ORIGINAL ARTICLE

Subcutaneous Tocilizumab Versus Placebo in Combination With Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis

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Objective. The efficacy and safety of subcutaneous tocilizumab (TCZ-SC) versus subcutaneous placebo (PBO-SC) was evaluated in patients with rheumatoid arthritis who had an inadequate response to disease-modifying antirheumatic drugs in the BREVACTA study.
Methods. Patients (n = 656) were randomized 2:1 to receive TCZ-SC 162 mg every other week or PBO-SC every other week for 24 weeks; 20% previously received anti–tumor necrosis factor treatment. Escape therapy with TCZ-SC 162 mg weekly was offered from week 12 for inadequate response. The primary end point was the American College of Rheumatology 20% improvement (ACR20) response at week 24. The key secondary outcomes were radiographic progression and safety.
Results. TCZ-SC was superior to PBO-SC for ACR20 response at week 24 (60.9% versus 31.5%; *P* < 0.0001). All secondary end points showed TCZ-SC to be superior to PBO-SC, including ACR50 and ACR70 response (40% and 20% for TCZ-SC, respectively, and 12% and 5% for PBO-SC, respectively; *P* < 0.0001 for both) and Disease Activity Score in 28 joints (DAS28) remission (DAS28 <2.6; 32% versus 4% [*P* < 0.0001]). The mean change in modified Sharp/van der Heijde score was significantly lower in the TCZ-SC group than the PBO-SC group (0.62 versus 1.23; *P* = 0.0149). Adverse events (AEs) and serious AEs (SAEs) were comparable between the TCZ-SC and PBO-SC groups; 4.6% and 3.7% of patients had at least 1 SAE, respectively, and infection was the most common SAE in 2.1% and 1.8% of patients, respectively. More injection site reactions occurred with TCZ-SC than PBO-SC (7.1% versus 4.1%). No anaphylaxis or serious hypersensitivity reactions occurred. There were 3 deaths in the TCZ-SC group and 0 in the PBO-SC group.
Conclusion. TCZ-SC every other week had significantly greater efficacy, including ACR end points and inhibition of joint damage, compared with PBO-SC. TCZ-SC was well tolerated and its safety profile was comparable with that of previous intravenous TCZ studies.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic progressive systemic autoimmune disease characterized by synovitis that leads to joint damage. The initial treatment involves conventional disease-modifying antirheumatic drugs (DMARDs), with refractory patients receiving therapy with biologic agents, including tumor necrosis factor α (TNFα), interleukin-6 (IL-6), and B cell and T cell inhibitors (1–10). When treatment outcomes are similar, patients prefer RA therapies delivered subcutaneously (SC) to those delivered in-

Significance & Innovations

- Tocilizumab (TCZ), given subcutaneously at 162 mg every other week, was statistically significantly superior to placebo (PBO) for the American College of Rheumatology 20% improvement criteria (ACR20) at week 24.

- Subcutaneous TCZ given every other week was superior to subcutaneous PBO for all secondary end points, including inhibition of joint damage on radiographs, ACR50/70 response, and Disease Activity Score in 28 joints remission.

- The safety profile of subcutaneous TCZ was consistent with that in studies of intravenous TCZ.

travenously (IV) and prefer medications delivered at home (11–13). SC administration allows the convenience of receiving treatment outside the clinic, which causes less disruption to daily routines.

Tocilizumab (TCZ) is a recombinant humanized anti–IL-6 receptor monoclonal antibody that blocks IL-6 from binding to the soluble and membrane-bound IL-6 receptor and was developed as an IV infusion. The efficacy and safety of IV administration of TCZ (TCZ-IV) is well documented (1,14–18). TCZ-IV is effective as monotherapy or in combination with DMARDs and is currently approved in >70 countries. Recently, SC administration of TCZ (TCZ-SC) was approved by the Food and Drug Administration for use in the US in patients with RA at a starting dose of 162 mg every other week in patients who weigh <100 kg, with an increase in frequency to 162 mg every week based on clinical response. In patients who weigh ≥100 kg, the starting dose is 162 mg every week. TCZ-SC every other week is also approved in Japan, and in the European Union, a starting dose of TCZ-SC every week is approved, with modification to every other week for the management of laboratory abnormalities.

TCZ-SC was initially evaluated in phase I/II studies (19). In SUMMACTA, a randomized double-blind phase III study, TCZ-SC 162 mg every week in combination with DMARDs showed efficacy and safety comparable with TCZ-IV 8 mg/kg every 4 weeks (20). To further characterize the efficacy and safety of a lower dose of TCZ-SC, the BREVACTA study compared TCZ-SC 162 mg every other week with SC administration of placebo (PBO-SC) every

other week in adult patients with moderate to severe RA who had an inadequate response to ≥1 DMARDs.

PATIENTS AND METHODS

Participants. Patients ≥18 years of age with RA for ≥6 months (revised 1987 American College of Rheumatology [ACR] criteria) (21) were eligible if they met the following major criteria: swollen joint count (SJC) ≥6 (66-joint count) and tender joint count (TJC) ≥8 (68-joint count) at screening and baseline, radiographic evidence of ≥1 joints with a definite erosion attributable to RA at screening, and a C-reactive protein (CRP) level ≥10 mg/liter and/or erythrocyte sedimentation rate (ESR) ≥28 mm/hour at screening. Patients were required to have had an inadequate response to ≥1 DMARDs that, in up to 20% of patients, could include ≥1 anti-TNF agents. Patients must have received ≥1 traditional DMARDs at a stable dose for ≥8 weeks prior to baseline. Prior to randomization, patients had to have discontinued etanercept for ≥2 weeks; infliximab, certolizumab, golimumab, abatacept, or adalimumab for ≥8 weeks; and anakinra for ≥1 week. Concomitant oral glucocorticoids (≤10 mg/day prednisone or equivalent) and nonsteroidal antiinflammatory drugs (up to the maximum recommended dose) were permitted if patients had a stable dose regimen ≥4 weeks prior to baseline.

The major exclusion criteria included ongoing rheumatic or inflammatory joint diseases other than RA, history of malignancy, known active current or history of recurrent infections, positive result for hepatitis B surface antigen or hepatitis C antibody, active tuberculosis, serious allergies to biologic agents, and history of diverticular disease or other symptomatic lower gastrointestinal conditions that might predispose to perforations.

The patients signed informed consent documents that were approved by an independent ethics committee or institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study design. The BREVACTA study (clinicaltrials.gov identifier: NCT01232569) was a multicenter, phase III, 2-arm, randomized, double-blind, placebo-controlled, parallel-group trial, with a double-blind period of 24 weeks followed by an open-label period of 72 weeks. Data to week 24, including the primary end point, are shown. Patients were stratified by geographic region and body weight (<60 kg, 60 to <100 kg, or ≥100 kg). Patients were randomized 2:1 to receive TCZ-SC 162 mg every other week or PBO-SC every other week for 24 weeks. From week 12, patients initially randomized to receive TCZ-SC or PBO-SC every other week could receive escape therapy with TCZ-SC 162 mg weekly at the investigators' discretion if there was <20% improvement in SJC and TJC from baseline. TCZ-SC and PBO injections were administered by prefilled syringe. After the first 6 treatments were administered in the clinic, SC injections could be administered at home by the patients or their caregivers or in the clinic.

Outcomes and assessments. The primary end point was the percentage of patients with an ACR 20% improvement in disease activity (ACR20) response at week 24 (22). Secondary end points included the proportion of patients who achieved an ACR50 or ACR70 response, remission based on the Disease Activity Score in 28 joints (DAS28; <2.6), and a change from baseline in the radiographic Sharp score as modified by van der Heijde (SHS) at week 24. The pharmacodynamic end point was the observed serum CRP level and ESR over 24 weeks.

Safety. Safety assessments included adverse events (AEs), laboratory and vital sign measurements, and physical examinations. The safety population included all patients who received ≥1 dose of the study drug and had ≥1 post-dose safety assessment. Patients were analyzed according to the first dose administered.

Immunogenicity. Blood samples were collected at baseline, week 12, and week 24 for antidrug antibody assessment. Samples positive in the initial screening assay were analyzed by confirmation assay. Assays were performed as previously described using a bridging enzyme-linked immunosorbent assay (23). If the confirmation assay was positive, a neutralizing assay was performed to test for the ability to inhibit TCZ activity.

Statistical analysis. For the primary end point, groups were compared using a Cochran-Mantel-Haenszel test adjusted for the stratification factors applied at randomization (geographic region and body weight) with a 2-sided alpha level of 5%. Patients who withdrew, patients who received escape therapy prior to week 24, or patients for whom the week-24 ACR20 response could not be determined were considered nonresponders. The intent-to-treat (ITT) population (all randomized patients who received ≥1 dose of the study drug) was used for the primary, secondary, and pharmacodynamic analyses. Patients were analyzed according to the randomized treatment group. The only imputation was the last observation carried forward for the SJC and TJC. Subgroup analyses for the ACR responses and safety were conducted across the 3 weight categories. For the sensitivity analysis, the primary analysis was repeated for the completer population (patients who had a valid week-24 assessment [had a response at week 24] and patients who had not received escape therapy).

All continuous secondary end points except for radiographic assessment were compared between groups using an analysis of covariance model that adjusted for the stratification factors applied at randomization and the baseline value for the end point being analyzed. All categorical secondary end points were analyzed as per the primary end point. For the SHS, the change between groups from baseline to week 24 was analyzed using the Van Eltern nonparametric method, after adjustment for the stratification factors applied at randomization. Linear extrapolation was applied to patients who withdrew/escaped prior to week 24 and had a valid radiograph reading at the time of withdrawal/escape.

Based on previous ACR20 response rates of patients in PBO and TCZ-IV 4 mg/kg groups in phase III TCZ-IV trials,

the expected ACR20 response was 23% and 46%, respectively. A sample size of 600 patients randomized 2:1 (400:200 patients) would ensure ≥90% power to detect differences between groups with a significance level of 5% and allow for safety profile assessment.

RESULTS

Patients. Of the 1,034 patients screened, 437 were randomized to receive TCZ-SC and 219 to receive PBO-SC (Figure 1). The ITT population comprised 656 patients (TCZ-SC, n = 437 and PBO-SC, n = 219). For the first dose, 438 patients received TCZ-SC and 218 patients received PBO-SC because a dose administration error occurred in 1 patient. The main reason for screen failure was lack of radiographic evidence of ≥1 joint with definite erosion attributable to RA. The percentage of patients who received escape therapy at week 24 was lower in the TCZ-SC group (16.5%) than the PBO-SC group (41.1%). During the 24-week period, 37 patients prematurely discontinued (28 patients [7%] in the TCZ-SC group and 9 patients [4%] in the PBO-SC group). The most common reasons for withdrawal were AEs or withdrawal of consent. Of the patients who completed 24 weeks, 340 patients (78%) were from the TCZ-SC group and 121 patients (56%) were from the PBO-SC group.

Baseline demographics and clinical characteristics were balanced between groups in the ITT population (Table 1) and safety population (data not shown). In the TCZ-SC group, 67% of patients weighed 60 to <100 kg, 27% weighed <60 kg, and 6% weighed ≥100 kg. The proportion of patients who had an inadequate response to ≥1 anti-TNF was 20.4% in the TCZ-SC group and 21.5% in the PBO-SC group (the study design capped patients who previously received anti-TNF at 20%).

Efficacy. The primary end point was met by showing the superiority of TCZ-SC 162 mg every other week over PBO-SC in ACR20 response rates at week 24 (Figure 2A). The proportion of patients in the TCZ-SC group who achieved an ACR20 response at week 24 was 60.9% (95% confidence interval [95% CI] 56.3–65.4%) and the proportion of patients in the PBO-SC group was 31.5% (95% CI 25.4–37.7%). The weighted difference between groups was 29.5% (95% CI 22.0–37.0%, P < 0.0001). The primary end point analysis was validated by the completer population (no imputation applied); 76.6% of the TCZ-SC group and 55.6% of the PBO-SC group achieved an ACR20 response at week 24. The weighted difference between groups in the completer population was 22.4% (95% CI 12.8–31.9%, P < 0.0001).

ACR50/70 response rates at week 24 were significantly higher for patients who received TCZ-SC compared with PBO-SC (Figure 2A). The weighted difference in the percentage of ACR50 and ACR70 responders was 27.9% (95% CI 21.5–34.4%, P < 0.0001) and 14.8% (95% CI 9.8–19.9%, P < 0.0001), respectively. The percentage of patients who achieved ACR20/50/70 responses over time was greater in the TCZ-SC group than in the PBO-SC group at all time points (data not shown). In exploratory analy-
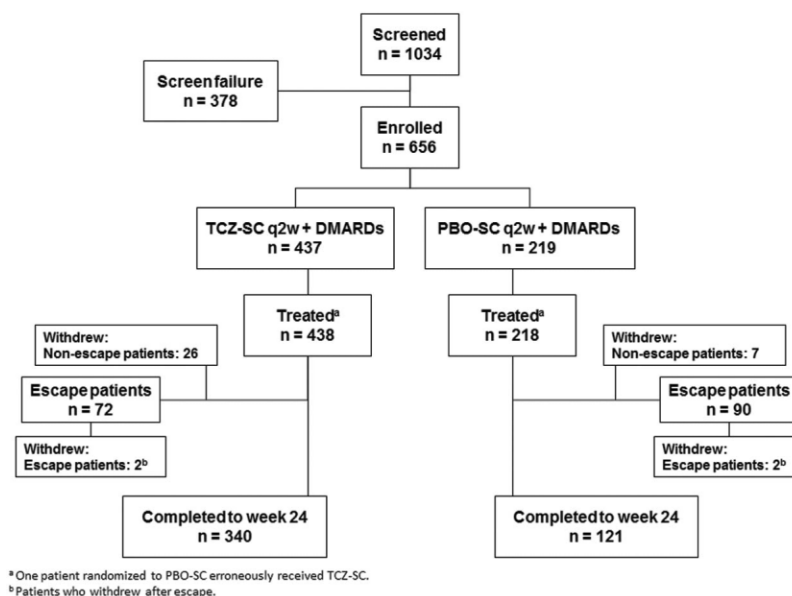
Figure 1. Patient disposition over 24 weeks. TCZ-SC = subcutaneous tocilizumab; q2w = every other week; DMARDs = disease-modifying antirheumatic drugs; PBO-SC = subcutaneous placebo.

ses, differences in ACR response rates between treatment groups were similar when focusing only on those patients who received concomitant methotrexate at baseline (see Supplementary Figure 1A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract) and those who received other DMARDs at baseline (see Supplementary Figure 1B, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). Similar trends were observed in patients with an inadequate response to DMARDs (see Supplementary Figure 1C, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract) and patients with an inadequate response to anti-TNF agents (see Supplementary Figure 1D, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract); however, ACR response rates were generally higher in patients with an inadequate response to DMARDs.

Of the patients who received escape therapy (TCZ-SC weekly), patients who were randomized to TCZ-SC every other week achieved ACR responses after initiating escape therapy (12 weeks after TCZ-SC every other week to escape ACR20: 58.2%). Patients who received escape therapy after being randomized to PBO-SC also achieved ACR responses (12 weeks after PBO-SC to escape ACR20: 72.2%) (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract).

The proportion of patients who achieved DAS28 remission (<2.6) at week 24 was significantly greater in the TCZ-SC group than in the PBO-SC group (Figure 2B). The weighted difference between groups was 28.6% (95% CI 22.5–35.2%, $P < 0.0001$). In an exploratory analysis, a numerically higher proportion of patients in the TCZ-SC group reached Clinical Disease Activity Index remission at week 24 compared with the PBO-SC group (11.4% versus 3.0%) (see Supplementary Table 2, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract).

The mean ± SD change from baseline in SHS at week 24 was lower in the TCZ-SC group (0.62 ± 2.692) than in the PBO-SC group (1.23 ± 2.816) (Figure 2D). Ad hoc analysis of erosion scores showed that the mean ± SD change from baseline at week 24 was significantly lower in the TCZ-SC group than in the PBO-SC group (0.26 ± 1.378 versus 0.65 ± 1.741; $P = 0.0078$) (see Supplementary Figure 2A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). Ad hoc analysis of the joint space narrowing score showed that the mean ± SD change from baseline at week 24 was not statistically significantly different between the TCZ-SC and PBO-SC groups (0.36 ± 1.744 versus 0.58 ± 1.710; $P = 0.2324$) (see Supplementary Figure 2B, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). The proportion of patients who demonstrated no progression at week 24 was 60% (235/391) for the TCZ-SC group and 56% (105/186) for the PBO-SC group.

CRP levels and ESR decreased rapidly after the initial dose in the TCZ-SC group (see Supplementary Figure 3, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). Thereafter, CRP levels remained below the upper limit of normal (ULN; 0.99 mg/dl) until week 24. CRP levels and ESR decreased slightly after treatment with PBO-SC, although the values were higher than in the TCZ-SC group and were greater than the ULN.

Safety results. Most patients experienced ≥1 AEs (62.7% in the TCZ-SC group and 57.8% in the PBO-SC

Table 1. Baseline demographics and clinical characteristics (ITT population)*		
	TCZ-SC 162 mg every other week (n = 437)	**PBO-SC every other week (n = 219)**
Demographics		
Women, no. (%)	375 (85.8)	181 (82.6)
Age, mean ± SD years	52.1 ± 11.45	52.0 ± 11.71
Weight, mean ± SD kg	70.32 ± 16.63	70.04 ± 15.76
Weight group, no. (%)		
<60 kg	119 (27.2)	58 (26.5)
60 to <100 kg	292 (66.8)	150 (68.5)
≥100 kg	26 (5.9)	11 (5.0)
Region, no. (%)		
Europe	101 (23.1)	49 (22.4)
North America	89 (20.4)	45 (20.5)
South America	176 (40.3)	89 (40.6)
Rest of the world	71 (16.2)	36 (16.4)
Concomitant medication, no. (%)		
MTX	361 (82.6)	174 (79.5)
Other DMARDs	76 (17.4)	43 (19.6)
Previous DMARDs, mean ± SD	1.3 ± 0.7	1.4 ± 0.8
Previously failed anti-TNF treatment, no. (%)	89 (20.4)	47 (21.5)
Laboratory tests		
RF positive, no. (%)	349 (80.8)†	178 (81.7)‡
ACPA positive, no. (%)	359 (83.7)§	180 (82.9)¶
CRP level, mean ± SD mg/dl	2.0 ± 2.62	1.9 ± 2.42
ESR, mean ± SD mg/dl	50.9 ± 24.76	49.4 ± 25.95
Disease activity		
Duration of RA, mean ± SD years	11.1 ± 8.24	11.1 ± 8.39
Tender joints (68-joint count), mean ± SD	28.1 ± 14.99	27.5 ± 14.42
Swollen joints (66-joint count), mean ± SD	17.5 ± 10.34	17.6 ± 9.94
DAS28, mean ± SD	6.7 ± 0.92	6.6 ± 0.94
SHS, mean ± SD	59.01 ± 65.90#	60.38 ± 66.47**
JSN, mean ± SD	28.18 ± 31.06#	28.73 ± 31.57**
Erosion, mean ± SD	30.84 ± 36.35#	31.65 ± 36.63**
Quality of life		
HAQ DI score (range 0–3), mean ± SD	1.6 ± 0.62	1.6 ± 0.63
Pain VAS (range 0–100), mean ± SD	57.8 ± 22.75	56.8 ± 22.32
Patient global assessment of disease activity (range 0–100), mean ± SD	63.6 ± 22.43	62.2 ± 20.83
Physician global assessment of disease activity (range 0–100), mean ± SD	61.1 ± 17.04	61.8 ± 17.44

* ITT = intent-to-treat; TCZ-SC = subcutaneous tocilizumab; PBO-SC = subcutaneous placebo; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; anti-TNF = anti–tumor necrosis factor; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; DAS28 = Disease Activity Score in 28 joints; SHS = modified Sharp/van der Heijde score; JSN = joint space narrowing; HAQ = Health Assessment Questionnaire; DI = disability index; VAS = visual analog scale.
† N = 432.
‡ N = 218.
§ N = 429.
¶ N = 217.
# N = 391.
** N = 186.

group) (Table 2). The most common AE was upper respiratory tract infection (6.4% in each group). One or more serious AEs (SAEs) were experienced by 4.6% of patients in the TCZ-SC group and 3.7% in the PBO-SC group; infection was the most common SAE (2.1% in the TCZ-SC group and 1.8% in the PBO-SC group). A greater percentage of patients in the TCZ-SC group discontinued because of AEs (2% in the TCZ-SC group and 1% in the PBO-SC group). Similar safety results were observed for escape therapy patients.

Three patients died; all deaths were in the TCZ-SC group and all were reported as related to TCZ treatment. One patient died from *Hemophilus influenzae* sepsis, 1 from sepsis (likely from gastrointestinal causes), and 1 from a lower respiratory tract infection and subsequent complications (see the brief narratives available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract).

AEs of special interest were observed more often in the TCZ-SC group than the PBO-SC group. No anaphylaxis,
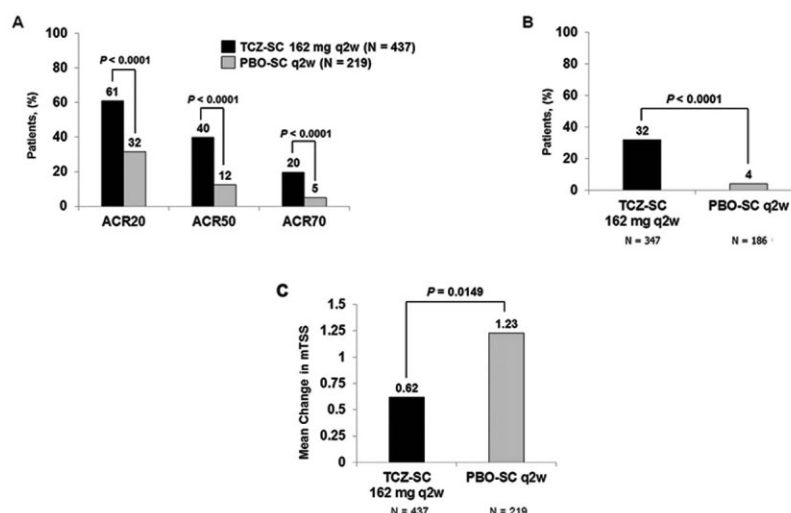
Figure 2. Disease activity, physical function, and radiographic outcomes at 24 weeks for patients in the intent-to-treat population. **A,** The proportion of patients treated with either subcutaneous tocilizumab (TCZ-SC; n = 437) or placebo (PBO-SC; n = 219) every other week (q2w) who achieved the American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70) at week 24. **B,** The proportion of patients who achieved remission based on the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (<2.6) at week 24. **C,** The mean change from baseline in the modified Sharp/van der Heijde score (mTSS) every other week.

serious hypersensitivity, stroke (ischemic or hemorrhagic), gastrointestinal perforations, or demyelinating disorders were observed up to 24 weeks in either group. While no hepatic SAEs occurred, 1 patient in the TCZ-SC group experienced a non-SAE of hepatic steatosis (grade 1) with associated elevations in aspartate aminotransferase (AST; <3 × ULN) and alanine aminotransferase (ALT; <5 × ULN) and withdrew from the study. Three malignancies

Table 2. Safety (safety population)*		
	TCZ-SC 162 mg every other week (n = 437)	PBO-SC every other week (n = 218)
AEs		
Total AEs	716	217
Patients with ≥1 AEs	274 (62.7)	126 (57.8)
Discontinuation due to AEs	9 (2)	3 (1)
Serious AEs		
Total	25	12
Patients with ≥1	20 (4.6)	8 (3.7)
Infections		
Total	167	78
Patients with ≥1	131 (30.0)	61 (28.0)
Serious infections		
Total	12	5
Patients with ≥1	9 (2.1)	4 (1.8)
Serious hypersensitivity reactions†	0	0
ISRs		
Total	35	9
Patients with ISRs	31 (7.1)	9 (4.1)
Pain	11 (2.5)	5 (2.3)
Erythema	10 (2.3)	1 (0.5)
Hematoma	5 (1.1)	3 (1.4)
Pruritus	3 (0.7)	0 (0)
Dose interruption or study withdrawal because of ISRs	0	0
Death	3 (<1)	0

* Values are the number (percentage). TCZ-SC = subcutaneous tocilizumab; PBO-SC = subcutaneous placebo; AEs = adverse events; ISRs = injection site reactions.
† Serious hypersensitivity was defined as a serious AE occurring during or within 24 hours of the injection or infusion, excluding ISRs, and evaluated as related to study treatment by the investigator.

occurred in the TCZ-SC group (1 non-SAE [basal cell carcinoma] and 2 SAEs [1 adenocarcinoma of the pancreas and 1 renal cancer]), all unrelated to study medication. One SAE of diverticular hemorrhage occurred in the TCZ-SC group; the patient had a history of diverticular bleeding but met the study entry criteria. In the opinion of the patient's gastroenterologist, the SAE of diverticular hemorrhage was a reoccurrence of the previous diverticular bleeding, and the investigator (MB) reported the event as unrelated to study medication; there was no association with thrombocytopenia. In the PBO-SC group, 1 serious opportunistic infection and 1 myocardial infarction were reported.

Injection site reactions (ISRs) were more common in the TCZ-SC group (7.1%) than in the PBO-SC group (4.1%) (Table 2). All ISRs were reported as not serious and as Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2; none required dose interruption or study withdrawal.

A summary of laboratory abnormalities is shown in Supplementary Table 3 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). Of the patients with elevated ALT or AST levels upon initiation of TCZ but normal values at baseline, most had increases of $\leq 3 \times$ ULN; shifts occurred in more patients in the TCZ-SC group than in the PBO-SC group (33% versus 13%). One patient in the TCZ-SC group discontinued treatment because of elevated liver transaminases.

Of the patients who experienced decreased neutrophil counts after initiating treatment, most experienced CTCAE grade 1 or 2 neutropenia. Grade 1 neutropenia was reported more frequently in the TCZ-SC group (11.6%) than the PBO-SC group (3.7%), and grade 2 neutropenia occurred only in the TCZ-SC group (5.1%). Grades 3 and 4 neutropenia occurred only in the TCZ-SC group (3.5% [n = 15] and 0.2% [n = 1], respectively). One patient in the TCZ-SC group discontinued because of grade 4 neutropenia (grade 2 at baseline prior to TCZ treatment). A nonserious grade 2 event of sinus infection occurred 7 days after the grade 4 neutropenia; the investigator reported this as unrelated to study medication. Only patients in the TCZ-SC group experienced ≥ 1 low platelet count postbaseline (7%); 94% were grade 1 events. No patients discontinued treatment because of thrombocytopenia; no grade 3 or 4 thrombocytopenia occurred. The proportion of patients with an increase in total cholesterol from <200 mg/dl at baseline to ≥ 200 mg/dl at the last observation was higher in the TCZ-SC group than in the PBO-SC group (45% versus 14%). Shifts in low-density lipoprotein cholesterol and triglyceride levels occurred more often in the TCZ-SC group than in the PBO-SC group.

Immunogenicity results. Seven patients in the TCZ-SC group (1.6%) and 3 patients in the PBO-SC group (1.4%) tested positive postbaseline in the anti-TCZ confirmation assay. Of these 10 patients, 6 in the TCZ-SC group (1.6%) and 1 in the PBO-SC group (0.5%) tested positive in the neutralizing assay. No patients who developed anti-TCZ antibodies experienced anaphylaxis, hypersensitivity reactions, or ISRs. No patients with positive results on the
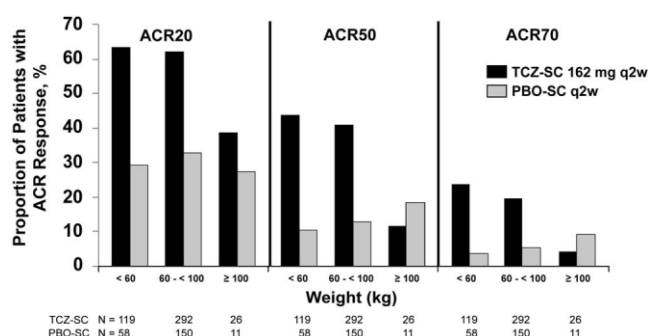

Figure 3. The proportion of patients treated with either subcutaneous tocilizumab (TCZ-SC; n = 437) or placebo (PBO-SC; n = 219) every other week (q2w) who achieved the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70) at week 24, stratified by weight (intent-to-treat population).

confirmation and neutralizing assays withdrew because of an insufficient therapeutic response or experienced loss of efficacy (defined as patients from the ITT population who withdrew as a result of insufficient therapeutic response after experiencing an ACR50 response or a DAS28-ESR–based European League Against Rheumatism good response).

Efficacy and safety by weight stratification. The percentage of patients who achieved ACR20, ACR50, and ACR70 responses was similar between the 2 lower weight categories (<60 kg and 60 to <100 kg) in the TCZ-SC group at week 24 (Figure 3). For both treatment groups, the proportion of patients who weighed ≥ 100 kg and achieved an ACR20 response was lower than the patients in the lower weight categories. The ACR20 response rates for patients who weighed ≥ 100 kg were numerically higher in the TCZ-SC group (38.5%) than in the PBO-SC group (27.3%); in contrast, ACR50 (11.5% versus 18.2%) and ACR70 (3.8% versus 9.1%) response rates were lower in the TCZ-SC group versus the PBO-SC group.

Regarding pharmacokinetics across the body weight groups, C_{trough} levels decreased with increasing body weight (mean $\pm$ SD TCZ blood concentration for the <60 kg group was 11.70 $\pm$ 7.91 μg/ml, for the 60 to <100 kg group was 6.17 $\pm$ 6.74 μg/ml, and for the ≥ 100 kg group was 2.04 $\pm$ 2.82 μg/ml).

The incidence of AEs and SAEs was similar in the treatment groups in the 2 lower weight categories (see Supplementary Table 4, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/abstract). In the TCZ treatment group, a higher percentage of patients who weighed ≥ 100 kg experienced ≥ 1 AE compared with patients in the lower weight categories. Patients in the highest weight category (≥ 100 kg) in both treatment groups experienced more SAEs than those in the lower weight categories, although the percentage was lower in the TCZ-SC group than in the PBO-SC group.

DISCUSSION

The BREVACTA study assessed the efficacy and safety of TCZ-SC 162 mg every other week in combination with

DMARDs in patients with RA who were inadequate responders to DMARDs (including anti-TNF). The study population had moderate to severe RA, as reflected by the high mean DAS28 score (6.6) and long duration of disease activity (11.1 years). The study met its primary end point by demonstrating the superiority of TCZ-SC every other week over PBO-SC in the percentage of patients who achieved an ACR20 response at week 24. TCZ-SC was generally well tolerated, and the associated AE profile was consistent with the known and well-established safety profile of TCZ-IV.

An analysis of all secondary end points, including ACR50/70, inhibition of joint damage, and DAS28 remission, also showed that TCZ-SC was superior to PBO-SC. Additional exploratory analyses demonstrated that differences in ACR20/50/70 response rates between TCZ-SC and PBO-SC patients were similar in patients with an inadequate response to DMARDs versus patients with an inadequate response to anti-TNF agents, and by patients receiving concomitant methotrexate or other DMARDs.

The TCZ-SC group experienced less joint damage at week 24 compared with the PBO-SC group. This assessment was made at week 24, although phase III studies usually assess radiographic end points at 1 year (16), which would allow more time to elapse to observe any changes in SHS since baseline.

Improvements in ACR20, ACR50, and ACR70 responses were observed in patients who received escape therapy with TCZ-SC every week. The responses in patients who switched from TCZ-SC every other week to TCZ-SC every week demonstrated that an increase in dosing frequency led to improvement in signs and symptoms of RA as measured by the ACR 20/50/70. Of the patients who switched from PBO-SC to TCZ-SC every week, the response was similar to that in the TCZ-SC every week group in SUMMACTA and greater than that in the patients who switched from TCZ-SC every other week to TCZ-SC every week (20). The lower ACR response rate in patients who received escape therapy (TCZ-SC every week) after being randomized to receive TCZ-SC every other week may reflect the inclusion of patients who were true biologic TCZ nonresponders and/or those who required a higher initial dose of TCZ to respond to the therapy.

Previous studies have observed that obesity is associated with poorer treatment outcomes in patients with RA (24). Patients who weighed ≥100 kg had poorer ACR20/50/70 responses than patients in the 2 lower weight categories. The ≥100 kg TCZ-SC group had numerically lower ACR50/70 responses than those in the PBO-SC group. The small number of patients in the ≥100 kg group may have accounted for the variation observed in response rates. However, in SUMMACTA (TCZ-SC every week), the proportion of patients who achieved an ACR response or DAS28 remission was similar across the 3 body weight categories at most time points (20). Because the TCZ-SC dose is fixed at 162 mg, TCZ-SC every other week does not provide adequate efficacy for patients who weigh ≥100 kg, which may be partly due to the very low blood concentrations of TCZ in the heaviest patient group, as demonstrated by C_{trough} levels.

There were 3 deaths in the TCZ-SC group (all due to infections) and none in the PBO-SC group. The number of deaths was small, and the death rate per 100 patient-years over the first 24 weeks of the BREVACTA study was 1.64 (95% CI 0.34−4.80). This was within the range of the first 24 weeks of the double-blind periods of the pivotal phase III TCZ-IV studies (protocol numbers WA17822, WA17823, WA17824, WA18062, and WA18063). The death rates ranged from 0 to 2.14 deaths per 100 patient-years, with the highest rate of 2.14 from a study of TCZ-IV 8 mg/kg monotherapy (protocol number: WA17824) (Roche: unpublished observations). Additionally, from the BREVACTA study, the incidence of infections and serious infections was similar between the treatment groups (Table 2).

The safety profiles of TCZ-SC and PBO-SC were similar to previous studies of TCZ-IV (1,14−18). Two SAEs (malignancies) that were considered unrelated to treatment occurred in the TCZ-SC group at a rate of 1.09 (95% CI 0.13−3.95) per 100 patient-years of exposure, which is similar to the rate observed previously with TCZ-IV (1.0 per 100 patient-years of exposure) over 52 weeks (25). As also observed in the TCZ-IV safety profile, decreases from baseline were seen for neutrophils and platelets in the TCZ-SC group. Increases were observed in transaminases and mean fasting lipid levels in a higher percentage of patients in the TCZ-SC group than in the PBO-SC group. There was no association between SAEs of bleeding events and thrombocytopenia, or serious hepatic events and elevation of liver function tests. One patient who died of sepsis experienced pancytopenia as reported from local laboratory results, which included grade 4 neutropenia. No other patients had associations between grade 4 neutropenia and serious infection. The number of patients who developed anti-TCZ antibodies was low, with no association between anti-TCZ antibody development and loss of clinical response or AEs. ISRs were more frequent in the TCZ-SC group than in the PBO-SC group, comparable to the incidence observed with other SC therapies in RA.

In summary, the superiority in efficacy of TCZ-SC 162 mg every other week over PBO-SC in combination with DMARDs was shown. The safety profile of TCZ-SC was comparable with that seen in previous studies of TCZ-IV. The TCZ-SC formulation is a convenient dosing option for patients with RA and will allow patients to self-administer the drug.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kivitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Borofsky, Zazueta, Rowell, Bao, Wright.

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ROLE OF THE STUDY SPONSOR

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ADDITIONAL DISCLOSURES

Dr. Bao is an employee of Genentech.

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