Systematic Review of Tocilizumab for Rheumatoid Arthritis: A New Biologic Agent Targeting the Interleukin-6 Receptor

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ABSTRACT

Background: Tocilizumab (TCZ), a humanized anti–interleukin-6 receptor monoclonal antibody, represents a new treatment strategy for patients with rheumatoid arthritis (RA) and is currently approved in the United States for RA patients who have failed to improve with at least one anti–tumor necrosis factor therapy.

Objective: The goal of this study was to summarize the efficacy and safety profile of TCZ.

Methods: A systematic literature review was conducted to identify English-language articles within PubMed and the Cochrane Library from January 1989 to August 2011 reporting results from Phase III TCZ double-blind, randomized controlled trials (RCTs), noncontrolled clinical trials, and open-label extensions with a duration ≥6 months. Study outcomes had to include at least one of the following: American College of Rheumatology (ACR) 20, 50, or 70 response rates; tender/swollen joint count; Health Assessment Questionnaire–Disability Index; radiographic outcomes and drug persistence. Phase II RCTs were included only if they contained relevant information not available in Phase III RCTs. Relevant studies were selected to evaluate TCZ's pharmacokinetics and pharmacodynamics.

Results: Ten published clinical trials (7 Phase III, 3 Phase II) for TCZ were retrieved (7833 articles initially identified) from PubMed and 31 from the Cochrane library. Compared with methotrexate (MTX) monotherapy, TCZ 8 mg/kg IV monotherapy had higher rates of ACR20 ($P < 0.001$), ACR50 ($P = 0.002$), and ACR70 ($P < 0.001$) scores at week 24. TCZ 8 mg/kg IV plus oral MTX had a higher ACR20 response rate than oral MTX plus placebo in patients with RA who failed to respond to MTX or anti–tumor necrosis factor therapy ($P < 0.001$). Patients receiving TCZ 8 mg/kg had less radiographic progression on the Genant-modified Sharp score (85% had no progression) than the control group (67% had no progression) ($P < 0.001$). The rate of serious infections was 4.7 events/100 patient-years of exposure in the TCZ groups. A greater frequency of neutropenia, thrombocytopenia, hyperlipidemia, and transaminitis was observed with TCZ compared with placebo.

Conclusion: The short-term efficacy and safety profile of TCZ is promising. Additional long-term safety data are needed to better characterize the risk–benefit profile of this agent. (*Clin Ther*. 2012;34:788–802) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: IL-6, juvenile idiopathic arthritis, MRA, rheumatoid arthritis, tocilizumab.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease characterized by persistent synovitis and progressive destruction of cartilage and bone.[1] It is associated with progressive joint damage, pain, fatigue, and disability, as well as the elevation of acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[2–5] It is a common disease, affecting about 1% of adults aged >35 years and >2% of adults aged >60 years in the United States.[6,7] Similar prevalence figures have been reported worldwide.[7,8] Even though the cause of RA is not fully understood, pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 play an important role in disease pathogenesis.[3,4] More than a decade of experience with anti-TNF therapy has shown these agents to be effective in a significant proportion of patients with RA. However, at least two thirds of patients with RA have a partial but in-

complete response to anti-TNF therapy.[9] Tocilizumab (TCZ) was introduced as a new approach for the treatment of RA because it targets the IL-6 pathway, which is important in the pathogenesis of RA.

IL-6 is a pleiotropic cytokine with a wide range of biologic activities in immune regulation, hematopoiesis, inflammation, and oncogenesis. Its activities are shared by IL-6–related cytokines such as leukemia inhibitory factor, ciliary neutrophic factor, and oncostatin M. There are 2 different IL-6–driven signaling pathways. One is mediated by membrane-bound IL-6 receptor (mIL-6R [CD 126])[10,11] via activation of glycoprotein 130; the second is mediated via proteolytic cleavage of the mIL-6R that leads to the generation of a soluble receptor for IL-6 (sIL-6R). sIL-6R is able to bind to IL-6 and can stimulate cells that lack endogenous mIL-6R.[12–14] IL-6 is produced by various cell types, including T cells, B cells, monocytes, fibroblasts, endothelial cells, and synovial cells.[10,15] Higher levels of IL-6 have been found in the synovium of patients with RA.[16] IL-6 can stimulate pannus formation through increased vascular endothelial growth factor (VEGF) expression and increase bone resorption as a result of osteoclastogenesis.[5,17] Systemic effects of IL-6 include regulation of acute-phase protein synthesis, as well as hepcidin production and stimulation of the hypothalamic-pituitary-adrenal axis, the latter 2 actions leading to anemia and fatigue, respectively.[5]

TCZ, a humanized anti–IL-6 receptor monoclonal antibody, represents a promising new treatment strategy for patients with RA and is currently approved in the United States for patients with RA who have failed to improve with at least one anti-TNF therapy. TCZ prevents IL-6 from binding to both mIL-6R and sIL-6R, thereby blocking the proinflammatory effects of IL-6.[15,18] The objective of this article was to review the pharmacology of TCZ and present results from pivotal trials regarding the efficacy, safety, and tolerability of TCZ in patients with RA.

METHODS

To review the pharmacology of TCZ, relevant studies were selected as part of a narrative review to determine the agent's pharmacokinetic and pharmacodynamic properties. Relevant information was extracted from the identified articles and their references to identify pertinent publications, including meta-analyses, review articles, and pharmacologic studies.

To establish the evidence base for the remainder of the review, a systematic literature review using PubMed and the Cochrane Library was conducted to identify English-language articles reporting results from randomized controlled trials (RCTs), controlled clinical trials of TCZ, noncontrolled clinical trials, and their open-label extensions following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic review.[19] The literature search used was performed by our group as part of the 2008 American College of Rheumatology (ACR) recommendations for the treatment of RA[20] and the ongoing 2012 update. As part of the systematic literature review for the RA guidelines, we searched PubMed from January 1989 through March 2010 for 6 older biologic agents (etanercept, infliximab, adalimumab, abatacept, anakinra, and rituximab) and 3 newer biologic agents (golimumab, certolizumab, and TCZ). From April 2010 through May 2011, we searched PubMed for TCZ and RA articles only, which resulted in a total of 7833 potential articles for RA and TCZ from combined PubMed searches from January 1989 through May 2011. An update to this search was made from May 2011 through August 2011 with 11 new potential articles. An additional search was done within the Cochrane library for TCZ using the same terms used in the PubMed search until August 2011 (n = 31). (See **Supplemental Appendix I** in the online version at doi: 10.1016/j.clinthera.2012.02.014.) Risk of bias for each of the selected RCTs was assessed according to Review Manager 5.1 (RevMan) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) used to prepare Cochrane systematic reviews. Agreement between the authors was established to finalize the assessment of risk of bias. A flow diagram for study selection is provided in **Figure 1**, and the risk of bias for each clinical trial retrieved is presented in **Supplemental Appendix II** (See **Supplemental Appendix II** in the online version at doi:10.1016/j.clinthera.2012.02.014).

As inclusion criteria, the studies required the TCZ trials to be conducted for an RA population with a comparator group and contain outcomes for ≥1 of the following: ACR20, 50, and 70 response rates; tender/swollen joint count; Health Assessment Questionnaire–Disability Index (HAQ-DI); radiographic outcomes; and drug persistence. For adverse events and safety, the studies must have had ≥1 of the following: drug terminations, adverse events, serious adverse events, infections, serious infections (defined by need
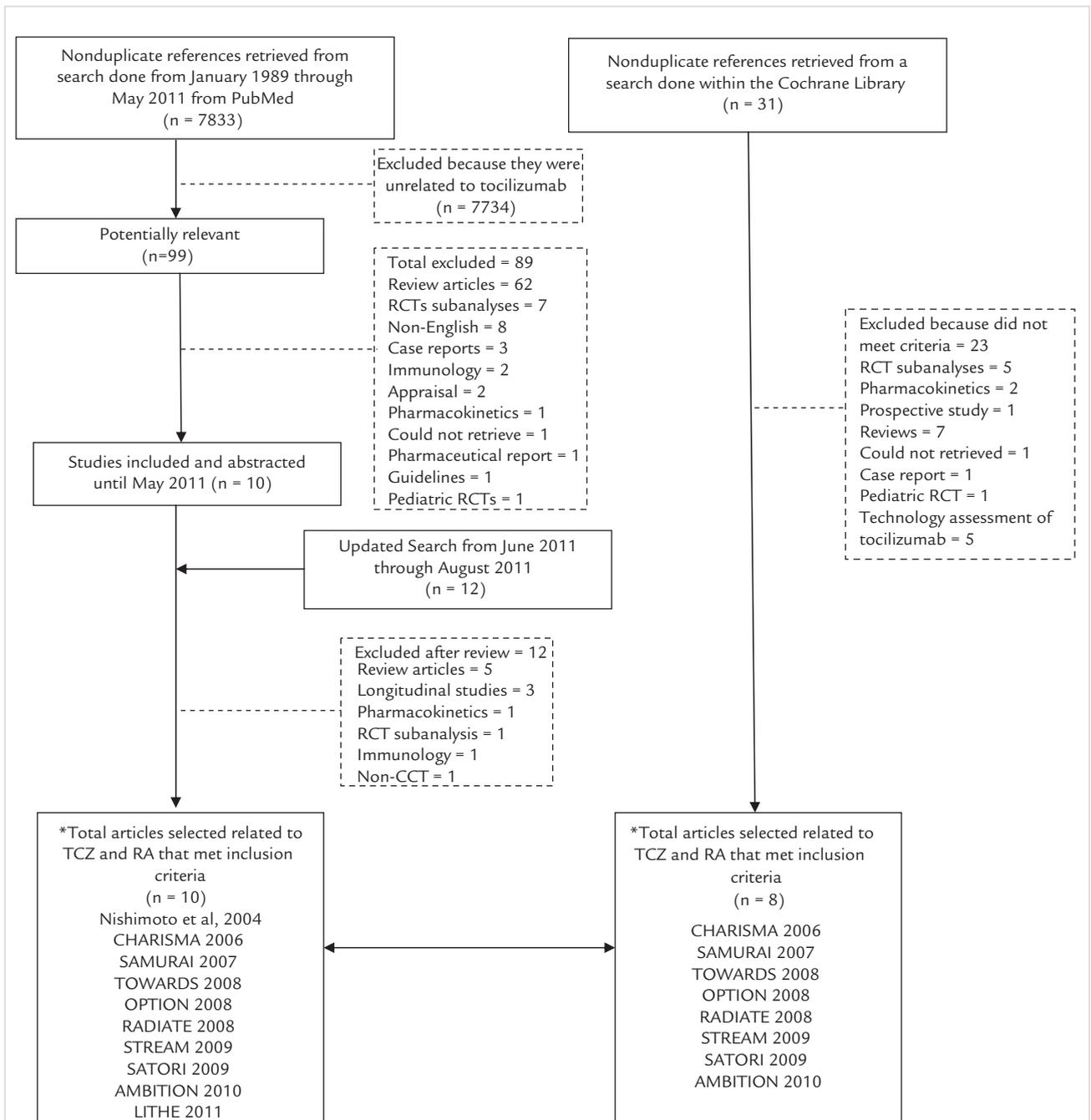
Figure 1. Flow chart of literature search for biologic agents from January 1989 through August 2011 within PubMed and the Cochrane Library. RCT = randomized controlled trials; CCT = controlled clinical trials. CHARISMA = Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody; SAMURAI = Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor; TOWARD = Tocilizumab in Combination With Traditional DMARD Therapy; OPTION = Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders; RADIATE = Research on Actemra Determining efficacy after Anti-TNF failurEs; STREAM = Safety and Efficacy of Tocilizumab, an anti-IL-6 receptor monoclonal antibody, in Monotherapy, in Patients With Rheumatoid Arthritis; SATORI = Study of Active Controlled TCZ Monotherapy for RA Patients with and Inadequate Response to Methotrexate; AMBITION = Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy; LITHE = Tocilizumab Safety and the Prevention of Structural Joint Damage. *All the 8 included studies from Cochrane library were part of the 10 included studies from the PubMed search, leading to a total of 10 unique studies included in our review.

for intravenous antibiotics or hospitalization), selected specific morbidities (eg, infusion or injection site reaction, cancer, heart failure, auto-antibody production), and mortality. (See Supplemental Appendix III in the online version at doi:10.1016/j.clinthera.2012.02.014 for further details on inclusion/exclusion criteria and search strategy.) We searched for the following terms: *IL-6, Actemra, tocilizumab, rheumatoid arthritis, IL-6 receptor inhibitor, joint damage, radiographic damage, myeloma receptor antibody (MRA),* and *clinical trials.*

The Phase III clinical trials were prioritized for more extensive discussion for this review over Phase II trials because these provided more extensive data on efficacy and safety. Non–Phase III clinical trials were selected and reviewed only if they provided unique information for dosing, long-term safety, or radiographic outcomes that were not contained in any Phase III clinical trials.

RESULTS
Pharmacology of TCZ

TCZ is a recombinant humanized monoclonal antibody of the immunoglobulin G1 subclass against the IL-6 receptor. Its molecular weight is ~150 Kd,[21] and it binds to sIL-6R in a dose-dependent manner and saturates the receptor at ~0.1 μg/mL. It also competitively inhibits IL-6 binding to sIL-6R; complete inhibition is seen at ~4 μg/mL.[22]

The pharmacokinetics of intravenous TCZ have been determined using a population pharmacokinetic analysis on a database composed of 1793 patients with RA treated with 1-hour infusions of TCZ 4 and 8 mg/kg IV every 4 weeks for 24 weeks.[23,24] TCZ is metabolized by the reticuloendothelial system like endogenous immunoglobulin G. The half-life is concentration dependent (first-order kinetics): up to 11 days for 4 mg/kg IV and up to 13 days for 8 mg/kg IV every 4 weeks at steady state.[25] C_{max} increases in proportion to increased dosages. After intravenous administration, it undergoes biphasic elimination from the circulation. At higher concentrations, the elimination is predominantly linear, whereas at a low TCZ concentration, the clearance is nonlinear.[24,25]

In patients with RA, the central volume of distribution was 3.5 L, and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.[24,25] Mean (SD) AUC at 28 days for TCZ 4 mg/kg IV was 13 (6) mg·h/mL, and the C_{min} and C_{max} concentrations were 1.47 (2.07) and 88 (41),

respectively. For TCZ 8 mg/kg IV, the AUC at 28 days was 34 (15) mg·h/mL and the C_{min} and C_{max} were 9.52 (10.1) μg/mL and 181 (85) μg/mL, respectively.[26] Maintenance of higher trough levels of serum TCZ seems to be important to achieve clinical efficacy, as reported in a small study.[1]

Efficacy and Safety of TCZ from Clinical Trials

Using results from the systematic literature review, 10 published clinical trials for TCZ were retrieved (double-blind, open-label extensions, and single-blind studies), including 7 randomized Phase III clinical trials,[27–33] one Phase II European clinical trial,[34] a Japanese 5-year extension study of an initial Phase II trial,[35] and a Phase II Japanese clinical trial.[36] These studies were selected from the initial 7833 articles on biologic agents identified from January 1989 through August 2011 in the PubMed library. Within the Cochrane library, 31 articles related to TCZ and RA were retrieved until August 2011, and 8 of the 10 articles retrieved and selected in PubMed were also retrieved in the Cochrane library. No additional study within Cochrane met inclusion criteria for this review.

Among the Phase II clinical trials retrieved, we included the Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) study[34] because this study provided information on the doses of TCZ that were subsequently used in the Phase III studies. The Safety and Efficacy of Tocilizumab, an anti-IL-6 receptor monoclonal antibody, in Monotherapy, in Patients With Rheumatoid Arthritis (STREAM) study was an open-label, long-term 5-year extension trial following an initial 3-month randomized Phase II Japanese trial[35] that provided more extensive information regarding long-term safety. A multicenter, 3-month clinical trial conducted in Japan[36] of TCZ monotherapy at 2 different doses (4 and 8 mg/kg) versus placebo (no actual therapy) showed TCZ was better over the placebo group. ACR20 response was better in the 2 TCZ arms compared with placebo ($P <$ 0.001 for both doses). ACR50 response rate was higher compared with placebo ($P < 0.001$ for both doses of TCZ). ACR70 was also significantly different from placebo ($P = 0.001$ for TCZ 4 mg/kg and $P =$ 0.002 for TCZ 8 mg/kg).

Seven Phase III clinical trials[27–33] evaluated the efficacy, safety profile, and radiographic progression of TCZ in patients with RA. The patient population, short-term safety profile, efficacy of TCZ, inflamma-

tory markers (ie, CRP, ESR), and clinical responses based on Disease Activity Score in 28 joints (DAS28) and ACR parameters that were measured in the Phase III clinical trials are summarized in Table I.

The ACR definition of improvement in RA was the primary efficacy measure in the TCZ trials. The ACR response criteria is a composite outcome derived from a core set of 7 measures, summarizing the improvement (ie, change) in disease activity from baseline. Although somewhat oversimplified, ACR response is defined by a decrease of ≥20%, 50%, or 70% in a formula that includes tender and swollen joint counts, the patient's and the physician's global assessments of disease activity, patient's assessment of pain, HAQ-DI score, and acute-phase reactants (CRP or ESR).[37,38] It is currently a key criterion for regulatory decisions by the US Food and Drug Administration with respect to antirheumatic drugs that seek an indication to reduce the signs and symptoms of RA.

Clinical Response to TCZ (Phase III Studies)

In the Study of Active Controlled TCZ Monotherapy for RA Patients With an Inadequate Response to Methotrexate (SATORI),[32] in addition to evaluating the efficacy and safety of TCZ, the investigators studied the effect of TCZ on VEGF. This trial consisted of 2 arms: TCZ 8 mg/kg monotherapy every 4 weeks and methotrexate (MTX) 8 mg monotherapy orally every week throughout the 24 weeks of the study without concomitant folic acid supplementation. At 24 weeks, 80% of the patients receiving TCZ achieved an ACR20 response rate versus 25% in the MTX group (P < 0.001). The ACR50 and ACR70 response rates in the TCZ group were higher than in the control group at all time points from week 4 in both TCZ doses compared with placebo. The reduction in DAS28 (P < 0.001) and modified HAQ (P < 0.05) was greater for the TCZ group versus placebo. TCZ also caused a greater reduction in VEGF levels compared with placebo (P < 0.001), which is thought to be a major contributor to angiogenesis and pannus formation in patients with RA.[5]

In 4 of the 5 multinational Phase III clinical trials, patients were required to have had an inadequate response to oral MTX or disease-modifying antirheumatic drugs (DMARD) but not have failed to improve with anti-TNF therapy. In the fifth trial, Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy (AMBITION),[29] the efficacy and safety

profile of TCZ 8 mg/kg IV monotherapy was compared with oral MTX 7.5 to 20 mg every week in patients with moderate to severe RA for whom treatment with MTX or biologic agents had not previously failed. Approximately 66% of the patients in the trial were MTX naive. At the end of 24 weeks, patients in the TCZ 8 mg/kg IV monotherapy group had a better ACR20 and ACR50 (P < 0.001 and P < 0.002, respectively) response than those receiving oral MTX 7.5 to 20 mg every week (Figure 2). TCZ 8 mg/kg also was superior to oral MTX as monotherapy in improving disease activity parameters, including DAS28 and functional ability assessed by using the HAQ-DI.

Tocilizumab in Combination With Traditional DMARD Therapy (TOWARD),[28] the Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders (OPTION),[27] and the Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE)[31] studies evaluated TCZ 4 and 8 mg/kg IV in combination with oral MTX 7.5 to 20 mg every week[27,31] or in combination with another DMARD[28] in patients with moderate to severe RA. In the TOWARD study,[28] the most commonly used DMARD at baseline was MTX. The patient population included those who had an incomplete response to previous MTX/DMARD therapy and were biologic agent naive or receiving anti-TNF therapy (as long as they did not have an incomplete response to anti-TNF). The duration of these studies was 24 weeks[27,28] and 2 years,[31] respectively, and the RA disease duration ≥6 months. The primary end point was the proportion of patients who achieved an ACR20/50/70 at 24 weeks, resulting in a 60%, 40%%, and 20% response, respectively (Figure 3). Other clinical responses based on DAS28, HAQ-DI, Functional Assessment of Chronic Illness Therapy–Fatigue, and the 36-item Short-Form Health Survey at 24 weeks were superior and statistically significant (Table I) in the TCZ groups of these trials. Different doses of TCZ were also tested (4 and 8 mg/kg), with the 8-mg/kg dose yielding numerically superior ACR response rates compared with placebo.

The Research on Actemra Determining effIcacy after Anti-TNF failurEs (RADIATE)[30] examined the efficacy and safety of TCZ in 499 patients with RA who failed to respond to anti-TNF therapy; most failed for lack of efficacy (Figure 4). Overall, patients who received TCZ 8 mg/kg and 4 mg/kg IV achieved an ACR20 response of 50% and 30%, respectively, compared with 10% in the group receiving oral MTX 10 to

Table I. Efficacy of Phase III clinical trials.

Name, Phase, Duration	OPTION, Phase III, RCT, 24 wk			TOWARD, Phase III, RCT, 24 wk		RADIATE, Phase III, RCT, 24 wk			AMBITION Phase III, RCT, 24 wk		LITHE Phase III, RCT, 24 wk		SAMURAI* Phase III, RCT, 52 wk		SATORI Phase III, RCT, 24 wk	
Population	Moderate to Severe RA, MTX-IR			Moderate to Severe RA, DMARD-IR		Moderate to Severe RA, Anti–TNF-IR			Moderate to Severe RA, not MTX Failures		RA <5 y, DMARD-IR		Moderate to Severe RA, DMARD-IR		Moderate to Severe RA, MTX-IR	
Treatment	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	PBO + MTX	TCZ 8 mg/kg + DMARD	PBO + DMARD	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	PBO + MTX	MTX	TCZ 8 mg/kg monotherapy	MTX + PBO	TCZ 8 mg/kg	TCZ 8 mg/kg	MTX 8 mg every week	TCZ 8 mg/kg + DMARD	MTX 8 mg every week, DMARD
ACR20, %	48[†]	59[†]	27	61[†]	25	30[†]	50[†]	10	53	70[†]	27	56[‡]	78[§]	34	80[§]	25
ACR50, %	32[†]	44[†]	11	38[†]	9	17[†]	29[†]	4	34	44[†]	10	32[‡]	64[§]	13	49	10
ACR70, %	12[†]	22[†]	2	21[†]	3	5	12[‡]	1	15	28[†]	2	13[‡]	44[§]	10	30	6
DAS28 remission (<2.6), %	13[‡]	27[†]	0.8	30[†]	3	8	30[†]	2	12	34	7	8[‡]	59[§]	3	43[§]	2
TSS (vdH) (mean change from baseline at wk 52)	ND			ND		ND			ND	ND	1.39	0.29[†]	2.3[‡]	6.1	ND	
HAQ-DI (mean change from baseline)	−0.52	−0.55[‖]	−0.34	−0.5[†]	−0.2	−0.31[b]	−0.39[†]	−0.05	−0.5	−0.7	52[‖,¶]	63[‡,¶]	−0.50[§]	−0.13	−0.40[‡]	−0.18
CRP (mean change from baseline)	−16.6[‖]	−25.1[†]	−3.5	−2.20[†]	−0.27	Not normalized	Normalized (<0.3 mg/dL)	Not normalized	−1.9	−2.8	NR	NR	NR		NR	
FACIT (mean change from baseline)	7.3[‡]	8.6[†]	4.0	8[†]	3.6	NR	NR	NR	NR	NR	NR	NR	NR		NR	
SF-36 (mean change from baseline)	9.7[†]	9.5[†]	5	8.9[†]	4.1	NR	NR	NR	NR	NR	NR	NR	NR		NR	
VEGF (mean change from baseline)	ND			ND		ND			ND		ND	ND	ND		−347[§]	−74

The, ACR response is defined by a decrease of ≥20%, 50%, or 70% in a formula that includes tender and swollen joint counts, the patient's and the physician's global assessments of disease activity, patient's assessment of pain, HAQ-DI score, and acute-phase reactants (CRP or ESR).

OPTION = Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders; RCT = randomized controlled trial; TOWARD = Tocilizumab in Combination With Traditional DMARD Therapy; RADIATE = Research on Actemra Determining efficacy after Anti-TNF failurEs; AMBITION = Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy; LITHE = Tocilizumab Safety and the Prevention of Structural Joint Damage; SAMURAI = Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor; SATORI = Study of Active Controlled TCZ Monotherapy for RA Patients with an Inadequate Response to Methotrexate; RA = rheumatoid arthritis; MTX = methotrexate; IR = inadequate response; DMARD = disease-modifying antirheumatic drug; anti-TNF = tumor necrosis factor antagonist; TCZ = tocilizumab; PBO = placebo; ACR = American College of Rheumatology; DAS28 = Disease Activity Score in 28 joints; TSS (vdH) = van der Heijde modified total Sharp score; ND = not determined; HAQ-DI = Health Assessment Questionnaire–Disability Index; CRP = C-reactive protein; NR = not reported; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; SF-36 = 36-item Short-Form Health Survey (physical); VEGF = vascular endothelial growth factor.

*ACR20, 50, 70, DAS28 and modified HAQ assessed unblinded.
[†] $P < 0.0001$.
[‡] $P < 0.01$.
[§] $P < 0.001$ all versus controls.
[‖] $P < 0.05$ versus controls.
[¶] Modified HAQ, % patients with decrease ≥0.3 unit.
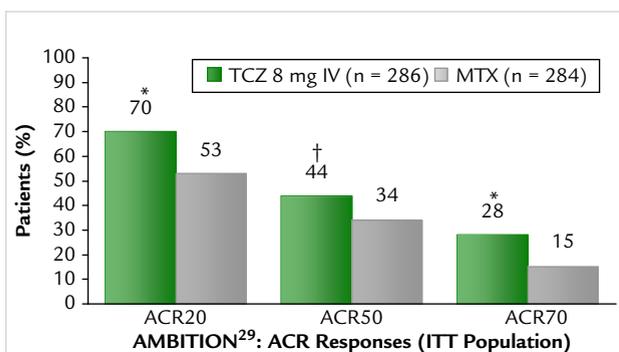
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Figure 2. Tocilizumab (TCZ) response rate compared with methotrexate (MTX) at 24 weeks in patients who were treated previously with MTX. The, ACR response is defined by a decrease of ≥20%, 50%, or 70% in a formula that includes tender and swollen joint counts, the patient's and the physician's global assessments of disease activity, patient's assessment of pain, HAQ-DI score, and acute-phase reactants (CRP or ESR). ACR = American College of Rheumatology; ITT = intention-to-treat. *$P < 0.001$; †$P = 0.002$ versus MTX. The mean MTX dose was 15.5 mg.[29]

25 mg every week plus placebo ($P < 0.001$). The authors also analyzed the differences in the rate of response to TCZ on the basis of type and number of anti-TNF therapies that the patients failed to respond to. The clinical response was comparable irrespective of the type or number of failed anti–TNF therapy (failed only 1 or failed >1), although the study was not powered to explicitly examine this subgroup analysis. Overall, significant improvement was observed in the various components of clinical response including swollen joint counts and tender joint counts ($P < 0.001$ for both TCZ dosage groups vs control), as well as physical function ($P < 0.001$ for TCZ 8 mg/kg IV and $P = 0.003$ for TCZ 4 mg/kg IV vs control).

Radiographic Progression With TCZ

The Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor (SAMU-RAI),[33] was a single-blind, 52-week study performed in Japan that evaluated the radiographic and clinical benefits that TCZ 8 mg/kg IV monotherapy versus conventional DMARD therapy provided to patients with active RA. Readers were blinded to treatment allocation. At 52 weeks, 56% of TCZ-treated patients had no radiographic progression compared with 39% of those receiving conventional DMARD ($P < 0.01$). The ACR20, ACR50, and ACR70 response achieved statistical significance for TCZ 8 mg/kg IV monotherapy compared with conventional oral DMARD therapy ($P < 0.001$, for each comparison). This finding indicated superiority of TCZ 8 mg/kg IV monotherapy; however, these clinical end points were assessed unblinded.

The LITHE study was the only multinational Phase III study that measured radiographic progression of RA.[31,39] This was a 3-arm trial of TCZ 4 mg IV, 8 mg IV, or placebo in combination with MTX 10 to 25 mg per week. The length of the controlled phase of the study was 2 years; however, only results from year 1 are published.[31] LITHE included patients with RA who had an incomplete response to MTX and who did not fail anti-TNF treatment. At 52 weeks, progression of structural damage from baseline was reduced by 74% and 70% with TCZ 8 mg/kg and 4 mg/kg, respectively, compared with controls ($P < 0.0001$), with mean changes in the Genant-modified Sharp score of 0.29, 0.34, and 1.39 for TCZ 8 mg/kg, 4 mg/kg, and placebo, respectively ($P < 0.0001$). At 2 years, patients in the TCZ 8 mg/kg plus MTX 10 to 25 mg per week group had significantly less radiographic progression (85% vs 67% compared with placebo; $P < 0.001$).[31,39]

Safety Profile and Laboratory Parameters

TCZ, at the 2 recommended doses of 4 and 8 mg/kg IV, is currently approved in the United States as monotherapy or in combination with MTX or other DMARD. The rates of treatment-emergent serious adverse events were generally low but increased slightly when TCZ was given in combination with MTX or DMARD. The rate of serious infections in the 6-month control studies with TCZ 4 and 8 mg/kg IV plus DMARD was 4.4 and 5.3 events/100 patient-years of exposure compared with 3.9 events/100 patient-years of exposure in the placebo plus DMARD group. In the monotherapy study, the rate of serious infections was 3.6 events/100 patient-years of exposure in the TCZ 8 mg/kg IV group and 1.5 events/100 patient-years of exposure in the oral MTX group. In the all-exposure population, the overall rate of serious infections was 4.7 events/100 patient-years; the most commonly re-
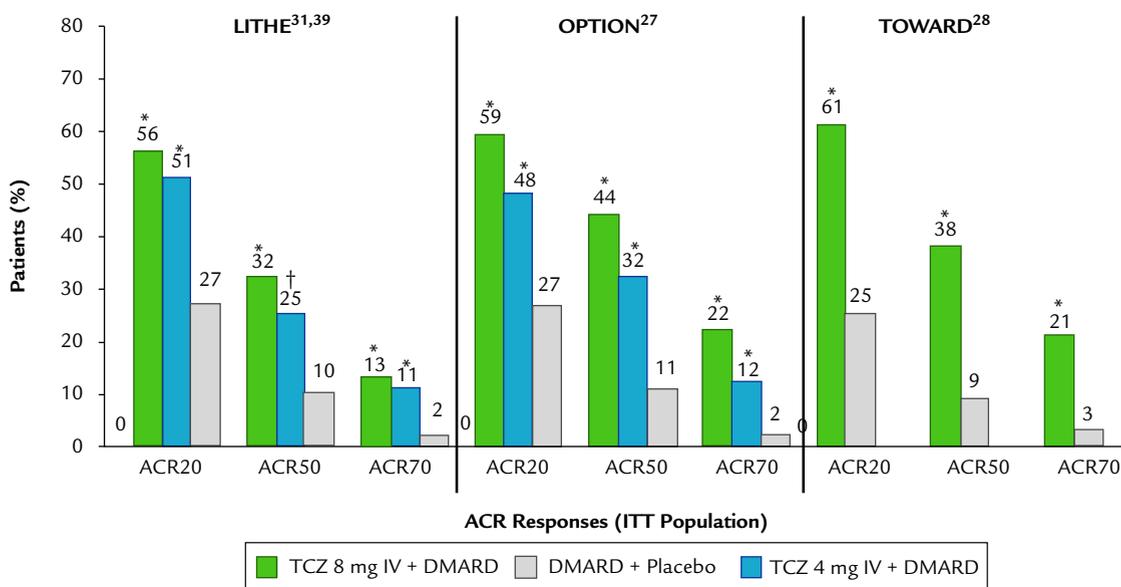
Figure 3. American College of Rheumatology (ACR) response rates with tocilizumab (TCZ) in patients at 24 weeks at 4 and 8 mg/kg plus disease-modifying antirheumatic drugs (DMARD) in the LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage), OPTION (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders), and TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) trials. The, ACR response is defined by a decrease of ≥20%, 50%, or 70% in a formula that includes tender and swollen joint counts, the patient's and the physician's global assessments of disease activity, patient's assessment of pain, HAQ-DI score, and acute-phase reactants (CRP or ESR). *$P < 0.0001$ versus placebo plus DMARD. ITT = intention-to-treat. †In the LITHE study, the difference between the tocilizumab 4 mg/kg plus MTX versus placebo plus MTX groups was significant at $P < 0.05$; for this comparison, however, the test fell after the break in hierarchical chain of the algorithm; therefore, statistical significance is not claimed.[27,28,31,39]

ported events included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis. Serious infections were rarely fatal (0.13/100 patients-years).[24,25]

Reports of gastrointestinal perforation with TCZ usage were rare, with an overall rate of 0.28 events/100 patient-years primarily reported as complications of diverticulitis.[24,25] TCZ may suppress inflammatory and systemic symptoms such as fever and delay the detection of diverticulitis. Most cases of gastrointestinal perforations[30] occurred in patients who were using systemic steroids, NSAIDs, or had a history of diverticulitis. Long-term follow-up is needed to evaluate whether there is a causal relationship between TCZ and gastrointestinal perforation.[24,25,30]

Serious TCZ infusion reactions (occurring during or within 24 hours of the start of infusion) were reported in 8%, 7%, and 5% of patients in the following

groups: 4 mg/kg TCZ plus DMARD, 8 mg/kg TCZ IV plus DMARD, and placebo plus DMARD, respectively. The most frequently reported event with the TCZ 4-mg/kg and 8-mg/kg IV dose during the infusion was hypertension (1% for both doses). The most frequently reported events occurring within 24 hours of completing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus, and urticaria. Clinically significant hypersensitivity reactions requiring treatment discontinuation were reported in 0.2% (9 of 4009) in the all-exposure population.[25]

In the 5 multinational Phase III trials, the incidence of TCZ antibodies was rare. Patients who developed them were mostly receiving concomitant MTX.[27] One Japanese Phase II trial had 2 patients with anti-TCZ antibodies.[36] Maini et al[34] reported 25 patients with anti-TCZ antibodies while they were receiving low-
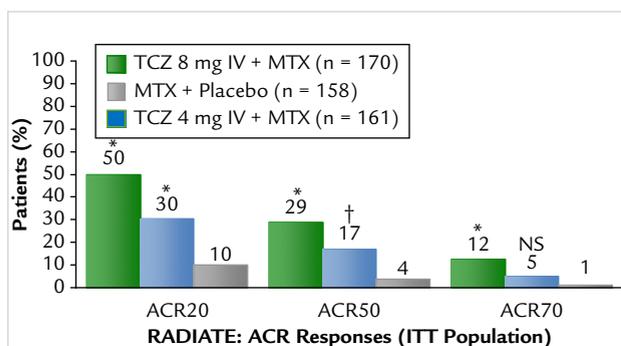
Figure 4. Efficacy and response rate of tocilizumab in patients exhibiting incomplete response (IR) to anti–tumor necrosis factor (TNF) therapy. *$P < 0.001$ and †$P = 0.001$ versus methotrexate (MTX) plus placebo. NS = not statistically significant versus MTX plus placebo. ACR = American College of Rheumatology; RADIATE = Research on Actemra Determining efficacy after Anti-TNF failurEs. The, ACR response is defined by a decrease of ≥20%, 50%, or 70% in a formula that includes tender and swollen joint counts, the patient's and the physician's global assessments of disease activity, patient's assessment of pain, HAQ-DI score, and acute-phase reactants (CRP or ESR).

dose TCZ monotherapy at 2 or 4 mg/kg IV. They also reported that anaphylaxis and anaphylactoid reactions occurred at low doses of TCZ (1 patient receiving TCZ monotherapy 4 mg/kg and 1 receiving combination therapy of TZC 2 mg/kg with MTX). In that small study, no patients receiving TCZ 8 mg/kg as either monotherapy or combination therapy developed anti-TCZ antibodies.

No cases of tuberculosis (TB) were reported in any of the 5 Phase III trials; however, there was one case of *Mycobacterium avium* complex[28] and one case of *Pneumocystis jiroveci* infection reported.[27] In a 5-year open-label extension of the STREAM[35] study, there were no reported cases of TB. Because the risk for active TB associated with TCZ has not been well established, the usual protocol for screening and surveillance for TB in anti-TNF therapy is also recommended for TCZ.[25] One patient died of reactivation of Epstein-Barr virus infection and consequent hemophagocytosis syndrome in a Japanese Phase II trial.[36]

Changes in the following laboratory parameters were observed with both doses: increase in hemoglobin and decreases in rheumatoid factor, CRP, ESR, and serum amyloid A. The most profound was a sustained decrease in CRP levels observed and maintained through week 24 in patients receiving 8 mg/kg IV of TCZ monthly plus oral MTX 7.5 to 25 mg every week; many patients achieved normal CRP levels with the 8-mg/kg dose.[24,25,27,28,30,31,34,39,40] However, the decrease in CRP seen with the TCZ 4 mg/kg IV plus oral MTX group was not sustained but rather oscillated between normal and elevated.

IL-6 stimulates the production of hepcidin, a liver peptide that modulates hemoglobin production by restricting iron availability and plays an important role in the pathogenesis of the anemia of chronic disease. Effective blockade of IL-6R can decrease hepcidin levels and result in an elevation in hemoglobin production, generally in the range of <13 g/dL.[28,40–42] This effect was only observed in patients who had anemia at baseline and did not occur for patients who had a normal hemoglobin at baseline.

TCZ tended to elevate liver enzymes (Table II) and lipid levels. The incidence of elevation of liver enzymes was higher in those patients treated with TCZ in these clinical trials, especially when combined with potentially hepatotoxic medications such as MTX. TCZ had an increased risk for elevating liver enzyme levels. In Phase III trials, 34% to 41% of patients had at least once occurrence of liver enzyme elevation 3 times the upper limit of normal when TCZ was given with either MTX or DMARD versus 17% in the placebo group. This elevation was not sustained, and in most patients, values normalized while either continuing TCZ or after temporary interruption of study treatment and/or lowering the dosage of MTX.[27,28]

Increases in mean fasting plasma lipid levels were seen in TCZ trials.[25,27–30,32,34,36] Elevations from baseline in lipid parameters were observed at the first assessment (6 weeks) after initiation of TCZ but remained stable thereafter. Seven patients in the OPTION,[27] 16 in TOWARD,[34] and 31 in the LITHE[31] studies initiated lipid-lowering therapy. This treatment decreased lipid levels back or close to normal. The package insert recommends that lipid levels be checked 4 to 8 weeks after initiating TCZ and every 6 months thereafter.[25,30,32–34,43] There were no ischemic cardiac disorders or events associated with TCZ treatment during these trials. One myocardial infarction occurred in the

Table II. Frequency of liver-associated enzyme abnormalities in tocilizumab (TCZ) Phase III clinical trials.

Liver Function Tests	Monotherapy		CombinationTherapy		
	TCZ 8 mg (n = 288)	MTX (n = 284)	TCZ 8 mg + DMARD (n = 1582)	TCZ 4 mg + MTX (n = 744)	Placebo + DMARD (n = 1170)
AST*					
>ULN to 3 × ULN	22%	26%	41%	34%	17%
>3 × ULN to 5 × ULN	0.3%	2%	2%	1%	0.3%
>5 × ULN	0.7%	0.4%	0.2%	0.1%	<0.1%
ALT*					
>ULN to 3 × ULN	36%	33%	48%	45%	23%
>3 × ULN to 5 × ULN	1%	4%	5%	5%	1%
>5 × ULN	0.7%	1%	1.5%	1.3%	0.3%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DMARD = disease-modifying antirheumatic drugs; MTX = methotrexate; ULN = upper limit of normal.
Source: GENETECH. Presciribing Information. http://www.gene.com/gene/products/information/actemra/pdf/pi.pdf. 2010 Accessed May 18, 2010.
*AST ULN = 40 U/L; ALT ULN = 55 U/L.

RADIATE study in the control group.[30] Increases in triglycerides to levels >500 mg/dL were rarely observed, without evidence of pancreatitis.[28] Patients with elevation in plasma cholesterol should be treated based on the guidelines for lipid management recommended by the National Cholesterol Education Panel Adult Treatment Panel III.[44] In Phase III trials, hyperlipidemia responded to lipid-lowering treatment.

In the 6-month controlled studies, authors reported "no clear relationship between decreases in neutrophils <1000/mm^3 and the occurrence of serious infections or neutropenic fever."[24–26,28] The neutropenia was transient, and in the majority of cases there was no need for discontinuation of TCZ treatment (Table III). Nevertheless, patients who had grade 4 neutropenia or an absolute neutrophil count <500 were withdrawn from these studies per protocol. Thrombocytopenia was also observed in these trials (1%–2% of patients with platelet counts <100,000; <1% with platelet counts <50,000) without associated clinically significant bleeding events.

Dosing, Administration, and Precautions

TCZ may be used as monotherapy or concomitantly with MTX or other DMARD. In the United States, the recommended starting dose of TCZ for adult patients is 4

mg/kg IV given once every 4 weeks as a 60-minute single intravenous infusion in patients with RA who had an inadequate response to one or more TNF antagonists. An increase from 4 to 8 mg/kg IV is based on clinical response, and the optimal time for dose escalation is left to the discretion of the clinician. Dose reduction from 8 to 4

Table III. Frequency of neutropenia and thrombocytopenia in tocilizumab (TCZ) Phase III clinical trials.

Decrease in Neutrophil and Platelet Count	TCZ 8 mg + DMARD (n = 1582)	TCZ 4 mg + MTX (n = 774)	DMARD + Placebo (n = 1170)
Neutrophils <1000/mm^3, %	3.4	1.8	0.1
Neutrophils <500/mm^3, %	0.3	0.4	0.1
Platelet count <100,000	1.7	1.3	0.5

DMARD = disease-modifying antirheumatic drugs; MTX = methotrexate.
Source: GENETECH. Presciribing Information. http://www.gene.com/gene/products/information/actemra/pdf/pi.pdf. Accessed May 18, 2010.

mg/kg IV is recommended for the management of certain dose-related laboratory changes, including elevation of liver enzymes, neutropenia, and thrombocytopenia. Detailed recommendations regarding dose adjustment associated with certain laboratory parameters are available in the package insert. TCZ should not be administered as an intravenous push or bolus or with other medications through the same intravenous line.[25]

No dose adjustment is indicated for minimal renal impairment (creatinine clearance <80 mL/min and ≥50 mL/min based on the Cockcroft-Gault equation); however, for moderate-to-severe renal impairment (creatinine clearance <50 mL/min based on the Cockcroft-Gault equation), there is limited experience and no specific recommendations for TCZ dose adjustment. It is not recommended for use in patients with active liver disease or hepatic impairment. Regardless of the patient's weight, the maximum recommended dose for TCZ is 800 mg per intravenous infusion.

Regular laboratory monitoring in patients receiving TCZ includes complete blood count with differential and liver function tests before initiation and during the course of therapy.

TCZ is listed as pregnancy category C. It has not been adequately studied in pregnant women. Efforts have been made to establish the risk of TCZ during pregnancy. A pregnancy registry exists to monitor outcomes exposed to this medication; results are not yet available. Because excretion of this medication in breast milk is unknown, its use is not recommended while breastfeeding.

Drug Interactions

Cytochrome P450 enzymes (CYP450) in the liver are down-regulated by infection and inflammation mediated by cytokines such as IL-6. Inhibition of IL-6 signaling in patients with RA treated with TCZ may restore CYP450 activities to higher levels than those in the absence of TCZ, leading to increased metabolism of drugs that are CYP450 substrates. It is therefore recommended to monitor drugs that are metabolized by CYP450 subclasses, especially those with narrow therapeutic indices (ie, warfarin, theophylline) or when the dose is individually adjusted.[24,25] Medications that could have a decrease in their therapeutic effect include oral contraceptives, lovastatin, simvastatin, and omeprazole. The dose of cyclosporine should be adjusted in the case of coadministration with TCZ because the cyclosporine concentration is decreased by this medication. Decreased concentration of the aforementioned medications can last up to 1 week after TCZ discontinuation.[25]

Pharmacoeconomic Considerations

TCZ is dispensed in vials of 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL, and the acquisition cost is US$295.00, US$699.00, and US$1299.00, respectively.[45] The estimated acquisition cost for a 75-kg (165-pound) person for the first 6 months of treatment with 4 mg/kg IV of TCZ is US$5964.00 and for 8 mg/kg IV of TCZ, it is approximately US$11,988.00. By way of comparison, the acquisition cost for 3 mg/kg IV of infliximab would be approximately US$11,090.00 when this agent is administered at weeks 0, 2, and 6 and then every 8 weeks for a 6-month period.[46] This makes the acquisition cost of these 2 agents comparable; however, because many patients treated with infliximab experience either dose escalation or increased frequency of the infusions to achieve efficacy,[47–50] the acquisition cost of infliximab might be higher than TCZ.

The UK National Institute for Health and Clinical Excellence[51] technology appraisal, in their TCZ report, concluded that TCZ with MTX is cost-effective as a second-line treatment only. They also agreed that for individuals who are intolerant to rituximab or for whom rituximab is contraindicated, adding TCZ to the current standard of care is cost-effective.

DISCUSSION

TCZ is a humanized monoclonal antibody against the IL-6 receptor that provides a promising treatment for the management of RA. Clinical trials results show that TCZ 8 mg/kg IV monotherapy has superior efficacy to oral MTX monotherapy. In combination with MTX, TCZ is comparable to the clinical efficacy seen with MTX + anti-TNF therapy.[52–54] TCZ is currently indicated as monotherapy or combination therapy with MTX or DMARD for patients with RA with refractory disease who have failed to improve with at least one anti-TNF agent, and the UK National Institute for Health and Clinical Excellence technology appraisal concluded that TCZ with MTX is cost-effective only as second-line treatment. Its efficacy as monotherapy makes it a reasonable alternative for those patients with MTX intolerance and/or who could not tolerate anti-TNF therapy. Rates of response were found to be

as early as 2 weeks at both the 4- and 8-mg/kg doses. TCZ has been predominantly tested and efficacious in the RA population that had an incomplete response to MTX and that has not failed to respond with an anti-TNF medication.[27–29,31] An important aspect to consider regarding Phase III trials performed in Japan[32,33] is that these studies used as comparator group placebo (no treatment) or fixed low doses of MTX (8 mg every week). These aspects could lead to an overestimation of the effect of TCZ, even after taking into consideration physiologic differences in the Japanese population compared with those of other countries. Even though not discussed in this review, TCZ is also effective in systemic onset juvenile idiopathic arthritis[55,56] and has been approved by the US Food and Drug Administration for this condition.

The risk of bias in the clinical trials selected for this review was low overall. Major points for concern were that some trials had some efficacy outcomes (secondary) unblinded, and others failed to report management of missing data. In addition, these studies were sponsored by pharmaceutical companies, and most of the investigators reported a conflict of interest related to honoraria received from the sponsoring pharmaceutical company. One investigator reported holding a patent for TCZ in one of the trials.[32]

As discussed earlier, TCZ had significant effects on laboratory parameters of inflammation, including ESR and CRP. The decrease in CRP is rapid and profound. It has been postulated that this may be partially due to a direct effect of blocking the IL-6 receptor on CRP in addition to the actual decrease in systemic inflammation,[57] but more studies are needed to confirm this hypothesis. Elevations in lipids were observed, but the clinical significance of this is unclear.[58–60] It has been postulated that when lipid levels increase secondary to response to RA treatment and control of systemic inflammation, the accompanying rise in cholesterol may not confer an increased risk for cardiovascular events[58]; more long-term cardiovascular data are needed to test this hypothesis.

Several strengths of this study include the systematic review of the literature, which is for the most part in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, and that most of the evidence-based information used in this review was derived from double-blind RCTs. Although our literature search procedures were extensive, this study has several limitations. First, this study

excluded non-English studies that could have relevant information regarding TCZ. Second, publication bias is another limitation of this and other reviews, which can lead to overestimation of the actual effect and benefit of TCZ. Third, the risk of selection bias remains possible, but this was minimized here by the systematic way that the articles were selected.

Short-term efficacy data are adequate, but longer-term safety surveillance studies are needed because the TCZ trials were not designed to assess long-term safety risk (infections, cardiovascular, and gastrointestinal perforation) in real-world settings. Comparative effectiveness and pharmacoeconomic data for TCZ and other biologic agents are also needed to help with more informed decision making and to select among the many available treatment options for patients with RA.

CONCLUSIONS

TCZ is a new therapeutic option for patients with RA with refractory disease who have failed to improve with at least one anti-TNF therapy. TCZ seems to have a safety profile similar to other biologic agents on the basis of current data available from published trials. Although the short-term efficacy and safety profiles are promising, additional long-term safety data are needed to better characterize the risk–benefit profile of this agent.

Crescendo, Abbott. All authors contributed equally to the literature review, data interpretation, and writing of the manuscript.

CONFLICTS OF INTEREST
The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL
Supplemental appendices accompanying this article can be found in the online version at doi:10.1016/j.clinthera.2012.02.014.

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APPENDIX I

A. PubMed search strategy for biologic articles from January 1989 through August 2011

We used the systematic review approach from a previous search done for disease-modifying antirheumatic agents (DMARD) and 6 biologic agents (etanercept, infliximab, adalimumab, anakinra, abatacept, and rituximab) for the treatment of rheumatoid arthritis (RA) that was performed in PubMed from January 1989 to December 2006. An updated search was done in PubMed until August 2011, which not only included the previous DMARD and 6 biologic agents but also included 3 new biologic agents (golimumab, certolizumab, and tocilizumab) approved for RA between 2007 and 2011. For efficacy, studies had to be "clinical trials," comparator group should be placebo or other therapies, and clinical outcomes should include American College of Rheumatology (ACR) 20, 50, and 70 among others; see Appendix III for more details. For safety, specific searches were done for toxicity monitoring and screening for tuberculosis (TB) using the following terms. For TB, the entry term "tuberculosis" was combined with the intervention terms. For monitoring of adverse effects, the entry terms "contraindications," "adverse effects," "drug monitoring," and "complications" were combined with the intervention terms. Details of this search are provided in the previous publication and are also summarized in Appendix II.[20] This library was then search for relevant studies of tocilizumab using the terms *rheumatoid arthritis* and one of the following terms: *tocilizumab*, *interleukin-6 receptor inhibitor*, *myeloma receptor antibody*, *clinical trials*, *joint damage*, and *radiographic joint damage*.

B. Cochrane library search strategy for tocilizumab articles within the database until August 2011

We searched the Cochrane library until August 2011 using he terms 'rheumatoid arthritis', "clinical trials" and any of the terms for tocilizumab – "tocilizumab", "interleukin-6 receptor inhibitor" and "myeloma receptor antibody".

Appendix II. Assessment of risk of bias* on selected studies for the systematic review of tocilizumab for rheumatoid arthritis.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
OPTION[27]	Low	Low	Low	Low	Low	Low	High
TOWARD[28]	Unclear	Unclear	Low	Low	Low	Low	High
RADIATE[30]	Unclear	Unclear	Low	Low	Low	Low	High
AMBITION[29]	Unclear	Unclear	Low	Low	Unclear	Low	High
LITHE[31]	Unclear	Unclear	High	High	Low	Low	High
CHARISMA[34]	Low	Low	Low	Low	High	Low	High
SAMURAI[33]	Low	Unclear	High	High	Low	Low	High
STREAM[35]	Unclear	Unclear	Low	Low	Low	Low	High
SATORI[32]	Low	Low	Low	Low	Low	Low	High
Nishimoto et al, 2004[36]	Unclear	Unclear	Low	Low	Low	Low	High

Random Sequence Generation: Low = the investigators provided a random component in the sequence generation process; High = nonrandom component in the sequence generation was provided; Unclear = insufficient information to permit judgment of low or high risk.

Allocation Concealment: Low = participants and investigators could not foresee assignment; High = participants and investigators could foresee assignment and thus introduce bias; Unclear = insufficient information to permit judgment of low or high risk.

Blinding of Participants and Personnel: Low = blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; High = no blinding or incomplete blinding of personnel and participants. Blinding attempted but likely this one could have been broken; Unclear = insufficient information to permit judgment of low or high risk.

Blinding of Outcome Assessment: Low = blinding of outcome assessment ensured and unlikely that the blinding could have been broken; High = no blinding or incomplete blinding of outcome; blinding attempted but likely this one could have been broken; Unclear = insufficient information to permit judgment of low or high risk.

Incomplete Outcome Data: Low = no missing data or data have been imputed using appropriate methods; reason for missing data related to true outcome; High = potentially inappropriate application of simple imputation; Unclear = insufficient information to permit judgment of low or high risk.

Selective Reporting: Low = study protocol available and all primary and secondary outcomes have been well reported; if protocol not available, this information is clear in the published reports; High = not all of the study's prespecified primary outcomes have been reported; Unclear = insufficient information to permit judgment of low or high risk.

Other Bias: Low = the study seems to be free of other sources of bias; High = there is at least one important risk of bias (ie, conflict of interest between sponsors and investigators); Unclear = insufficient information to permit judgment of low or high risk.

OPTION = Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders; TOWARD = Tocilizumab in Combination With Traditional DMARD Therapy; RADIATE = Research on Actemra Determining efflcacy after Anti-TNF failurEs; AMBITION = Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy; LITHE = Tocilizumab Safety and the Prevention of Structural Joint Damage; CHARISMA = Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody; SAMURAI = Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor; STREAM = Safety and Efficacy of Tocilizumab, an anti-IL-6 receptor monoclonal antibody, in Monotherapy, in Patients With Rheumatoid Arthritis; SATORI = Study of Active Controlled TCZ Monotherapy for RA Patients with an Inadequate Response to Methotrexate.

Source: Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

*Legend for risk of bias.

Appendix III. Inclusion/exclusions criteria of studies for efficacy/indications and adverse events/safety.

Criteria	Efficacy/Indications	Adverse Events/Safety
Study design	Per ACR RA guidelines, RCTs, CCTs, quasi-experimental designs, cohort studies (prospective or retrospective), and case-control studies were considered. For the tocilizumab review, RCTs and CCTs were considered. Priority given to Phase III RCTs. Quasi-experimental designs, cohort studies (prospective or retrospective), and case-control studies were not selected for final review in this article even though they were initially selected during the main search.	Per ACR RA guidelines, RCTs, CCTs, quasi-experimental designs, cohort studies (prospective or retrospective), case-control studies, uncontrolled open-label extension trials, and case series (n > 30) were considered. For the tocilizumab review, RCTs, CCTs, and open-label studies were used as long as they were extensions of initial RCTs to assess safety. Quasi-experimental designs, cohort studies (prospective or retrospective), and case-control studies were not selected for final review in this article even though they were initially selected during the main search.
Study population	RA as specified by the authors	RA as specified by the authors; cohorts that contain other rheumatic diseases in addition to RA were included for the ACR guidelines search.
Intervention	Per ACR RA treatment guidelines search, articles must had at least 1 intervention arm for any of the 9 biologic agents or DMARD at FDA-approved doses and routes of administration: abatacept, 10 mg/kg every 4 weeks; adalimumab, 40 mg every 2 weeks; anakinra, 100 mg/d; certolizumab, 400 mg SQ initially, then 200 mg every other week or 400 mg monthly; etanercept, 25 mg twice a week or 50 mg/week; golimumab, 50 mg SQ every 4 weeks; infliximab, 3–10 mg/kg 0, 2, and 6 weeks and then every 8 weeks; rituximab, two 1000-mg doses, 2 weeks apart; and tocilizumab, 4 mg/kg IV every 4 weeks (may increase to 8 mg/kg). Methotrexate up to 25 mg/week; leflunomide 100 mg QD × 3 then 20 mg QD or 20 QD; sulfasalazine, 1.0–3.0 g QD; hydroxychloroquine, 200–400 mg QD (up to 6.4 mg/kg per day); minocycline, 100–200 mg QD. Other concomitant therapies did not influence the selection. However, publications providing results for combinations of biologic agents were not abstracted.	Per ACR RA treatment guidelines, search articles must had at least 1 intervention arm for the 9 biologic agents or 5 DMARD at FDA-recommended dosages and routes: abatacept, 10 mg/kg every 4 weeks; adalimumab, 40 mg every 2 weeks; anakinra, 100 mg/d; certolizumab, 400 mg SQ initially, then 200 mg every other week or 400 mg monthly; etanercept, 25 mg twice a week or 50 mg/week; golimumab, 50 mg SQ every 4 weeks; infliximab, 3–10 mg/kg 0, 2, and 6 weeks and then every 8 weeks; rituximab, two 1000-mg doses, 2 weeks apart; and tocilizumab, 4 mg/kg IV every 4 weeks (may increase to 8 mg/kg). Methotrexate, up to 25 mg/wk; leflunomide, 100 mg QD × 3 then 20 mg QD or 20 QD; sulfasalazine, 1.0-3.0 g QD; hydroxychloroquine, 200–400 mg QD (up to 6.4 mg/kg per day); minocycline,100–200 mg QD. Other concomitant therapies did not influence the selection. Publications providing combined results for biologic agents were included.
	Within this search, we did a specific search looking for tocilizumab articles with at least one intervention arm for tocilizumab 4 mg/kg IV every 4 weeks (may increase to 8 mg/kg) monotherapy or combined with other concomitant therapies. Only clinical trials of tocilizumab were considered for this review. Study designs besides RCTs were excluded. Pediatric RCTs were excluded.	Within this search, we did a specific search looking for tocilizumab articles with at least 1 intervention arm for tocilizumab 4 mg/kg IV every 4 weeks (may increase to 8 mg/kg). Other concomitant therapies did not influence the selection. Only clinical trials of tocilizumab were considered for this review, and other study designs besides RCTs were not included in this review. Open-label extensions of clinical trials were included for tocilizumab as long as they were for at least 5 years.
Comparator	Placebo and/or other therapies	Placebo and/or other therapies
Study outcomes	One or more of the following: tender joints; swollen joints; physician global assessment; patient global assessment; pain; Disease Activity Scale; ACR response criteria 20, ACR50, or ACR70; EULAR improvement criteria; Health Assessment Questionnaire; 36-item Short-Form Health Survey; radiographic outcomes; and drug survival/terminations. If >1 time points were available for the outcome assessments, data were abstracted at the time of the primary end point or the last data available.	One or more of the following: drug terminations, adverse events, serious adverse events, infections, serious infections (defined by need for intravenous antibiotics or hospitalization), selected specific morbidities (eg, infusion or injection site reaction, cancer, heart failure, autoantibodies production), and mortality.
Sample size	No restrictions	No restrictions

ACR = American College of Rheumatology; CCTs = controlled clinical trials; DMARD = disease-modifying antirheumatic drugs; EULAR = European League Against Rheumatism; FDA = US Food and Drug Administration; QD = once daily; RA= rheumatoid arthritis; RCTs = randomized controlled trials; SQ = subcutaneously.