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Reducing or Maintaining the Dose of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis in Clinical Remission: A Randomized, Open-Label Trial

Raimon Sanmarti,[1] Douglas J. Veale,[2] Emilio Martin-Mola,[3] Alejandro Escudero-Contreras,[4] Carlos González,[5] Liliana Ercole,[6] Rocío Alonso,[6] João E. Fonseca,[7] and the ToSpace Study Group

Objective. To evaluate the efficacy and safety of increasing the dose interval of subcutaneous tocilizumab (TCZ-SC) in patients with rheumatoid arthritis (RA) who are in clinical remission.

Methods. RA patients with active disease and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or to a biologic agent were entered into a single-arm treatment phase with 162 mg of TCZ-SC administered once weekly (TCZ-SC 162 mg qw) as monotherapy or in combination with a csDMARD for 24 weeks. Patients who achieved clinical remission at weeks 20 and 24 were randomized to continue with the same regimen or to switch to 162 mg TCZ-SC administered every 2 weeks (TCZ-SC 162 mg q2w) for 24 weeks (open-label). Patients with a Disease Activity Score in 28 joints (DAS28) of <2.6 were considered to be in clinical remission.

Results. In total, 179 (45%) of 401 patients in the single-arm phase achieved clinical remission and were randomized to continue to receive TCZ-SC 162 mg qw (n = 89) or to switch to TCZ-SC 162 mg q2w (n = 90) for 24 weeks. At week 48, significantly more patients treated with TCZ-SC 162 mg qw remained in clinical remission compared to patients who received TCZ-SC 162 mg q2w (90% versus 73%; $P = 0.004$). The results of other efficacy measures revealed greater efficacy with TCZ-SC 162 mg qw, but none of the efficacy outcomes in this group were significantly different from those in patients treated with TCZ-SC 162 mg q2w, except for the mean change from baseline in the DAS28 score at week 48 (mean change –4.07 points [SD 1.29] versus –3.65 points [SD 1.35]; $P = 0.034$). Tolerability and safety parameters were similar between the treatment groups.

Conclusion. Increasing the dose interval of TCZ-SC in patients with RA was associated with a lower likelihood of maintaining remission after 24 weeks and was not associated with better tolerability. However, most patients were able to sustain remission with a half-dose of TCZ-SC, and therefore this strategy deserves further investigation.

INTRODUCTION

The efficacy and safety of biologic disease-modifying antirheumatic drugs (bDMARDs) have been well established in patients with rheumatoid arthritis (RA) who experience an inadequate response to conventional synthetic DMARDs (csDMARDs) such as methotrexate (1,2). A significant proportion of RA patients achieve sustained remission or low disease activity following treatment with bDMARDs, and optimizing their administration after achievement of the therapeutic objective is an attractive option for safety or

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[1]Raimon Sanmarti, MD, PhD: Hospital Clinic of Barcelona and IDIBAPS, Barcelona, Spain; [2]Douglas J. Veale, MD: St. Vincent's University Hospital and University College Dublin, Belfield, Dublin, Ireland; [3]Emilio Martin-Mola, MD, PhD: Hospital Universitario La Paz, Madrid, Spain; [4]Alejandro Escudero-Contreras, MD: Rheumatology Service, Reina Sofia Hospital, Maimonides Institute for Research in Biomedicine of Cordoba, University of Cordoba, Cordoba, Spain; [5]Carlos González, MD, PhD: Hospital Gregorio Marañón, Madrid, Spain; [6]Liliana Ercole, MD, Rocío Alonso, PharmD: Roche Farma, Madrid, Spain; [7]João E. Fonseca, MD, PhD: Universidade de Lisboa and Hospital de Santa Maria CHLN, Lisbon, Portugal. Members of the ToSpace Study Group are listed in Appendix A.

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Address correspondence to Raimon Sanmarti, MD, PhD, Hospital Clinic of Barcelona, Arthritis Unit Rheumatology Service, Villarroel, 170, 08036 Barcelona, Spain. E-mail: sanmarti@clinic.cat.

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economic reasons (3). Discontinuation of bDMARDs highly increases the risk of losing remission and experiencing a disease relapse with radiographic progression of RA, and therefore discontinuation of bDMARDs is not recommended as an optimizing strategy (3–5). In contrast, reducing/tapering the dose of bDMARDs may maintain the therapeutic objective in patients with RA and could be considered for a potential strategy in those patients who achieve sustained remission or low disease activity (6). Although information is limited, dose-reduction strategies may also be cost effective (7,8). Thus, bDMARD dose optimization is included in the recommended strategies of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) for patients with established RA who are in sustained remission or have low disease activity (9,10).

Tocilizumab (TCZ) is the first interleukin-6 inhibitor approved for the treatment of RA. This bDMARD is effective in the treatment of RA in several clinical settings, including for the treatment of csDMARD-naive patients and patients who have shown an inadequate response to csDMARDs or other bDMARDs. TCZ is most commonly administered in combination with methotrexate but is also efficacious as a monotherapy, and it is considered the bDMARD of choice when monotherapy is preferred. TCZ was initially developed as an intravenous formulation, but a subcutaneous (SC) formulation was recently developed (11). The clinical efficacy and safety of TCZ administered subcutaneously (TCZ-SC) has been found to be similar to that of intravenous TCZ (12,13). Findings from a retrospective study suggested the possibility of a dose reduction with intravenous TCZ in a substantial proportion of RA patients without a disease flare (14). However, neither the efficacy nor the safety of a dose reduction of TCZ, either by the intravenous or the SC route of administration, has been evaluated in patients with RA in randomized controlled trials.

Therefore, as part of a multinational project (the TOZURA study) (15), we performed this randomized, open-label trial in patients with RA who achieved sustained clinical remission after having received 24 weeks of TCZ-SC (dose of 162 mg) administered once weekly (TCZ-SC 162 mg qw). In this patient cohort, we assessed the efficacy and safety of continuing with the same weekly regimen (TCZ-SC 162 mg qw) for 24 weeks or switching to TCZ-SC (dose of 162 mg) administered every 2 weeks (TCZ-SC 162 mg q2w).

PATIENTS AND METHODS

Study design. This study was part of an international project (the TOZURA study) comprising 11 studies in 22 countries that was designed as an open-label, single-arm study to evaluate the efficacy and safety of weekly TCZ-SC (162 mg) as monotherapy or in combination with csDMARDs for 24 weeks in patients with moderate-to-severe RA who had an inadequate response to csDMARDs or to tumor necrosis factor inhibitor (TNFi) agents or who were methotrexate naive. The methods and global results of this phase IV study program have been published elsewhere (15).

The present study was a continuation of this single-arm study and was performed at 46 sites in Spain, Ireland, and Portugal between September 2013 and March 2016. The study was performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the ethics principles contained in the Declaration of Helsinki. The ethics committees of each participating site approved the study, and all patients provided their written informed consent to participate. Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx, and further details on Roche's Global Policy on the Sharing of Clinical Information and instructions on how to request access to related clinical study documents are provided at https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Patients. Inclusion and exclusion criteria for the initial single-arm phase of the study are described in detail elsewhere (15). Briefly, included patients were patients ages ≥18 years who exhibited active RA, defined according to the 1987 revised ACR criteria for RA or the 2010 ACR/EULAR classification criteria for RA (16,17), and who had demonstrated intolerance to or an inadequate response to csDMARDs or a first-line TNFi. Patients were excluded if they had undergone major surgery within 8 weeks prior to screening or had a major surgery scheduled within 6 months from baseline, exhibited a rheumatic or inflammatory joint disease other than RA, had ACR functional class IV RA (18), or presented other safety issues or had received or were receiving treatments that precluded proper evaluation of drug efficacy. Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract) presents the full set of inclusion and exclusion criteria.

Patients who achieved clinical remission at weeks 20 and 24 of the single-arm phase were included in the randomized continuation phase, which is the focus of the present report.

Interventions, randomization, and masking. All patients in the single-arm phase received 162 mg of TCZ-SC once weekly for 24 weeks on an outpatient basis, administered as monotherapy or in combination with a csDMARD, as clinically indicated. Concomitant treatment with csDMARDs was allowed if the csDMARD was administered at a stable dose for at least 4 weeks prior to the initiation of the single-arm phase. Similarly, patients who were receiving nonsteroidal antiinflammatory drugs (up to the maximum recommended dose) or glucocorticoids (≤10 mg of prednisone or equivalent) were allowed to continue receiving these drugs if they had achieved a stable dose at least 4 weeks prior to the initiation of the single-arm phase. Patients who exhibited an inadequate response to at least 3 months of TNFi therapy had discontinued this drug prior to inclusion in the single-arm phase.

Patients who achieved clinical remission, defined as a Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) of <2.6 (19), at weeks 20 and 24 of the single-arm phase of the study were randomized in a 1:1 ratio to receive, in an open-label manner, continued treatment with TCZ-SC 162 mg qw or to switch to TCZ-SC 162 mg q2w. Randomization was centralized and performed using a computer-generated system, and patients were stratified according to body weight (<60 kg, 60 kg to <100 kg, or >100 kg), Clinical Disease Activity Index (CDAI) score (<10 or ≥10) (20), and type of TCZ-SC regimen in the single-arm phase (monotherapy or in combination with csDMARDs).

Study assessments. Week 0 (i.e., baseline visit) of the single-arm phase was also the baseline evaluation of the randomized phase. Study assessments in this phase were scheduled every 4 weeks for 24 weeks, with an additional 8-week follow-up period.

Efficacy outcome measures in the randomized phase included assessment of the mean change from baseline in the following indices: DAS28, Simplified Disease Activity Index (SDAI) (21), CDAI, tender and swollen joint counts of 28 joints, serum C-reactive protein (CRP) levels, ESR, pain intensity scores (assessed on a 100-mm visual analog scale), patient and physician global health assessments (numeric rating scales of 0–100), and scores on the Health Assessment Questionnaire (HAQ) disability index (DI) (22). Patients with a DAS28 score of <2.6 were considered to be in clinical remission. Treatment response was defined according to the ACR improvement response criteria (levels of at least 20%, 50%, 70%, and 90% improvement in RA disease activity from the baseline visit of the single-arm phase) and EULAR response criteria (no response, moderate response, or good response) (23,24). Low disease activity was defined using the CDAI score (CDAI <10) and SDAI score (SDAI <11). Patients with a HAQ DI score of <0.5 were considered to have no significant functional disability. No radiographic assessments were performed.

Safety assessments included incidence of any adverse events (AEs) as reported in response to an open-ended question and as determined by physical examination and vital signs. AEs of special interest included serious and/or medically significant infections, myocardial infarction/acute coronary syndrome, gastrointestinal perforations, malignancies, anaphylaxis/hypersensitivity reactions, demyelinating disorders, stroke, serious and/or medically significant bleeding events, and serious and/or medically significant hepatic events.

Statistical analysis. We estimated that a sample size of 420 patients would be needed from the participating sites contributing to the combined total of 2,000 patients required for the global project. However, pivotal studies of TCZ-SC have

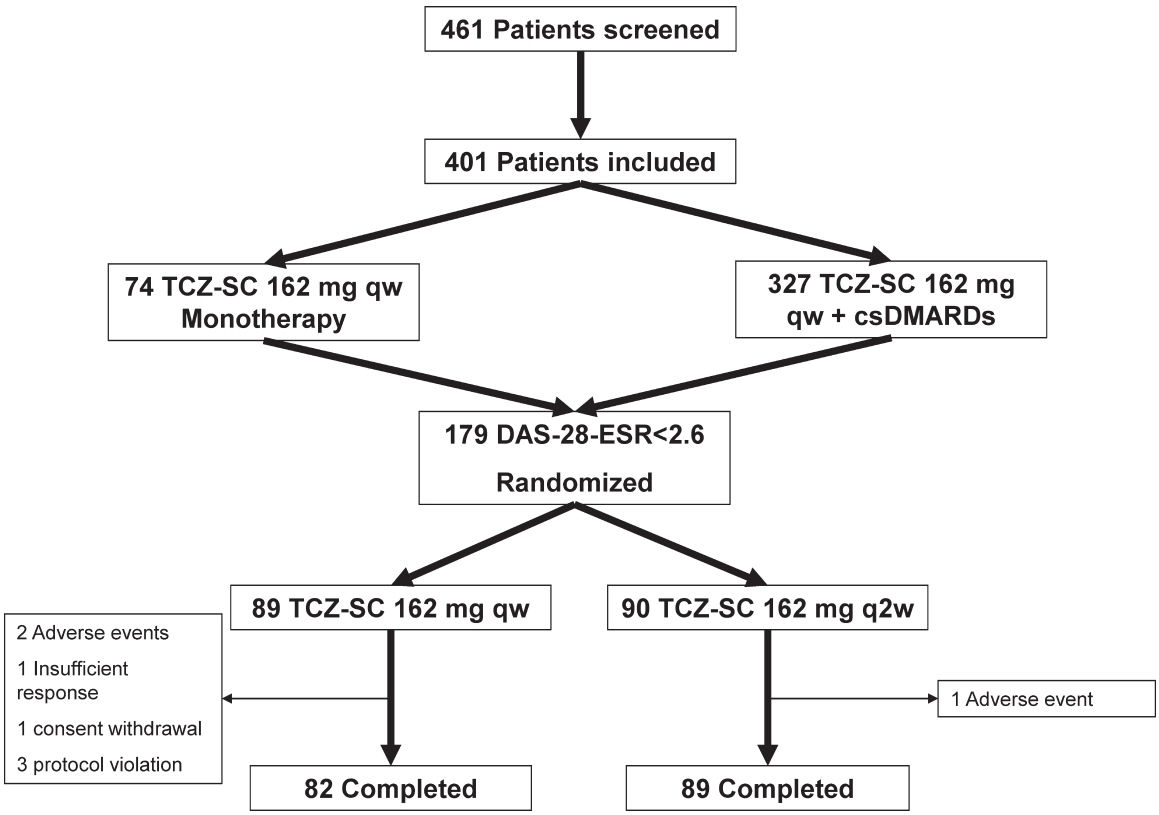

Figure 1. Disposition of the study patients. TCZ-SC = subcutaneous tocilizumab; qw = once weekly; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; q2w = every 2 weeks.

suggested that one-third of these patients (i.e., 140 patients) would achieve clinical remission in the single-arm phase of the study and would be included in the randomized phase. This sample size was expected to provide an 83% power to detect a between-group difference of 0.6 (i.e., the limit of clinical relevance) in the mean change from baseline in the DAS28.

Efficacy analyses were performed in the full analysis set (FAS) population, which was defined as all patients included in the study who received at least one dose of TCZ-SC. Efficacy analyses were also performed in the per protocol (PP) population, which was defined as patients in the FAS population who exhibited no major protocol violations of the selection criteria and who completed the study without major protocol violations. Missing data were imputed using the last observation carried forward (LOCF) approach. Safety analyses were performed in the FAS population.

Continuous outcomes are presented as the mean ± SD, and categorical outcomes are presented as absolute and relative frequencies. Student's *t*-tests were performed to compare scores and mean changes from baseline in the DAS28 and other quantitative outcomes in paired samples. Categorical outcomes were compared using the chi-square test or Fisher's exact test. All tests were 2-sided and considered significant at *P* values less than 0.05.

Several post hoc analyses were performed. A sensitivity analysis for efficacy outcomes was performed using nonresponder imputation instead of LOCF, in which participant dropouts were assumed to be nonresponders regardless of actual response status at the time of dropout. Logistic regression analysis was performed in the TCZ-SC 162 mg q2w group to further investigate potential factors for maintaining remission. The dependent variable was remission (i.e., a DAS28 score <2.6) at week 48. Independent variables included age, body mass index, disease duration, rheumatoid factor/anti–citrullinated protein antibody (ACPA) status, and DAS28 score at week 24. Treatment-by-subgroup interactions were also analyzed using logistic regression analysis to determine whether the identified factors explained differences between the TCZ-SC 162 mg qw and TCZ-SC 162 mg q2w groups.

In addition, efficacy results were analyzed according to the monotherapy/combination therapy status and the CDAI-defined remission status (i.e., CDAI <2.8 versus CDAI ≥2.8) at the time of randomization. Time to relapse, defined as a DAS28-ESR score of ≥2.6, was analyzed using Kaplan-Meier curves and a univariate Cox proportional hazards model.

All analyses were performed using SAS version 9.2 (SAS Institute).

RESULTS

Disposition and baseline characteristics of the patients. A total of 401 patients of the 461 screened were included in the single-arm phase of the study, and 179 (45%) of these patients exhibited clinical remission at weeks 20 and 24 (Figure 1). The distribution of patients in clinical remission was not significantly different between the TCZ-SC monotherapy group and the group receiving TCZ-SC in combination with csDMARDs. Patients who achieved clinical remission were randomized to continue to receive TCZ-SC 162 mg qw (n = 89) or switched to TCZ-SC 162 mg q2w (n = 90) for 24 weeks. All 179 patients were included in the FAS population.

The demographic and clinical characteristics of the patients at baseline were similar between the 2 treatment groups (Table 1). More than 80% of the patients had received a csDMARD at the time of entry in the randomized phase. The most common csDMARD was methotrexate, which was being taken by 62% of the TCZ-SC 162 mg qw–treated patients and 66% of the TCZ-SC 162 mg q2w–treated patients.

Efficacy results. Significantly more patients treated with TCZ-SC 162 mg qw remained in clinical remission, as evaluated using the DAS28, at week 48 when compared to

Table 1. Demographic and clinical characteristics at study entry in patients who entered the randomized phase of the study*

Characteristic	Tocilizumab 162 mg qw (n = 89)	Tocilizumab 162 mg q2w (n = 90)
Age, mean ± SD years	52.5 ± 12.2	52.6 ± 12.5
Women, no. (%)	72 (80.9)	68 (75.6)
White ethnic origin, no. (%)	85 (95.5)	88 (97.8)
Weight, mean ± SD kg	69.6 ± 13.4	70.1 ± 12.7
Disease duration, mean ± SD years	6.5 ± 7.3	6.4 ± 6.4
Rheumatoid factor positive, no. (%)	71 (79.8)	67 (74.4)
ACPA positive, no. (%)	65 (73.0)	64 (71.1)
CRP, mean ± SD mg/liter	12.2 ± 20.4	11.5 ± 15.9
DAS28-ESR score, mean ± SD	5.62 ± 0.95	5.61 ± 1.01
SDAI score, mean ± SD	41.45 ± 24.9	40.92 ± 21.42
CDAI score, mean ± SD	29.27 ± 10.9	29.64 ± 12.13
HAQ DI score, mean ± SD†	1.21 ± 0.68	1.20 ± 0.7
Glucocorticoid use, no. (%)	52 (58.4)	53 (58.9)
Prednisone or equivalent daily dose, mean ± SD mg/day	5.5 ± 2.1	7.1 ± 5.5
Current treatments, no. (%)		
Any csDMARD	71 (79.8)	76 (84.4)
Methotrexate	55 (61.8)	59 (65.6)
Leflunomide	10 (11.2)	13 (14.4)
Hydroxichloroquine	4 (4.5)	4 (4.4)
Sulfasalazine	2 (2.2)	2 (2.2)

* With the exception of current treatments, which are described at the time of randomization, all characteristics are described at the time of entry into the single-arm phase of the study. ACPA = anti–citrullinated protein antibody; CRP = C-reactive protein; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; csDMARD = conventional synthetic disease-modifying antirheumatic drug.
† Data on Health Assessment Questionnaire (HAQ) disability index (DI) scores were missing for 1 patient in the subcutaneous tocilizumab every week (qw) group and 1 patient in the subcutaneous tocilizumab every 2 weeks (q2w) group.

patients who received TCZ-SC 162 mg q2w (90% versus 73%, respectively; $P = 0.004$). Post hoc analysis using non-responder imputation in the FAS population yielded similar results with regard to sustained clinical remission (89% versus 73%, respectively; $P = 0.007$). Time to relapse was longer in patients treated with TCZ-SC 162 mg qw than in patients treated with TCZ-SC 162 mg q2w, although the difference was not statistically significant (hazard ratio 0.87, 95% confidence interval [95% CI] 0.54–1.41; log-rank test $P = 0.561$) (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract).

The frequency of low disease activity, as determined using the DAS28, was also significantly higher in the TCZ-SC 162 mg qw arm than in the TCZ-SC 162 mg q2w arm. More patients achieved CDAI- or SDAI-defined clinical remission or low disease activity with the weekly dose of TCZ-SC than with TCZ-SC given every 2 weeks, but the differences were not statistically significant (Figure 2). We observed no differences in functional disability as evaluated with the HAQ DI at week 48; the proportion of patients with a HAQ DI score of <0.5 was 55% among those treated with TCZ-SC 162 mg qw and 57% among those treated with TCZ-SC 162 mg q2w ($P = 0.83$).

Furthermore, no significant differences between the 2 treatment groups were observed in the various patient-reported outcomes evaluated. More patients treated with TCZ-SC 162 mg qw achieved ACR improvement responses as compared to patients treated with TCZ-SC 162 mg q2w, but these differences were not statistically significant. Moreover, the EULAR treatment response was significantly better in patients treated with TCZ-SC 162 mg qw compared to patients treated with TCZ-SC 162 mg q2w (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract).

Evaluation of continuous disease activity outcomes revealed no significant differences between the 2 treatment groups, except for the mean change from baseline in the DAS28. Reductions in the DAS28 score were significantly greater in the TCZ-SC 162 mg qw group compared to the TCZ-SC 162 mg q2w group (mean change in DAS28 –4.07 points [SD 1.29] with TCZ-SC 162 mg qw versus –3.65 points [SD 1.35] with TCZ-SC 162 mg q2w; $P = 0.034$) (Table 2). Patients treated with TCZ-SC 162 mg qw showed a greater reduction of the DAS28-ESR score compared to those treated with TCZ-SC 162 mg q2w (estimated treatment difference –0.386 [95% CI –0.674 to –0.097]). The time course of the changes from baseline in the disease activity measures is

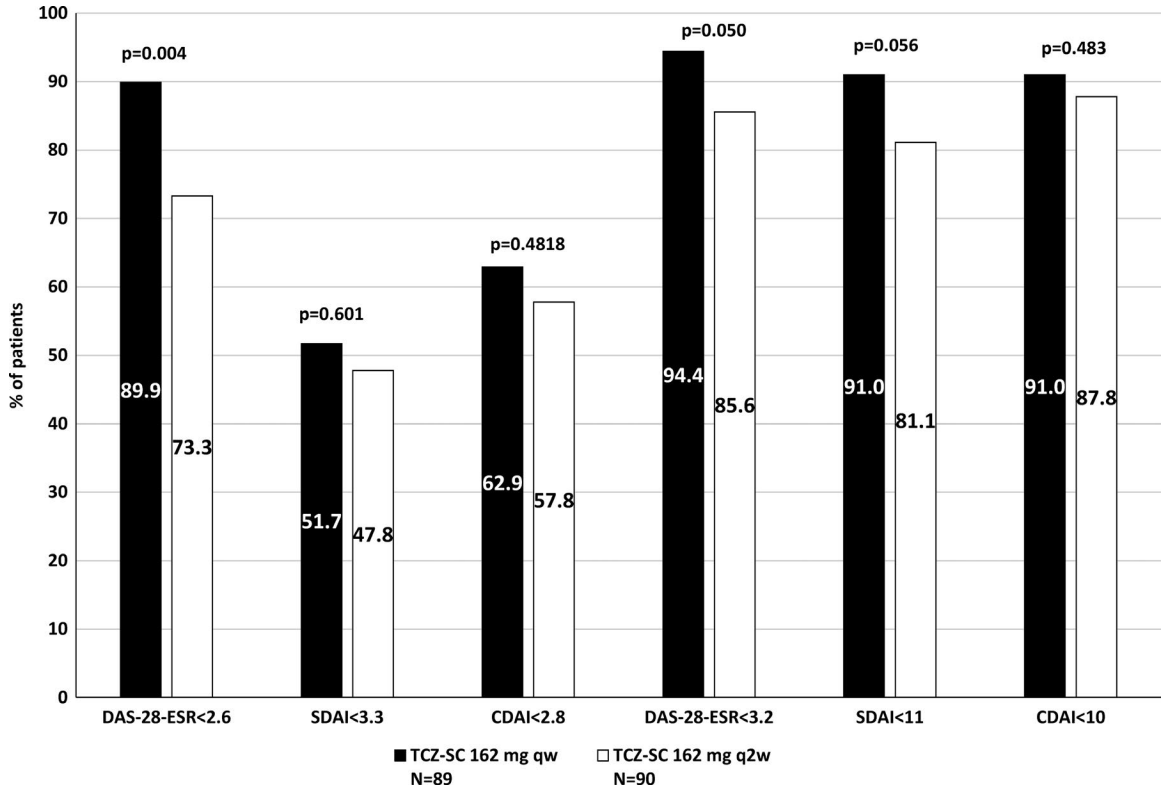

Figure 2. Measures of clinical remission and low disease activity at week 48 in the full analysis set (last observation carried forward) of rheumatoid arthritis patients treated with 162 mg subcutaneous tocilizumab (TCZ-SC) once weekly (qw) or every 2 weeks (q2w) for 24 weeks. DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index.

Table 2. Mean change from baseline (week 0) to week 48 in measures of disease activity and function in the full analysis set (last observation carried forward) of patients with rheumatoid arthritis*

Efficacy measure	Tocilizumab 162 mg qw (n = 89)	Tocilizumab 162 mg q2w (n = 90)
DAS28-ESR	−4.07 ± 1.29	−3.65 ± 1.35
SDAI†	−36.93 ± 25.75	−34.69 ± 21.75
CDAI	−25.74 ± 11.29	−24.87 ± 12.67
Tender joint count	−13.96 ± 8.68	−13.27 ± 12.20
Swollen joint count	−8.82 ± 6.51	−8.64 ± 7.33
C-reactive protein†	−7.56 ± 15.60	−7.35 ± 13.82
ESR	−31.19 ± 25.67	−28.47 ± 20.89
Physician global assessment	−50.00 ± 20.55	−50.74 ± 23.59
Patient global assessment	−44.30 ± 24.85	−41.42 ± 26.38
Patient pain score	−42.99 ± 24.71	−39.59 ± 27.66
HAQ DI score†	−0.65 ± 0.66	−0.65 ± 0.58

* Values are the mean ± SD change from week 0 to week 48 in the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR), Simplified Disease Activity Index (SDAI) (scale 0–86), Clinical Disease Activity Index (CDAI) (scale 0–76), tender and swollen joint counts of 28 joints, serum C-reactive protein levels, ESR, physician and patient global assessments of health on 100-mm visual analog scales (VAS), patient assessment of pain on 100-mm VAS, and Health Assessment Questionnaire (HAQ) disability index (DI) scores (range 0–3.0, in 0.125 increments). No significant between-group differences were observed, except in the DAS28-ESR ($P = 0.034$).
† Data were missing as follows: for the SDAI, 1 patient in the subcutaneous tocilizumab (TCZ-SC) every 2 weeks (q2w) group; for C-reactive protein levels, 3 patients in the TCZ-SC q2w group; for the HAQ DI, 1 patient in the TCZ-SC once weekly (qw) group and 1 patient in the TCZ-SC q2w group.

presented in Supplementary Figure 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract).

Results of the PP population analysis were in the same direction and magnitude as that in the FAS population (data not shown).

Post hoc analysis of factors predictive of remission at week 48 and their impact on treatment effect. Multiple logistic regression analysis of the TCZ-SC 162 mg q2w group showed that only body mass index and DAS28 scores at week 24 were significantly associated with remission at week 48 (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract). A 1-point increase in the body mass index was associated with a 12% reduction in the likelihood of remission at week 48. An increase of 1 point in the DAS28 score at week 24 was associated with a 61% reduction in the likelihood of remission.

The multiple logistic regression model performed in the entire sample to investigate treatment-by-subgroup interactions for age, body mass index, disease duration, rheumatoid factor/ACPA status, and DAS28 at week 24 did not reveal any significant interactions, with the exception of the rheumatoid factor/ACPA status (data not shown). The rheumatoid factor/ACPA status could not be investigated, because all patients who were negative for these markers in the TCZ-SC 162 mg qw group were in remission at week 48.

Post hoc subgroup analyses of remission and disease activity measures. The proportion of patients who remained in clinical remission was higher in the TCZ-SC 162 mg qw treatment group than in the TCZ-SC 162 mg q2w treatment group, regardless of the monotherapy/combination therapy status or the CDAI-defined remission status at the time of randomization. In these subgroup analyses, results of other efficacy outcome measures showed a similar trend, in most cases. Better outcomes were observed in patients who were considered to be in remission based on the CDAI score at baseline (see results in Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40905/abstract)

Safety and tolerability results. Overall, the proportion of patients who reported at least 1 treatment-emergent AE (TEAE) was 56% in the TCZ-SC 162 mg qw group and 70% in the TCZ-SC 162 mg q2w group, and the proportion of patients with a TEAE that required dose modification was 17% and 26%, respectively (Table 3). There were 3 serious AEs, none of them considered related to the study drug: 1 patient in the TCZ-SC 162 mg qw group presented with a metastatic malignant melanoma and did not recover by the end of the follow-up, another patient in the TCZ-SC 162 mg qw group had an episode of ileus from which he recovered, and 1 patient in the TCZ-SC 162 mg q2w group presented with a diverticular perforation and fully recovered by the end of the study. Three patients showed TEAEs of special interest: in the TCZ-SC 162 mg qw group, 1 female patient showed a significant increase in the levels of alanine aminotransferase (more than 3 times the upper limit of normal [ULN]) and bilirubin (more than 2 times the ULN), while in the TCZ-SC 162 mg q2w group, 1 patient developed herpes zoster and 1 patient developed varicella infection.

Table 3. Tolerability and safety results*

Parameter	Tocilizumab 162 mg qw (n = 89)	Tocilizumab 162 mg q2w (n = 90)
Any TEAE	50 (56.2)	63 (70.0)
At least 1 TEAE of special interest	1 (1.1)	2 (2.2)
At least 1 serious TEAE	2 (2.2)	1 (1.1)
At least 1 TEAE leading to dose modification	15 (16.9)	23 (25.6)
Al least 1 TEAE leading to discontinuation	1 (1.1)	2 (2.2)

* Values are the number (%) of patients. Qw = once weekly; q2w = every 2 weeks; TEAE = treatment-emergent adverse event.

The results with regard to the frequency of AEs that led to drug discontinuation were similar in both study groups. The most common TEAEs were infections/infestations (28% and 30% in the TCZ-SC 162 mg qw and TCZ-SC 162 mg q2w schedules, respectively), and were primarily upper respiratory infections (10% and 8%, respectively).

Based on the laboratory findings, 42 patients (47%) in the TCZ-SC 162 mg qw group and 33 patients (37%) in the TCZ-SC 162 mg q2w group exhibited neutropenia during this phase of the study; 3 patients in the q2w group showed grade 3 neutropenia (≥10.0 to <50.0 × 10^9/liter). Sixteen patients (18%) in the TCZ-SC 162 mg qw group and 15 patients (17%) in the TCZ-SC 162 mg q2w group had thrombocytopenia; there were no cases of grade 3 or 4 thrombocytopenia. The proportion of patients who exhibited an increase in the serum glutamic oxaloacetic transaminase (SGOT) level was 25 (28%) in the TCZ-SC 162 mg qw group and 14 (16%) in the TCZ-SC 162 mg q2w group; there were 2 cases of a grade 3 SGOT increase (>5 to 20 times the ULN) in the qw group. Finally, 28 patients (31%) in the TCZ-SC 162 mg qw group and 25 patients (28%) in the TCZ-SC 162 mg q2w group showed an increase in the level of serum glutamic pyruvic transaminase (SGPT); 3 patients in the qw group were categorized as having grade 3 SGPT (>5 to 20 times the ULN). There were no relevant findings in the biochemistry analyses (data not shown).

DISCUSSION

This randomized, open-label trial shows that increasing the dose interval of TCZ-SC to 162 mg every 2 weeks in patients who had achieved sustained clinical remission with 162 mg once weekly is associated with a lower likelihood of maintaining remission after 24 weeks compared to continuation with the standard regimen of 162 mg once weekly.

To our knowledge, this is the first study to evaluate the efficacy of increasing the dose interval of TCZ-SC and the first randomized trial to compare TCZ dose reduction with a standard regimen. In 22 RA patients who were receiving 8 mg/kg intravenous TCZ every 4 weeks and had low disease activity (i.e., a DAS28 score of ≤3.2 and/or low disease activity judged by a rheumatologist), van Herwaarden et al (14) retrospectively evaluated the rate of success after reducing the dose of TCZ to 4 mg/kg. This dose reduction was successful (i.e., the patients were maintained on a dose of 4 mg/kg because they still had low disease activity) in 77% of patients at 3 months and 55% of patients at 6 months (14). That retrospective study used quite different criteria to define success, but their findings support the notion that reducing the dose of TCZ in RA patients who are in remission or have low disease activity may be associated with a loss of efficacy in a significant proportion of patients.

Several randomized controlled trials have evaluated the effects of halving the dose of DMARDs, including etanercept (25–27), abatacept (28), rituximab (29), or any DMARD (30). The results of these studies are reviewed in detail elsewhere but suggest that a half-dose of the DMARD in patients who achieved remission at the full dose is a feasible option (6,31). However, our results suggest that continuation with the recommended dose of TCZ-SC is associated with better results, and the results of a recent meta-analysis partially support our findings. Henaux et al (3) meta-analyzed 7 studies that evaluated tapering strategies via dose reduction or spacing strategies. Those authors found that such strategies were associated with a slight, but significant, increased risk of remission loss (risk ratio 1.23, 95% CI 1.06–1.42) but were not associated with an increased risk of low disease activity loss or an increased risk of radiographic progression (3).

Despite these differences in the proportion of patients who maintained remission between the half-dose and full-dose groups, we should remember that ~3 in 4 patients in the half-dose group maintained remission according to the DAS28 score, and no significant differences were found in the rates of remission or low disease activity using other disease activity indices such as the SDAI or CDAI or using ACR response criteria. Therefore, we may consider that this strategy is an interesting option for a substantial proportion of patients who are being treated with TCZ-SC. In fact, the initial dose recommended by the US Food and Drug Administration is 162 mg every 2 weeks, which has demonstrated efficacy in RA, both in combination with csDMARDs (32) or as monotherapy (12).

However, there are several issues to resolve before this strategy may be considered to be a truly feasible option for those patients who have started with the full weekly dose of TCZ-SC. Methods, and especially definitions of success, vary greatly between studies, which makes comparison with our results very difficult. However, the overall rate of remission in our study after 24 weeks with TCZ-SC 162 q2w (73%) was similar to the rates of success reported with a half-dose of DMARDs in other randomized controlled trials, including rates of remission of 44%, 79%, and 82% with etanercept (25–27), a rate of no relapse of 66% with abatacept (28), and a rate of no relapse of 61% with any DMARD (30). Notably, these previous studies used a longer follow-up period (>1 year in all studies). Therefore, our study duration is a limitation and the proportion of patients who remained in remission with a half-dose of TCZ-SC with longer follow-up periods should be further investigated.

Second, we must try to identify those patients receiving treatment with TCZ-SC who are more suitable for a dose reduction. Our post hoc analysis identified some factors that identify candidates for dose reduction; namely, the body mass index and the DAS28 score at week 24. However, another post hoc analysis evaluated the potential interactions between these variables and the treatment strategies tested in our trial, and found no statistically significant interactions, which suggests that in our study, continuation with full doses of TCZ-SC was superior to halving the dose, regardless of these characteristics. Our post hoc subgroup analysis showed that the differences between these 2 dos-

ing strategies with TCZ-SC are not affected by the monotheraphy/combination therapy status at baseline. The challenge of identifying patients who are more suitable for a TCZ-SC dose reduction remains. A recent systematic review found very limited and low-quality information on potential markers for successful dose reduction or discontinuation of biologic agents in RA (33). Some studies with adalimumab have suggested that a higher trough level of adalimumab may be a good marker for reducing the dose; however, in our study, we did not determine drug serum levels (34,35).

Finally, we should ascertain whether patients who experience a relapse after a dose reduction of TCZ-SC can be restarted on full doses of this agent and achieve remission. A retrospective study with intravenous TCZ suggests that it is possible to reduce the dose of this agent and successfully titrate up the dose in patients who experience a flare (14).

Halving the dose of TCZ-SC was not associated with better tolerability or safety as compared with continuing with the full weekly dose. In contrast, a previous small-sized retrospective study of intravenous TCZ found a somewhat better tolerability with a reduced dose (36). That study examined a group of 19 patients treated with 8 mg/kg intravenous TCZ, and the dose was reduced at the investigator's discretion when the patient reached remission or exhibited neutropenia or thrombocytopenia. The rate and severity of infections were lower in that group than in a group of 63 patients who continued to receive 8 mg/kg of intravenous TCZ (36).

In addition to the previously noted short duration of follow-up, the major limitations of our study were the lack of blinding and the lack of radiographic assessment. The lack of blinding may have biased the results against the half-dose group. Patients randomized to receive a half-dose of TCZ may have had negative expectations concerning the outcomes of the intervention and may have exhibited worse results because of this nocebo effect (6). Qualitative studies have demonstrated that RA patients associated a risk of relapse with dose-optimization strategies (6), which supports the nocebo effect. The lack of radiographic data in our study, together with the short duration of follow-up, limited the amount of information on disease progression that we could obtain.

In conclusion, reducing the dose of TCZ-SC to 162 mg every 2 weeks in patients with RA who acheived sustained remission at the recommended dose of 162 mg once per week was associated with a lower likelihood of maintaining remission after 24 weeks when compared to continuing with the standard regimen of this agent. Moreover, dose reduction was not associated with better tolerability. However, most patients did remain in remission with a half-dose of TCZ-SC, and this strategy therefore warrants further investigation in randomized controlled trials with longer follow-up periods and a comparison between a continuation strategy and a strategy that includes dose reduction and restarting of full doses in cases of relapse.

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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. Sanmarti 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. Sanmarti, Veale, Martin-Mola, Fonseca.
Acquisition of data. Sanmarti, Veale, Escudero-Contreras, González, Fonseca.
Analysis and interpretation of data. Sanmarti, Ercole, Alonso.

ROLE OF THE STUDY SPONSOR

Roche Pharma SA was involved in the study design and analysis and collection of the data, and provided support for third-party writing assistance for the manuscript (furnished by Fernando Rico-Villademoros, MD, PhD, of COCIENTE S.L), and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Roche Pharma SA.

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APPENDIX A: THE TOSPACE STUDY GROUP

Members of the ToSpace Study Group are as follows: Cristina Alcañiz, José María Álvaro-Gracia, Alejandro Balsa, José Luis de Pablos, Consuelo Díaz Miguel, and José Manuel Rodríguez (Madrid, Spain); Jose Alves (Amadora, Portugal); Elena Aurrecoechea and Jaime Calvo (Torrelavega, Spain); Joaquín Belzunegui (San Sebastián, Spain); Francisco Blanco (A Coruña, Spain); Rafael Caliz

(Granada, Spain); Javier Calvo and José Román Ivorra (Valencia, Spain); Helena Canhão and Helena Santos (Lisbon, Portugal); Eugenio Chamizo (Mérida, Spain); Javier del Pino (Salamanca, Spain); Concepción Delgado (Zaragoza, Spain); César Díaz (Barcelona, Spain); Antonio Fernández Nebro (Málaga, Spain); Alexander Fraser (Limerick, Ireland); Antonio Gomez (Sabadell, Spain); Blanca Hernández, Federico Navarro, and Juan Povedano (Seville, Spain); Antonio Juan Mas (Palma de Mallorca, Spain); David Kane and Bryan Whelan (Dublin, Ireland); Carlos Marras (Murcia, Spain); Juan Moreno (Cartagena, Spain); José Pérez Venegas (Jerez, Spain); Manuel Pombo (Santiago de Compostela, Spain); Elena Riera (Terrasa, Spain); Antonio Rosas (Las Palmas de Gran Canaria, Spain); John Ryan (Cork, Ireland); José Santos (Toledo, Spain); Maria Santos (Almada, Portugal); Jesús Tornero (Guadalajara, Spain); Juan Víctor Tovar (Elche, Spain); Eduardo Ucar (Bilbao, Spain); Carlos Vasconcelos (Porto, Portugal); Raúl Veiga (Fuenlabrada, Spain); Paloma Vela (Alicante, Spain).