasts. It was originally identified as a hepatocyte growth factor, and as a B-cell stimulatory factor that induces the final maturation of B cells into antibody-producing cells. IL-6 has been shown to be involved in such diverse processes as transition of acute to chronic inflammation, T-cell activation, initiation of hepatocyte acute-phase protein synthesis and stimulation of hematopoietic precursor cell growth and differentiation [McInnes and Schett, 2007]. IL-6 is also produced by synovial and endothelial cells leading to local production in joints affected by inflammatory processes such as RA. Several conditions have been linked to the effects of IL-6 on cell proliferation including RA, systemic juvenile idiopathic arthritis, psoriasis, mesangial proliferative glomerulonephritis, multiple myeloma and Castleman's disease.

Patients with RA show elevated IL-6 levels in serum and synovial fluid, so IL-6 was selected as a logical target for drug therapy.

Intravenous TCZ 8 mg/kg in combination with MTX has been approved since 2008 in Japan, since 2009 in Europe and since January 2010 in US for the treatment of moderate to severe active RA in adult patients with inadequate response to, or who are intolerant of, prior DMARD or TNF antagonist therapy. In Japan it is also approved for polyarticular juvenile idiopathic arthritis,

systemic-onset juvenile idiopathic arthritis and Castleman's disease.

The indications and approved dosages are different in the US compared with the rest of the world. Since January 2011 in the US TCZ has been indicated for patients who have failed TNF antagonists and patients with moderately to severely active RA at a starting dose of 4 mg/kg every 4 weeks, with an increase to 8 mg/kg according to clinical response.

Pharmacological properties

Elevated levels of IL-6 in the serum and synovial fluid of RA patients contribute to the chronic inflammatory process characterizing this disease and correlate positively with disease activity. TCZ is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits IL-6 signal transduction. TCZ binds selectively and competitively to soluble and membrane-expressed IL-6 receptors, in either blocking IL-6 signal transduction that occurs via binding directly to the membrane receptor or by the binding of the sIL-6 R/IL-6 complex to gp130. *In vivo*, maximum (>90%) IL-6 receptor saturation was achieved when serum TCZ concentrations were >1 µg/ml. In dose-ranging studies, serum levels of inflammatory markers were normalized in most RA patients, who had detectable levels of TCZ in serum, especially with the 8 mg/kg dose. The dose-response curve for TCZ flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in TCZ concentrations such that clinically meaningful increases in efficacy were not demonstrated in patients treated with >800 mg of TCZ [European Medicines Agency, 2010]. Therefore, TCZ doses exceeding 800 mg per infusion are not recommended. TCZ displays dose-dependent, nonlinear pharmacokinetics and has a long elimination half-life, allowing IV administration every 4 weeks. The elimination of TCZ is biphasic: the total clearance is concentration dependent and is equal to the sum of linear and nonlinear clearance. The nonlinear clearance plays a major role at low TCZ concentrations. At higher TCZ concentrations, the nonlinear clearance pathway is saturated and clearance is mainly determined by the linear clearance [European Medicines Agency, 2010]. In pharmacokinetic analyses no influence was seen related by age, sex or ethnicity. While no studies have been undertaken to assess the effect of renal or hepatic impairment on the pharmacokinetic

parameters of TCZ, patients with mild renal impairment (creatinine clearance of at least 50 ml/min) in phase III had similar pharmacokinetics to those with normal renal function [Frey *et al.* 2010; Nishimoto and Kishimoto, 2008].

Overview of the phase III study program of tocilizumab

An overview of the phase III study program of TCZ is given in Table 1.

Efficacy

AMBITION Study: monotherapy

The AMBITION Study [Jones *et al.* 2010, 2008] evaluated 673 patients, who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX naïve. Doses of 8 mg/kg of TCZ were given every 4 weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 to a maximum of 20 mg weekly over an 8-week period). The primary end point was the proportion of patients who achieved an American College of Rheumatology (ACR20) response at week 24.

This study reflected an earlier RA population (approximately 40% of patients had active RA of <2 years duration) who were primarily naïve to MTX treatment (67% of patients) at the time of enrollment. In addition, approximately 43% of patients were DMARD naïve.

The highest ACR response rates across the five pivotal studies were observed in this study. This

was a noninferiority study in patients receiving TCZ 8 mg/kg alone every 4 weeks *versus* the active comparator, MTX, which was administered with a rapid dose-escalation regimen to 20 mg weekly. Only one dosing schedule of TCZ (8 mg/kg every 4 weeks) was studied as monotherapy in this phase III program. This regimen demonstrated not only noninferiority, but also statistical superiority compared with treatment with MTX. The response rates were: ACR20 (70%), ACR50 (44%) ACR70 (28%); with a 34% remission rate (proportion of patients with Disease Activity Index (DAS28) <2.6).

OPTION Study: MTX inadequate responders

In this double-blind, randomized, placebo-controlled, parallel group phase III study, 623 patients with moderate to severe active RA were treated to receive TCZ 8 mg/kg ($n=205$), TCZ 4 mg/kg ($n=214$), or placebo ($n=204$) intravenously every 4 weeks, with MTX at stable pre-study doses (10–25 mg/week). Rescue therapy with TCZ 8 mg/kg was offered at week 16 to patients with less than 20% improvement in both swollen and tender joint counts. The primary end point was the proportion of patients with 20% improvement in signs and symptoms of rheumatoid arthritis according to American College of Rheumatology criteria (ACR20 response) at week 24.

At 24 weeks, ACR20 responses were seen in more patients receiving TCZ in the 4 mg/kg group, 54 (26%) in the placebo group; odds ratio 4.0 (95% CI 2.6–6.1), $p < 0.0001$ for 8 mg/kg *versus* placebo and odds ratio 2.6 (95% CI 1.7–3.9), $p < 0.0001$ for 4 mg/kg *versus* placebo. More patients receiving TCZ than those receiving placebo had at least one adverse event

Table 1. Overview of the phase III study program of tocilizumab.

Patient Population	Number of patients	Treatment arms	Clinical end point	Study duration
MTX-naïve/free AMBITION	673	TCZ monotherapy vs. MTX	Signs and symptoms	6 months + LTE
MTX IR OPTION	623	TCZ + MTX vs. MTX	Signs and symptoms	6 months + LTE
MTX IR LITHE	1190	TCZ + MTX vs. MTX	Prevention of joint damage in physical function and disability	2 years + 3-year extension (ongoing)
DMARD IR TOWARD	1220	TCZ + DMARD vs. DMARD	Signs and symptoms	6 months + LTE
Anti-TNF IR RADIATE	499	TCZ + MTX vs. MTX	Signs and symptoms	6 months + LTE

Total number of patients: 4205.

MTX, methotrexate; IR, inadequate responder; TCZ, tocilizumab; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; LTE, long-term extension.

(143 [69%] in the 8 mg/kg group; 151 [71%] in the 4 mg/kg group; 129 [63%] in the placebo group). The most common serious adverse events were serious infections or infestations, reported by six patients in the 8 mg/kg group, three in the 4 mg/kg group, and two in the placebo group.

Clinically important and statistically significant improvements in Health Assessment Questionnaire (HAQ), Short Form 36 (SF-36), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores were seen with TCZ when compared with control [Alten *et al.* 2008; Smolen *et al.* 2008].

LITHE Study: MTX inadequate responders

This study had three primary end points: proportion of patients who achieved ACR20 response criteria at week 24, prevention of structural joint damage (evaluated by radiographs) at week 52 (with confirmation at week 104) and physical function at week 52 (with confirmation at week 104).

Patients were randomly assigned to receive TCZ 4 ($n=399$) or 8 mg/kg ($n=398$) (TCZ4 or TCZ8) or placebo ($n=393$) every 4 weeks + MTX. From week 16, stepwise (first 4 mg/kg and then 8 mg/kg) blinded rescue therapy was allowed if patients had <20% improvement in swollen joint count (SJC) and tender joint count (TJC). At 52 weeks, all patients with <70% improvement in SJC and TJC initiated open-label TCZ8; patients with $\geq 70\%$ improvement could also initiate OL TCZ8 according to investigator judgment.

Primary end points were change from baseline to year 2 in Genant-modified Total Sharp Score (GmTSS) [Genant *et al.* 1998] and physical function (area under the curve [AUC] change from baseline to year 2 in Health Assessment Questionnaire Disability Index [HAQ-DI]) [Fries *et al.* 1982]. Efficacy data were reported by original treatment group at randomization.

RA patients treated for 1 year with TCZ 8 mg/kg or 4 mg/kg in addition to MTX experienced significant inhibition in progression of joint damage and improvement in RA signs/symptoms compared with MTX alone.

The intention to treat (ITT) population included 1190 patients (393 control, 399 TCZ 4 mg/kg

[TCZ4], and 398 TCZ 8 mg/kg [TCZ8]). At year 2, most patients in all treatment arms were on TCZ8. Radiographic progression was inhibited by 81% and 70% in the original TCZ8 and TCZ4 groups compared with the original control group. More TCZ8 and TCZ4 patients than controls experienced no radiographic progression. Mean change from baseline at week 104 in the joint space narrowing score (JSN) was 294 for TCZ4, 353 for TCZ8, and 294 for placebo patients. Physical function, assessed by HAQ-DI AUC, significantly improved in TCZ patients *versus* controls. At year 2, proportions achieving ACR70 response were higher in patients randomized to TCZ4 or TCZ8 than in controls. The proportion of patients in DAS28 remission on TCZ8 increased during year 2 (48% [132/275] at year 1 *versus* 65% [156/241] at year 2) [Kremer *et al.* 2010, 2008; Fleishmann *et al.* 2009] (Table 2).

TOWARD Study: DMARD inadequate responders

This study was primarily designed to assess the safety of the 8 mg/kg dose in combination with DMARDs. It evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg TCZ or placebo were given every 4 weeks, in combination with stable DMARD dosage.

The ACR response rate was comparable to the results of the OPTION trial. ACR20 (61%), ACR50 (38%), and ACR70 (21%) *versus* placebo ACR20 (25%), ACR50 (9%), and ACR70 (3%). Disease Activity Index (DAS28) remission was reached in 30% with TCZ and in 3% with placebo [Genovese *et al.* 2008].

RADIATE Study: TNF-antagonist failures

The RADIATE study examined the efficacy and safety of TCZ in patients with RA who had an inadequate clinical response or were intolerant to one or more TNF-antagonist therapies. The TNF-antagonist agent was discontinued prior to randomization (etanercept ≥ 2 weeks, infliximab/adalimumab ≥ 8 weeks, leflunomide 8 weeks, leflunomide ≥ 12 weeks and all DMARDs other than MTX ≥ 12 weeks before baseline). Doses of 4 or 8 mg/kg of TCZ or placebo were given every 4 weeks, in combination with stable MTX (10–25 mg weekly). The primary end point was the proportion of patients who achieved an ACR20 response at week 24.

Table 2. Data from the 2-year LITHE study.

Patient disposition (safety population)	N	Withdrawals % (n)	Completed % (n)	Rescue % (n)	Initiated OL TCZ8 at 52 weeks, % (n)	Completed 104 wks on initial therapy % (n)
Placebo + MTX	392	27 [104]	73 [288]	50 [196]	68 [266]	5 [21]
TCZ4 + MTX	399	22 [89]	78 [310]	24 [97]	63 [253]	9 [37]
TCZ8 + MTX	399	22 [88]	78 [311]	15 [60]	62 [248]	12 [48]
Efficacy (ITT population)		Mean GmTSS from BL [SD] (n)	No GmTSS progression % (n/m)	Adjusted mean AUC HAQ-DI from BL (n)	ACR70 % (n/n)	DAS28 remission % (n/n)
Placebo + MTX	393	1.96 [5.96] [294]	66[195/294]	-139.4 [366]	12 [48/393]	53 [72/136]
TCZ4 + MTX	399	0.58 [2.36] [343]	75[256/343]	-287.5 [376]	24 [97/399]	55 [124/224]
TCZ8 + MTX	398	0.37 [1.55] [353]	83[292/353]	-320.8 [374]	22 [89/398]	65 [156/241]

(n/n) patients with response/evaluable patients. If ACR70 could not be calculated because of missing data, patient was defined as nonresponder at that time point.

MTX, methotrexate; IR, inadequate responder; TCZ, tocilizumab; TCZ4, tocilizumab 4 mg/kg; TCZ8, tocilizumab 8 mg/kg; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; ITT, intention to treat; OL, open-label; GmTSS, Genant-modified Total Sharp Score; AUC, area under the curve; HAQ-DI, Health Assessment Questionnaire Disability Index; BL, baseline; ACR, American College of Rheumatology; DAS, Disease Activity Index.

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 ($p < 0.0001$ for both TCZ groups *versus* control). At week 4 more patients achieved ACR20 in 8 mg/kg TCZ *versus* controls ($p = 0.0008$). Patients responded regardless of most-recently failed TNF-antagonist or the number of failed treatments. DAS28 remission (DAS28 < 2.6) rates at week 24 were clearly dose-related, being achieved by 30.1%, 7.6%, and 1.6% of 8 mg/kg, 4 mg/kg, and control groups ($p = 0.0001$ for 8 mg/kg and $p = 0.053$ for 4 mg/kg *versus* control) [Emery *et al.* 2008; Kremer *et al.* 2008].

Japanese studies

SAMURAI. This 52-week multicenter randomized, X-ray reader blinded study included patients with disease duration between 6 months and 5 years and an inadequate response to at least 1 DMARD, and compared switching to TCZ 8 mg/kg monotherapy ($n = 158$) with MTX alone or in combination with other DMARDs ($n = 148$). According to the primary end point, change in X-ray progression using a modified total Sharp score (TSS), TCZ was significantly more effective in limiting joint damage. In addition, ACR50 and DAS28 remission rates were 64% and 59% with TCZ, compared with 13% and 3% with DMARDs [Nishimoto *et al.* 2007].

SATORI. This 24-week double-blind, multicenter, randomized study evaluated the efficacy and safety of TCZ 8 mg/kg monotherapy in MTX inadequate responders, alone or in combination with MTX 8 mg weekly, the approved dose in Japan. The primary end point of ACR20 was significantly better with TCZ (80.3%) compared with MTX (52.5%). Further, ACR50 and DAS28 remission were 49% and 43.1% with TCZ, compared with 11% and 1.6% with MTX [Nishimoto *et al.* 2009] (Tables 3, 4, and 5).

Quality of life outcomes

HAQ-DI

Mean decreases (improvement) from baseline in HAQ-DI score were consistently significantly greater in the TCZ groups compared with the placebo + MTX/DMARD groups in the DMARD inadequate responder population, monotherapy and TNF-antagonist failure population.

Consistent with other RA disease indices the time to a clinically relevant improvement (decrease in HAQ-DI ≥ 0.22) in HAQ-DI was rapid in the TCZ groups.

SF-36

The onset of benefit was seen at the first time point assessed: week 8, regardless of RA duration or prior treatment.

Table 3. ACR responses in MTX/placebo-controlled trials (percentage of patients).

Response rate week 24	AMBITION MTX naive		LITHE Inadequate response to MTX		OPTION Inadequate response to MTX		TOWARD Inadequate response to DMARD		RADIATE Inadequate response to TNF blocking agent		
	MTX	TCZ 8 mg/kg	Placebo + MTX	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 4 mg/kg + MTX	Placebo + DMARDs	TCZ 8 mg/kg + DMARDs	Placebo + MTX	TCZ 4 mg/kg + MTX
	N = 284	N = 286	N = 393	N = 399	N = 398	N = 204	N = 213	N = 205	N = 413	N = 158	N = 161
ACR20											
	53%	70%***	27%	51%	56%***	27%	48%	59%***	25%	10%	30%
ACR50											
	34%	44%**	10%	25%	32%***	11%	32%	44%***	9%	4%	17%
ACR70											
	15%	28%**	2%	11%	13%***	2%	12%	22%***	3%	1%	5%
MTX, methotrexate; TCZ, tocilizumab; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; ACR, American College of Rheumatology. * $p < 0.05$, tocilizumab versus placebo + MTX/DMARD. ** $p < 0.01$, tocilizumab versus placebo + MTX/DMARD. *** $p < 0.0001$, tocilizumab versus placebo + MTX/DMARD.											

Table 4. DAS and EULAR responses at week 24 in rheumatoid arthritis patient populations.

AMBITION MTX naïve		LITHE Inadequate response to MTX		OPTION Inadequate response to MTX		TOWARD Inadequate response to DMARD		RADIATE Inadequate response to TNF blocking agent	
TCZ 8 mg/kg	MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + DMARD	Placebo + DMARD	TCZ 8 mg/kg + MTX	Placebo + MTX
<i>N</i> = 286	<i>N</i> = 284	<i>N</i> = 398	<i>N</i> = 393	<i>N</i> = 205	<i>N</i> = 204	<i>N</i> = 803	<i>N</i> = 413	<i>N</i> = 170	<i>N</i> = 158
Change in DAS28 [mean (SD)]									
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14)***
DAS <2.6 response (%)									
Week 24	33.6%	12.1%	33.3%***	3.8%	27.5%***	30.2%***	3.4%	30.1%***	1.6%
EULAR response (%)									
None	18%	35%	26%	65%	21%	20%	63%	32%	84%
Moderate	42%	48%	34%	29%	42%	40%	33%	31%	15%
Good†	40%	17%	41%***	6%	38%***	40%***	4%	37%***	2%
MTX, methotrexate; TCZ, tocilizumab; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; ACR, American College of Rheumatology; DAS, Disease Activity Index.									
†The <i>p</i> value compares across all of the EULAR categories.									
* <i>p</i> < 0.05, tocilizumab <i>versus</i> placebo + MTX/DMARD.									
** <i>p</i> < 0.01, tocilizumab <i>versus</i> placebo + MTX/DMARD.									
*** <i>p</i> < 0.0001. tocilizumab <i>versus</i> placebo + MTX/DMARD.									

Table 5. Components of ACR response.

Week 24	OPTION		RADIATE			
	TCZ 4 mg/kg + MTX		Placebo + MTX		TCZ 8 mg/kg + MTX	
	N = 213	N = 205	N = 204	N = 161	N = 170	N = 158
Component (mean)	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
Number of tender joints [0-68]	Week 24* 19	Week 24* 32	Week 24 25	Week 24* 21	Week 24* 17	Week 24 30
	33	32	33	31	32	30
	-7.0 [-10.0, -4.1]	-9.6 [-12.6, -6.7]		-10.8 [-14.6, -7.1]	-15.1 [-18.8, -11.4]	
Number of swollen joints [0-66]	10	19.5	21	13	11	18
	20			19.5	19	19
	-4.2 [-6.1, -2.3]	-6.2 [-8.1, -4.2]		-6.2 [-9.0, -3.5]	-7.2 [-9.9, -4.5]	
Pain†	33	60	57	43	65	64
	61			63.5	33	48
	-11.0 [-17.0, -5.0]	-15.8 [-21.7, -9.9]		-12.4 [-22.1, -2.1]	-23.9 [-33.7, -14.1]	
Patient global assessment†‡	34	65	64	46	70	71
	66			70	36	51
	-10.9 [-17.1, -4.8]	-14.9 [-20.9, -8.9]		-10.0 [-20.3, 0.3]	-17.4 [-27.8, -7.0]	
Physician global assessment†	26	64	64	39	66	43
	64			66.5	28	
	-5.6 [-10.5, -0.8]	-9.0 [-13.8, -4.2]		-10.5 [-18.6, -2.5]	-18.2 [-26.3, -10.0]	
Disability index (HAQ)‡	1.01	1.55	1.55	1.39	1.34	1.58
	1.64			1.67	1.75	1.70
	-0.18 [-0.34, -0.02]	-0.21 [-0.37, -0.05]		-0.25 [-0.42, -0.09]	-0.34 [-0.51, -0.17]	
CRP (mg/dl)	1.17	2.61	2.36	1.77	0.28	3.06
	2.79			3.11	2.80	3.705
	-1.30 [-2.0, -0.59]	-2.156 [-2.86, -1.46]		-1.34 [-2.5, -0.15]	-2.52 [-3.72, -1.32]	

MTX, methotrexate; TCZ, tocilizumab; ACR, American College of Rheumatology; HAQ, Health Assessment Questionnaire; CRP, C-reactive protein.

*Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference.

† Visual analog scale: 0 = best, 100 = worst.

‡ Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking.

In the DMARD inadequate responder population, there were statistically significant improvements in the mean change from baseline in both physical (PCS) and mental component scores (MCS) at week 24 in both TCZ groups. For both PCS and MCS, the difference in treatment effect between placebo + DMARD was higher in the TCZ 8 mg/kg group compared with TCZ 4 mg/kg + MTX.

The proportion of patients achieving a clinically meaningful improvement (>5 , in the SF-36 PCS at week 24 was achieved for a significantly higher percentage in the TCZ groups compared with the placebo + DMARD group (66% for the TCZ 8 mg/kg + DMARD group [$p < 0.0001$] versus 62% for the TCZ 4 mg/kg + MTX group [$p = 0.0004$] versus 45% in the placebo + DMARD group).

For the MCS, clinically meaningful improvements in the SF-36 MCS (>5) at week 24 were achieved for a significantly higher percentage of patients in the TCZ 8 mg/kg + DMARD group compared with the placebo + DMARD group (49% versus 36%, $p < 0.0001$). Although a higher proportion of patients in the TCZ 4 mg/kg + MTX group achieved a clinically relevant improvement in MCS in comparison with the control group (44%), this difference did not reach statistical significance.

Clinically relevant improvements (>5) in the mean PCS were observed as early as week 8 (first scheduled assessment) in both TCZ groups compared with week 24 in the placebo + DMARD group. For MCS, clinically relevant improvements were observed at week 16 in the TCZ 8 mg/kg + DMARD group and week 24 in the TCZ 4 mg/kg + MTX group compared with week 24 in the placebo + DMARD group. A clinically relevant improvement in the mean MCS was not achieved in the placebo + DMARD group.

When the eight individual domains that comprise the SF-36 were analyzed using analysis of variance, there were highly statistically significant improvements in all domains for the TCZ 8 mg/kg + DMARD group ($p < 0.0001$). The largest difference observed was for bodily pain; however, at week 24, the mean change from baseline in all eight domains was within the range defined as a clinically relevant improvement (change 5–10 points) [Alten *et al.* 2008].

The difference in the adjusted means between the TCZ 8 mg/kg + MTX group and the placebo + MTX group at week 24 was statistically significant for the PCS. Mean changes in the MCS were lower in the TNF-antagonist failure population in comparison with the DMARD inadequate responder population (4.9 in the TCZ 8 mg/kg + MTX group and 3.5 in the TCZ 4 mg/kg + MTX group at week 24); however, these changes still represent greater improvements in the TCZ groups compared with the placebo + MTX group (change from baseline of 3.1). A separation between the TCZ + MTX groups and the placebo + MTX group was observed as early as the first scheduled assessment at week 8.

In the TNF-antagonist failure population, improvements were apparent across all of the individual domains but the greatest numerical change was the improvement in bodily pain score, with the greatest change being noted in the TCZ 8 mg/kg + MTX group.

FACIT-Fatigue

The onset of improvement with TCZ was apparent within 4 weeks of initiating treatment, regardless of duration RA, or prior treatments.

For the DMARD inadequate responder population, statistically significant improvements in FACIT-F scores at week 24 were observed for both TCZ groups compared with placebo + DMARD ($p < 0.0001$). The mean change in both TCZ groups was above the threshold for clinically relevant improvement in fatigue (≥ 5 ; at week 24, 7.6 and 7.8 in the TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + DMARD groups, respectively). Consistent with this, the proportions of patients who achieved clinically relevant changes in FACIT-F at week 24 were statistically significantly higher in the TCZ groups in comparison with the control group (59% in the TCZ 4 mg/kg + MTX group, 59% in the TCZ 8 mg/kg + DMARD group and 44% in the placebo + DMARD group). The median time to achievement of a clinically relevant improvement in FACIT-F at week 24 was 85 days in the placebo + DMARD group and 57 days in both TCZ groups.

In the monotherapy study, the mean changes and numbers of patients with clinically relevant changes were greater in the TCZ 8 mg/kg group compared with the MTX group. The mean

improvement in FACIT-F score at week 24 was greater in the TCZ 8 mg/kg group compared with the DMARD inadequate responder population (9.2). A similar proportion of patients achieved clinically relevant improvements at week 24 in comparison with the DMARD inadequate responder population (64%).

In the TNF-antagonist failure population, there was a greater mean improvement in FACIT-F score at week 24 in the TCZ 8 mg/kg + MTX group in comparison with the DMARD inadequate responder population (10.0). The treatment effect at week 24 in the TCZ 8 mg/kg was statistically significant ($p = 0.0150$). In contrast, the mean change in FACIT-F score at week 24 was lower in the TCZ 4 mg/kg group compared with the DMARD inadequate responder population (6.2). In this study, clinically relevant changes in FACIT-F score at week 24 were observed for more patients in the TCZ 8 mg/kg + MTX group than either the placebo + MTX or TCZ 4 mg/kg + MTX group (62% versus 48% and 46%, respectively).

Key findings

- TCZ the onset of improvement in each measure of quality of life was rapid.
- TCZ was consistently more effective than control in improving patients' quality of life, as measured by patient-reported outcomes, including the HAQ-DI, SF-36, and FACIT-F.
- Across the three populations studied, a higher proportion of patients treated with TCZ achieved clinically relevant improvements in functional ability (i.e. a decrease in HAQ-DI of ≥ 0.25), clinically relevant improvements in fatigue (increase in FACIT-F of ≥ 5) and clinically relevant improvements in SF-36 physical and mental health scores (increase of ≥ 5).

The greatest improvements, numerically, were observed with the TCZ 8 mg/kg dose in all populations studied Table 6.

Laboratory evaluations demonstrating efficacy

Treatment with TCZ resulted in a marked decrease in mean levels of acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A rapidly after TCZ administration. Consistent with the effect on acute phase reactants, treatment with TCZ was associated with reduction in platelet count within the normal range.

Table 6. SF-36, HAQ and FACIT-F Responses at Week 24.

AMBITION MTX naïve		LITHE inadequate response to MTX	OPTION inadequate response to MTX	TOWARD inadequate response to DMARD	RADIATE inadequate response to TNF blocking agent
TCZ 8 mg/kg	MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + DMARD	Placebo + MTX
N = 286	N = 284	N = 398	N = 393	N = 803	N = 170
Change in PCS [mean (SD)]	8.4 (0.7)	8.1 (0.6)**	5.6 (0.7)	8.9 (0.4)***	8.0 (0.9)**
10.2 (0.7)					2.2 (1.3)
Change in MCS [mean (SD)]	5.0 (0.9)	4.2 (0.8)	2.8 (0.9)	5.3 (0.6)**	4.1 (1.3)
6.7 (0.9)					4.1 (1.9)
Change in HAQ-DI [mean (SD)]	-0.52 (0.05)	-0.5 (0.04)**	-0.3 (0.04)	-0.47 (0.03)***	-0.39 (0.05)***
-0.70 (0.05)					-0.05 (0.07)
Change in FACIT-F [mean (SD)]	7.0 (0.8)	6.4 (0.7)	5.4 (0.8)	8.0 (0.5)***	8.8 (1.0)*
9.4 (0.8)					4.2 (1.6)

MTX, methotrexate; TCZ, tocilizumab; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; PCS, physical component score; HAQ-DI, Health Assessment Questionnaire Disability Index; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue.

* $p < 0.05$, tocilizumab versus placebo + MTX/DMARD.

** $p < 0.01$, tocilizumab versus placebo + MTX/DMARD.

*** $p < 0.0001$, tocilizumab versus placebo + MTX/DMARD.

Importantly, the 8 mg/kg dose suppressed CRP levels continuously. Elevated CRP levels are widely recognized to predict radiological progression of joint destruction and, thus, the consistent and persistent normalization of CRP levels by the TCZ 8 mg/kg dose provided initial evidence of the potential for TCZ 8 mg/kg to inhibit joint destruction in moderate to severe active RA. In addition, the inhibition of joint damage shown in the supportive SAMURAI study, evaluating DMARD inadequate responder Japanese RA patients treated with TCZ 8 mg/kg monotherapy *versus* standard of care, provides initial evidence of the possibility that TCZ treatment will be shown to have this benefit in a broader patient population. This result was also shown in the 2-year data of the LITHE Study. Clinical data are supported by pharmacokinetic/pharmacodynamic analyses, which demonstrate that the TCZ exposure required to attain CRP normalization, good EULAR response and DAS remission is more readily achieved by the 8 mg/kg dose.

A highly statistically significant improvement in hemoglobin levels occurred after treatment with TCZ in combination with DMARD/MTX or as monotherapy compared with placebo + MTX/DMARD ($p < 0.0001$) at week 24. Mean hemoglobin concentrations increased by 6–7 g/l by 4 weeks in the TCZ4 and TCZ8 but not in the placebo group and continued to increase to 9.2 in TCZ4 patients and 12.4 in TCZ8 patients until week 24. The greatest improvement was observed in patients with anemia of chronic disorder associated with RA; mean hemoglobin levels increased by week 2 and remained within normal range through week 24.

Summary of efficacy. The key findings were as follows:

- The primary end point (proportion of ACR20 responders at week 24) was met in all studies.
- TCZ monotherapy demonstrated not only noninferiority, but also statistical superiority over active MTX.
- Consistent and statistically significant improvements were demonstrated by ACR50 and ACR70 with TCZ treatment compared with control in all patient populations studied (MTX naïve, DMARD naïve, DMARD inadequate responders and TNF-antagonist inadequate responders).
- The highest ACR response, EULAR, and DAS28 remission rates were observed with the TCZ 8 mg/kg dose.
- Normalization of CRP and hemoglobin levels was more common with the 8 mg/kg dose.

Safety

A summary of patients and clinical trials in the all-exposed safety population is given in Figure 1.

General safety profile

The evaluation of the safety profile of TCZ 8 mg/kg every 4 weeks shows that this dose regimen has a favorable risk–benefit profile.

Approximately 90% of eligible patients in the controlled 24-week studies have entered the long-term extension program. Evaluation of patients receiving open-label TCZ 8 mg/kg in the long-term safety analysis confirms the efficacy profile and further reinforces the safety profile of this product. Importantly, the safety profile of TCZ 8 mg/kg is well characterized in treatment durations of at least 3 years, with increasing numbers of patients entering their fourth year of TCZ treatment. As with other biological therapies used for the treatment of RA, vigilance for serious infections is a critical aspect of patient management. There does not appear to be an increase in the rate of infection, malignancy, or other serious adverse effects following prolonged treatment with TCZ 8 mg/kg [van Vollenhoven *et al.* 2009a, 2009b].

Potential risks, with TCZ treatment, usually not treatment limiting, were identified with regard to neutropenia (neutrophil count $< 1 \times 10^9/l$, 3.4%, with counts $< 0.5 \times 10^9/l$, 0.3% of patients), elevations of hepatic aminotransferases and lipid parameters.

Clinically significant neutropenia was observed infrequently in patients receiving TCZ and there was no apparent association between decreases in neutrophil counts and the nature or frequency of infections; however, caution is recommended when considering initiation of TCZ treatment in patients with a low neutrophil count and in patients with an absolute neutrophil count $< 0.5 \times 10^9/l$, treatment is not recommended. No effects on bone marrow or neutrophil function have been reported with TCZ in animal studies.

Figure 1. Summary of patients and clinical trials in the all-exposed safety population.

MTX, methotrexate; IR, inadequate responder; TCZ, tocilizumab; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug.

* Includes patients in the control arm of study.

† All-exposed population = all patients who have received at least one dose of TCZ in the controlled phase or extension studies.

Source: van Vollenhoven *et al.* [2009b]. ACR Oral presentation no. 1955.

Transient mild and moderate elevations of hepatic transaminases have been observed commonly with TCZ treatment, particularly when TCZ is administered in combination with DMARDs (mainly MTX) (see liver enzyme elevations).

Initiation of TCZ may be associated with elevation of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides. In patients who had an adverse change in lipid profile, based on lipid elevations alone, initiation of treatment with a statin was effective.

Live vaccination should not be given concurrently with TCZ as clinical safety has not been established.

Infections

Serious infections occurred at a rate of 5.2 per 100 patient-years with the 8 mg/kg dose, compared with rates of 4.4 per 100 patient-years with the 4 mg/kg dose, and 3.8 per 100 patient-years in control-treated patients in the clinical

studies. Most serious infections, in both dose groups, were pneumonia and cellulitis. There was one opportunistic infection of *Pneumocystis jirovecii* pneumonia in a patient with preexisting chronic obstructive pulmonary disease (COPD). All but one of the serious infections resolved without sequelae, and the majority of patients continued in the study without a recurrence.

There were events of diverticulitis with gastrointestinal (GI) perforation which occurred more commonly in the 8 mg/kg dose group, compared with the 4 mg/kg group followed for ≤1 year. The majority of serious infections responded as expected to antibiotics and recovery occurred in the expected time frame. The rates seen with the 8 mg/kg dose are comparable with those reported for other biologic treatments for RA (5.3 per 100 patient years).

- Rates of serious infections, including opportunistic infections, were elevated over control and do not increase over time.

- Rates of serious infections are consistent with those observed with TNF antagonists [Strangfeld *et al.* 2009; Dixon *et al.* 2006].

Risk mitigation:

- TCZ treatment should not be initiated in patients with active infection;
- TCZ should be interrupted if a patient develops a serious infection or an infection that could become serious until the infection is controlled;
- screen for tuberculosis (TB) prior to initiating TCZ; if positive, initiate TB treatment according to clinical practice guidelines;
- live attenuated vaccines should not be given while on TCZ (Table 7).

GI perforation

In controlled clinical trials, GI perforations occurred at a rate of 0.26 per 100 patient years, with comparable incidence in the 8 and 4 mg/kg groups. Most patients experiencing this event had multiple risk factors, and in long-term safety follow up in which most patients are receiving 8 mg/kg, the rate did not appear to increase.

GI perforations have been reported to be associated with RA and its relevant therapies such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs, and biologics. However, the rate of GI perforations among patients currently treated with biologics and glucocorticoids was higher for patients who were only receiving biologics. Neither treatment with biologics nor with MTX was significantly associated with GI perforations [Curtis *et al.* 2011]. Perforations may occur in the absence of clear

pathognomonic symptoms or premonitory clinical signs. Vigilance is recommended for any patient who develops signs or symptoms suggestive of active diverticular or peptic ulcer disease.

Patients with a history of diverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations or evidence of serious uncontrolled concomitant GI disease should not be treated with TCZ (Table 8).

Lipid levels

Moderate, reversible increases in mean serum levels of total cholesterol, HDL cholesterol (HDL-C) and triglycerides occurred in patients treated with TCZ. Sustained elevations in total cholesterol of ≥ 6.2 mmol/l and LDL cholesterol (LDL-C) of ≥ 4.1 mmol/l occurred in 24% and 15% of patients treated with TCZ [European

Table 8. Gastrointestinal safety.

	All exposed population $n=4009$ (rate/100 PY*)
Gastrointestinal safety	
Esophagus	0.1
Stomach and duodenum	0.1
Jejunum and ileum	0.3
Appendix	0.2
Colon	1.9 (1.7)
Abdominal abscess	0.1
PY, per year. *Total exposure = 9414.3 PY.	

Table 7. Infections, serious infections and cardiovascular events.

	Initially randomized population $n=4199$ (rates/100 PY)			All exposed population $n=4009$ (rates/100 PY)
	Controls $n=15,555$	TCZ 4 mg/kg + DMARDs $n=774$	TCZ 8 mg/kg + DMARDs $n=1870$	
Overall AEs and infections				
All AEs	339.0	358.0	381.6	278.2
Infections	95.9	101.8	102.3	108.01
SAEs	14.4	13.6	14.5	14.4
Serious infections	3.4	3.5	4.9	4.7
Cardiovascular events				
MI	0.49 [4]	0.18 [1]	0.17 [2]	0.25 [24]
Stroke	0.24 [2]	0 [0]	0.33 [4]	0.19 [4]
PY, per year; TCZ, tocilizumab; DMARD, disease-modifying antirheumatic drug; AE, adverse event; SAE, serious adverse event; MI, myocardial infarction.				

Medicines Agency, 2010]. In TOWARD in patients receiving TCZ 8 mg/kg plus DMARD combination therapy, 1.4% of TCZ compared with <1% of DMARD alone recipients experienced an increase in triglyceride levels from <500 mg/dl to $\leq$ 500 mg/dl, but the increase was not associated with clinical symptoms (particularly pancreatitis). A >30% increase in the total cholesterol:HDL-C ratio was reported in 12% of TCZ 8 mg/kg plus DMARD and 7% of DMARD alone recipients; a >30% increase in the LDL-C:HDL-C ratio occurred in 20% and 12% of patients in the corresponding treatment groups.

The atherogenic index was generally unchanged among patients receiving TCZ monotherapy for 1 year in patients with early arthritis in SAMURAI; 27 patients received lipid-lowering therapy during study and their cholesterol levels improved.

However, apart from ischemic heart disease in one patient, there were no treatment-related cardiovascular serious adverse events.

Other adverse events

Demyelinating disorders. The impact of treatment with TCZ on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should closely be monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of TCZ in patients with pre-existing or recent onset demyelinating disorders.

Malignancies. At present clinical data are not sufficient to access the overall incidence following TCZ therapy. Exposure-adjusted incidence was similar in the ACTEMRA groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years). In the all-exposure population, the rate of malignancies remained consistent (1.10 events per 100 patient-years) with the rate observed in the 6-month, controlled period (Table 9).

Liver enzyme elevations. The addition of potentially hepatotoxic drugs (e.g. MTX) to TCZ monotherapy resulted in transient elevations in alanine transaminase (ALT)/aspartate transaminase (AST) $>3 \times$ the upper limit of normal (ULN; elevations were observed in 2.1% of patients on TCZ 8 mg/kg compared with 4.9% of patients on MTX, and in 6.5% of patients who received TCZ 8 mg/kg + DMARD compared with 1.5% of patients on placebo + DMARD). Elevations of ALT/AST $>5 \times$ ULN were observed in 0.7% of TCZ monotherapy patients and 1.4% of TCZ + DMARD patients, the majority of whom were discontinued permanently from TCZ treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. The incidence of indirect bilirubin greater than the ULN is 6.2% in patients treated with 8 mg/kg TCZ.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials (Table 10).

Table 9. Malignancies.

	Initially randomized population $n=4199$			All-exposed population $n=4009$
	Controls $n=15,555$	TCZ 4 mg/kg + DMARDs $n=774$	TCZ 8 mg/kg + DMARDs $n=1870$	
Total exposure (PY)	825	565	1194	9414
Rate/100 PY (number of events)				
Overall malignancies	0.7 [6]	1.6 [9]	0.7 [8]	1.1 [105]
Solid cancers	0.4 [3]	0.5 [3]	0.3 [4]	0.4 [37]
Nonmelanoma skin cancer	0.4 [3]	0.9 [5]	0.3 [4]	0.6 [61]
Hematologic/lymphatic	0	0	0	0.0 [4]
Other	0	0.2 [1]	0	0.0 [3]

PY, per year; TCZ, tocilizumab; DMARD, disease-modifying antirheumatic drug.

Table 10. Liver enzymes.

	Initially randomized population				
	TCZ 8 mg/kg <i>n</i> = 288 % (<i>n</i>)	MTX <i>n</i> = 284 % (<i>n</i>)	TCZ 4 mg/kg + DMARD <i>n</i> = 774 % (<i>n</i>)	TCZ 8 mg/kg + DMARD <i>n</i> = 1582 % (<i>n</i>)	DMARD <i>n</i> = 1170 % (<i>n</i>)
ALT	<i>n</i> = 269	<i>n</i> = 269	<i>n</i> = 706	<i>n</i> = 1465	<i>n</i> = 1080
>1–3 × ULN	34 (91)	32 (86)	43 (302)	46 (672)	19 (206)
>3–5 × ULN	1 (3)	3 (7)	4 (28)	4 (63)	<1 (9)
>5 × ULN	<1 (2)	1 (3)	1 (7)	1 (20)	<1 (3)
AST	<i>n</i> = 283	<i>n</i> = 269	<i>n</i> = 743	<i>n</i> = 1502	<i>n</i> = 1123
>1–3 × ULN	21 (59)	25 (67)	32 (241)	39 (583)	15 (163)
>3–5 × ULN	<1 (1)	1 (3)	1 (7)	2 (23)	<1 (3)
>5 × ULN	<1 (2)	<1 (1)	–	<1 (3)	<1 (1)
Dose held	8 (23)	10 (28)	3 (19)	3 (39)	<1 (8)
Discontinued	<1 (1)	1 (4)	1 (10)	1 (21)	<1 (2)

TCZ, tocilizumab; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug; ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

Infusion-site reactions

Infusion-site reactions occurred in 7% *versus* 5% in TCZ 8 mg/kg and DMARD + placebo recipients. Nonserious rash events (including dermatitis and pruritus) occurred at a higher incidence in the 8 mg/kg TCZ + MTX groups without change or discontinuation of study treatment.

Dosage and administration

In Europe, TCZ is indicated for patients with RA with inadequate DMARD response. Since January 2011 in the US the indication for the treatment of adult patients, who have had an inadequate response to one or more TNF antagonists was extended to patients with moderately to severely active RA.

TCZ may be used as monotherapy or concomitantly with MTX or other DMARDs. The recommended dosage of TCZ for use in adult RA patients in Europe is 8 mg/kg and in the US the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response, administered every 4 weeks as an intravenous infusion over 60 minutes.

The minimal dose of TCZ should be 480 mg and doses exceeding 800 mg per infusion are not recommended.

TCZ should not be initiated in patients with active infections and patients should be screened for latent tuberculosis infections prior to initiating therapy.

TCZ has not been studied and its use should be avoided in combination with biological DMARDs such as TNF antagonists, IL-1 receptor antagonists, anti-CD20 monoclonal antibodies, and selective costimulation modulators because of the possibility of increased immunosuppression and increased risk of infection [Food and Drug Administration, 2011; Genentech, 2010; Roche, 2009].

Tocilizumab and the management of rheumatoid arthritis

The initiation of DMARD therapy within 3 months of diagnosis was recently recommended by the EULAR [Smolen *et al.* 2010].

Although the gold standard therapy with MTX has a well-established place in the treatment algorithm, many patients do not fulfill remission criteria with MTX alone or DMARD combination. It has been shown that combination therapy with biologicals plus MTX or other DMARDs is more effective in preventing disease progression.

TCZ has established its therapeutic benefit as monotherapy and also in combination with DMARDs and in patients who failed other biologic agents.

Very good efficacy data, especially improvements in HR-QoL measures, were observed in all investigated patient populations. The tolerability profile of TCZ is acceptable. More results are needed to determine the comparative efficacy and safety of TCZ *versus* other biological

agents. This information will be presumably be provided by the ongoing trials and long-term extension of the trials described in this review. These data have been confirmed in a recently published Cochrane review [Singh *et al.* 2011].

Conclusion

Phase III studies evaluating the efficacy and safety of treatment with 8 mg/kg TCZ in combination with MTX have demonstrated significant and clinically important decreases in disease activity with rapid onset of action and continuing improvements over 24 and 52 weeks in the most-studied population of RA patients who had previously experienced an inadequate response to MTX. Improvements in disease activity parameters, reduction in markers of inflammation, and increases in hemoglobin were consistently achieved with TCZ 8 mg/kg + MTX. Statistically significant improvements were also observed for patient-reported outcomes related to physical and mental health (SF-36) and fatigue (FACIT-fatigue).

TCZ at 8 mg/kg + MTX was well tolerated in this patient population. Serious infections were reported infrequently, although slightly more often in the TCZ 8 mg/kg + MTX group (six events) than in the placebo + MTX group (two events). In addition, infusion reactions were infrequent and mostly mild which did not require treatment.

As expected from the mechanism of action, TCZ treatment was associated with decreases in mean absolute neutrophil and platelet counts within the normal range. The majority of patients who demonstrated neutropenia, these observations were transient and were not of clinical significance. Elevations of hepatic aminotransferases were transient and episodic and were managed by temporary interruption of either TCZ or a concomitant medication, or no intervention. Few patients required discontinuation per protocol and there was no evidence of clinical hepatitis or hepatic dysfunction associated with TCZ. Elevations of lipid parameters (LDL and HDL) suggesting the need for treatment were observed in a minority of patients; treatment with lipid-lowering agents was effective, and not associated with hepatic effects. TCZ treatment was not associated with an increase in cardiovascular events, and the rate of these events per 100 years is consistently lower than rates described in RA epidemiologic studies.

TCZ is an important new treatment option in patients with moderate to severe RA.

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Conflict of interest statement

None declared.

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