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ORIGINAL ARTICLE

Subcutaneous tocilizumab alone or with a csDMARD in rheumatoid arthritis patients: subanalysis of Italian data from a multicenter phase IIIb/IV trial

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Abstract

To assess, in a setting close to real life, the efficacy and safety of weekly subcutaneous tocilizumab (TCZ-SC) 162 mg, alone or with a conventional synthetic DMARD (csDMARD), in moderate-to-severe RA patients with inadequate response to DMARDs or anti-TNFα drugs. This national, multicenter, open-label, phase IIIb trial is part of an umbrella study (TOZURA). Patients were treated for 52 weeks followed by 8 weeks drug-free to evaluate immunogenicity. The primary end point was the Clinical Disease Activity Index (CDAI) change from baseline at weeks 2 and 24. Other efficacy parameters, including sleep quality, and the safety and immunogenicity were also assessed up to week 52. Of 288 patients enrolled in 43 Italian centers, 78.8% received TCZ-SC (86.8% females; mean age 54.7 ± 12.1 years; mean disease duration 7.8 ± 7.5 years; DMARD-IRs 94.7%). Of these, 78.0% completed the 52-week period and 52.0% received concomitant methotrexate. TCZ-SC yielded a significant reduction in median CDAI from baseline already at week 2, which progressed up to week 24 and remained stable thereafter ($P < 0.0001$ at each time point). A significant, rapid, and sustained improvement of the other efficacy variables was also observed. Patients were deemed as ready for home administration after a median of 2.0 (range 1–8) administrations, with a rate (since the last visit) of 80.6% and 95.5% at weeks 2 and 52, respectively. TCZ-SC displayed low immunogenicity and no unexpected toxicities. TCZ-SC, alone or with a csDMARD, yielded rapid and sustained efficacy in DMARD/anti-TNFα-IR RA patients, with acceptable toxicity. Home administration seems feasible.

Keywords csDMARD · Efficacy · Immunogenicity · Inadequate responders · Rheumatoid arthritis · Sleep quality · Subcutaneous tocilizumab

Significance and Innovations
- This is the first Italian study exploring the efficacy and safety of TCZ-SC, alone or with a csDMARD in DMARD/anti-TNFα-IR RA patients, in a setting close to real life.
- TCZ-SC, alone or with a csDMARD, yielded rapid and sustained efficacy, also in terms of sleep quality improvement, with acceptable toxicity.
- Home administration of TCZ-SC seems a feasible option.

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease which, in Italy, affects approximately 0.5% of the population [1]. Despite the dramatic improvements in patient management, RA is still associated with morbidity and mortality and poses a significant humanistic and economic burden on patients [2, 3]. From the patient's perspective, the achievement of acceptable levels of pain, physical and mental function, and fatigue, as assessed by patient reported outcomes (PROs), remains an unmet need [3]. Notably, the information routinely collected may not entirely capture the disease impact experienced by patients. In this regard, an important issue that is rarely assessed in clinical studies is the quality of sleep. RA patients often suffer from poor sleep, and this may have debilitating effects on physical and/or cognitive functioning and health [4, 5].

New advances in the knowledge of RA biology have led to the development of several new drugs in the last 15 years, which differ for both the targets and the route of administration. Among these, intravenous (IV) tocilizumab (TCZ) has been the first humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody to be approved, alone or in combination with methotrexate (MTX), for the treatment of moderate to severe RA both in treatment-naïve patients and after failure of disease modifying antirheumatic drugs (DMARDs) or intolerance to other approved drugs [6–11]. However, as TCZ-IV requires monthly infusions, which is inherently inconvenient for some patients and is associated with increased costs [12], a formulation of subcutaneous (SC) TCZ has been developed, which proved effective and safe in RA patients [13–18].

The randomized, double-blind SUMMACTA trial assessed the safety and efficacy of weekly (qw) TCZ-SC 162 mg vs TCZ-IV 8 mg/kg plus DMARDs in moderate-to-severe RA patients. At week 24, TCZ-SC was not inferior to TCZ-IV with regard to the American College of Rheumatology (ACR)20, ACR50, and ACR70 responses, DAS28, and physical function improvements [18]. Also the overall safety profile was comparable, except for injection site reactions (ISRs), which were more frequent in the TCZ-SC arm [18]. Neutralizing antibodies were found in 0.8% of patients in both arms and caused no serious reactions or loss of efficacy [18].

Following these studies, TCZ-SC at the recommended dose of 162 mg qw received approval, so that TCZ became the first anti-IL-6R biologic available as SC and IV formulations for both monotherapy and combination therapy with MTX. However, to better clarify the feasibility of TCZ-SC as a therapeutic option for RA patients, also in light of the possible risk for immunogenicity, it is important to collect data on its efficacy and safety in a real-world setting.

TOZURA is an international, open-label phase IIIb/IV umbrella study undertaken to evaluate the efficacy and safety of TCZ-SC 162 mg qw, administered as monotherapy and/or in combination with MTX and/or other non-biologic DMARDs [19], in a setting close to real life. Here, data from the subanalysis of the phase IIIb Italian study are reported, which includes, besides the objectives of the umbrella study, the evaluation of sleep quality and of the number of visits required to consider patients ready for TCZ-SC home administration.

Methods

Study design and patient population

This national, multicenter, open-label, single-arm phase IIIb trial (ClinicalTrials.gov ID: NCT01941940) is part of an umbrella study assessing the efficacy and safety of TCZ-SC, administered alone or with a conventional synthetic DMARD (csDMARD), in patients with active RA. After ≥ 52 weeks of open-label treatment, patients were asked to stop TCZ administration for ≥ 8 weeks to collect a drug-free serum sample for immunogenicity assessment.

The primary study end point was the Clinical Disease Activity Index (CDAI) change from baseline (BL) at weeks 2 and 24. Secondary end points comprised the assessment, up to week 52, of CDAI change from BL in patients who had achieved CDAI remission, Disease Activity Score 28 for RA with erythrosedimentation rate (DAS28-ESR), Simplified Disease Activity Index (SDAI), ACR response scores, European League Against Rheumatism (EULAR) response criteria, Tender Joint Count 28 (TJC28)/Swollen Joint Count 28 (SJC28), inflammatory markers, and physical functioning (by the Health Assessment Questionnaire, HAQ), along with the drug safety, tolerability, and immunogenicity. Two additional objectives were included, which were specific of this study: the sleep quality evaluation at weeks 24 and 52 (through the Pittsburgh Sleep Quality Index [PSQI] questionnaire [20]; secondary objective) and the number of visits required to consider patients ready for the home administration of TCZ-SC (exploratory objective). PSQI is an 18-question questionnaire covering 7 areas (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). Using a scale from 0 to 3, a global score ranging from 0 to 21 is calculated, with higher values indicating worse sleep quality.

Patient population

The patient population consisted of adults diagnosed with active RA according to the revised 1987 ACR criteria [21] or 2010 EULAR/ACR criteria [22] and classified as moderate-to-severe disease based on CDAI ≥ 10 and DAS28 ≥ 3.2 at screening. Patients were included if TNFα-IR, MTX-IR or

DMARD-IR, or intolerant [11]. The use of stable oral nonsteroidal anti-inflammatory drugs (up to the maximum recommended dose), corticosteroids (≤ 10 mg/day prednisone or equivalent), and csDMARDs was permitted.

Patients with severe ongoing infections, other autoimmune or concomitant serious diseases, laboratory abnormalities or hypersensitivity to the active substance or to any of the recipients were not eligible. Pregnant women were excluded too.

The study was approved by each institutional ethics committee/review board, and all patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study treatment

TCZ was supplied in a 1-mL ready-to-use, single-use prefilled syringe, delivering 162 mg/0.9 mL solution of drug. Patients received a qw injection of TCZ-SC as a single fixed dose, irrespective of body weight, for ≥ 52 weeks. After this period, if deemed as appropriate by the treating physician, patients could continue treatment until the drug became commercially available in Italy. SC injections had to be given within ± 3 days from the visit day and on the same day every week. Patients were trained to perform SC injections, and in case of demonstrated competence by the patients and/or caregivers, home administration was permitted and a diary card was provided to record home dosing. The injection sites were inspected by the site personnel at each visit. Study discontinuation or withdrawal could be decided at any time by the investigator and patients. Yet, in case of premature discontinuation, patients were asked to return to the clinic for a study completion/early withdrawal visit and could undergo follow-up assessments.

Clinical assessments

Information was retrieved regarding medical history and demographic data. Surgical and medical histories and concomitant diseases were summarized by primary system organ class (SOC) and preferred term (PT). Moreover, the following efficacy parameters were assessed in the full analysis set (FAS): CDAI and CDAI change from BL in patients who had achieved CDAI remission, DAS28-ESR, SDAI, SJC28/TJC28, ACR20/50/70 response and EULAR good/moderate response, ESR, CRP, Patient's Global Assessment of Disease Activity by VAS (PtGDA-VAS), Physician's Global Assessment of Disease Activity by VAS (PhGDA-VAS), Patient's Assessment of Pain by VAS, Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and PSQI. The analysis of the primary end point was performed also in the per-protocol analysis set (PPAS, comprising all patients in the FAS who did not experience any major protocol violations and who had an evaluation of the primary end point, i.e., CDAI at week 24).

As for safety, the incidence of adverse events (AEs), treatment-related AEs, serious AEs (SAEs) and AEs of special interest, including local injection site reactions, hypersensitivity, and anaphylaxis after TCZ injection and immunogenicity, was determined and presented for the FAS. AE terms were assigned a PT and were classified by primary SOC according to the latest version of the MedDRA thesaurus, and AE intensity was graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0. Other safety assessments included laboratory results, physical examination, and vital signs. Notably, an internal data monitoring committee was set up in the global umbrella program to regularly review all safety data and ensure ongoing safety of participants.

Finally, patient compliance was assessed by evaluating the diary card used to record home injections and reconciliation of all empty drug supply boxes and unused pre-filled syringe.

Data collection

The PROs and efficacy assessments were performed within 24 h prior to the first dose of TCZ (BL). Patients attended visits at weeks 1, 2, and 4 and then every 4 weeks up to week 24, at weeks 38 and 52, and then every 3 months up to the end of study. At the end of the treatment period or in case of early withdrawal, a follow-up visit was performed after 4 weeks by phone and after 8 weeks at the clinic, irrespective of the duration of treatment, to assess immunogenicity, AEs, and concomitant medications (to be included in the electronic case report form [eCRF]). The primary reason for premature interruption was documented on the eCRF. Patients who withdrew because of anaphylaxis or hypersensitivity reactions had to return ≥ 6 weeks after the last dose to provide serum samples for immunogenicity testing. Moreover, safety information was collected every month via phone calls between week 24 and week 52 and after week 52 if the patient continued on TCZ-SC until it became commercially available in Italy. At the discretion of the investigator, the patient could attend the clinic for unscheduled visits at any time for additional safety monitoring.

Statistical analysis

The sample size was calculated for the primary end point (i.e., the change in CDAI score at weeks 2 and 24). The sample size estimation was focused on estimation of 95% (two-sided) confidence interval (CI) for the difference in paired means. Assuming that the standard deviation (SD) was known to be 15, a two-sided 95% CI for the difference in paired means that would not exceed a clinical reasonable margin of 2 units could be obtained with a

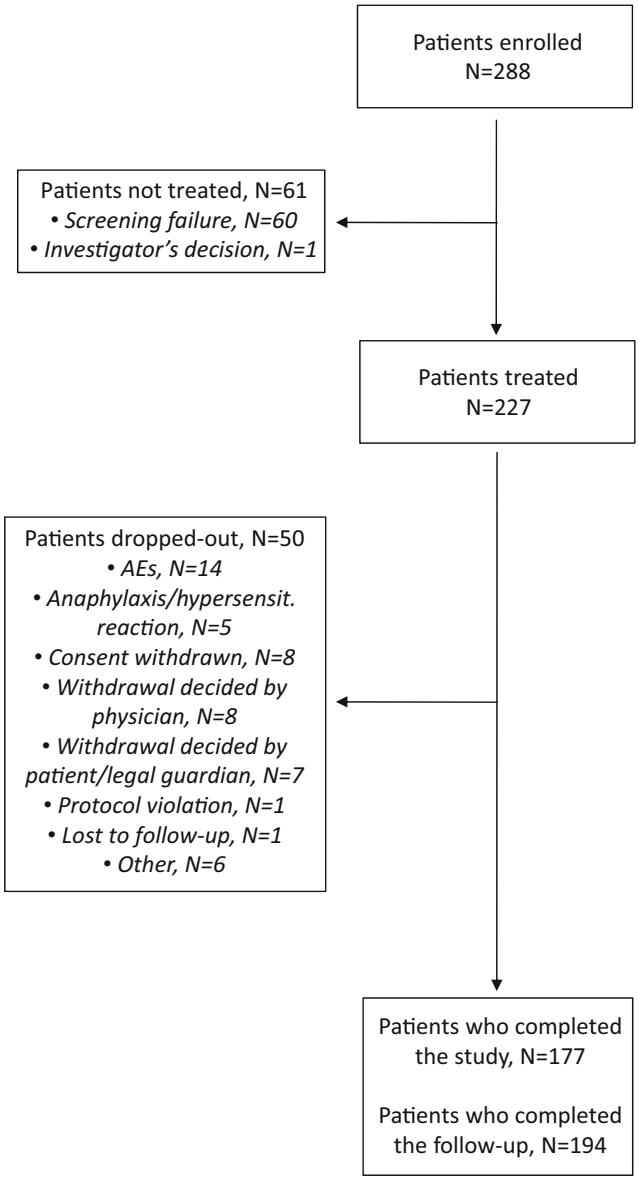

Fig. 1 Patient disposition. *AEs,* adverse events

sample size of 217 patients. Considering also a hypothesis of a SD of 10, with the above 217 patients, the two-sided 95.0% CI for the difference in paired means would extend of 1.331 from the observed mean. Based on the above assumption, the 95% CI would extend from the observed mean from a minimum equal to ± 1.331 (SD = 10) to a maximum of ± 2.000 (SD = 15 taking into account a percentage of enrolled patients not receiving any study drug of about 3%); the sample size was of 225 patients. The primary analysis population for safety and efficacy parameters was the FAS, which included all recruited patients who received ≥ 1 dose of TCZ-SC.

The analysis of the results was exploratory. For continuous variables, the number of observations (*N*), mean, SD, median, range, and first and third quartiles were reported, whereas, for qualitative variables, absolute and relative frequencies were

Table 1 Demographic and clinical characteristics

Characteristic	FAS *N* = 227
Females	197 (86.8)
Postmenopausal	123 (62.4)
Age (years)	54.7 ± 12.1
Caucasian	216 (95.2)
BMI	25.4 ± 4.7
Time from RA diagnosis (years)	7.8 ± 7.5
Comorbidities	157 (69.2)
Vascular disorders	77 (49.0)
Endocrine disorders	49 (31.2)
Muscoskeletal and connective tissue disorders	40 (25.5)
Metabolism and nutrition disorders	37 (23.6)
DMARD-IRs	215 (94.7)
Anti-TNFα-IRs	12 (5.3)
TCZ as monotherapy	47 (20.7)
TCZ + csDMARDs	180 (79.3)
MTX	118 (52.0)
Hydroxychloroquine	32 (11.9)
Leflunomide	22 (8.1)
Sulfasalazine	6 (2.2)
Chloroquine	2 (0.7)
Previous RA-related surgical procedures	23/224 (10.3)
Structural joint damage	106/197 (53.8)
RF status	
Positive	139 (61.2)
Negative	66 (29.1)
Missing	4 (1.8)
Unknown	18 (7.9)
ACPA status	
Positive	116 (51.1)
Negative	61 (26.9)
Missing	13 (5.7)
Unknown	37 (16.3)
CDAI	31.1 ± 12.0
CDAI in patients achieving CDAI remission[#]	27.4 ± 10.0
DAS28-ESR	5.8 ± 1.1
SDAI	48.7 ± 45.8
TJC28	11.3 ± 6.2
SJC28	7.9 ± 5.2
ESR	39.2 ± 24.5
CRP	17.6 ± 42.5
PtGDA-VAS	61.3 ± 23.5
PhGA-VAS	57.4 ± 19.2
Pain-VAS	58.2 ± 23.6
HAQ-DI	1.0 ± 0.7
FACIT-F	72.4 ± 16.8
PSQI	11.2 ± 2.8

Data are expressed as mean ± standard deviation or frequencies (*N* [%])

BMI body mass index, *RA* rheumatoid arthritis, *DMARD-IRs* disease-modifying antirheumatic drug-inadequate responders, *anti-TNFα-IR* anti-tumor necrosis factor α-inadequate responders, *TCZ* tocilizumab, *csDMARD* conventional synthetic DMARD, *MTX* methotrexate, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *CDAI* Clinical Disease Activity Index, *DAS28-ESR* Disease Activity Score 28 for rheumatoid arthritis with erythrosedimentation rate, *SDAI* Simplified Disease Activity Index, *TJC28* Tender Joint Count 28, *SJC28* Swollen Joint Count 28, *ESR* erythrosedimentation rate, *CRP* C-reactive protein, *PtGDA-VAS* Patient's Global Assessment-Visual Analogue Scale, *PhGA-VAS* Physician's Global Assessment-VAS, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *PSQI* Pittsburgh Sleep Quality Index

[#] Defined as a CDAI ≤2.8 during any two consecutive visits, not including the baseline visit

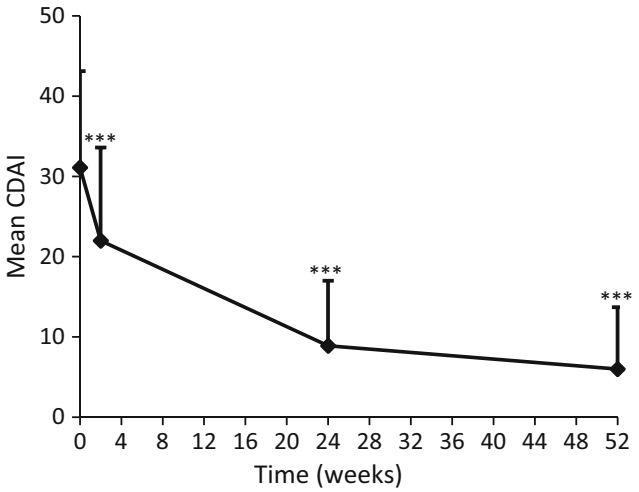

Fig. 2 Mean CDAI (± SD) at weeks 2, 24, and 52 of treatment with TCZ-SC. ***$P < 0.0001$ vs baseline. *CDAI,* Clinical Disease Activity Index, *SD,* standard deviation

described. The default significant level was 5%; CI was at 95%, and all tests were two-sided, unless otherwise specified.

Project management, monitoring, data management, statistical analysis, and reporting of the study were carried out by the Contract Research Organization Quintiles s.r.l (Cassina De' Pecchi, Milan, Italy). All analyses were conducted using the SAS System version 9.2 (or higher).

Results

Patient population

Overall, 288 patients were enrolled in 43 Italian centers: 78.8% received TCZ-SC ($N = 227$), whereas 20.8% ($N = 60$) were excluded for screening failure and 0.3% ($N = 1$) for investigator's decision (Fig. 1). Seventy-eight percent ($N = 177$) of treated patients completed the 52 weeks of treatment, 22.0% ($N = 50$) dropped out (mainly for adverse events [$N = 19$, 38%]), and 85.5% ($N = 194$) completed the follow-up period (Fig. 1). The most common reasons for not completing the 8-week follow-up period were AEs and consent withdrawn in 27.3% ($N = 9$) of cases/each.

The main demographic and clinical characteristics of the FAS are listed in Table 1. Briefly, 86.8% ($N = 197$) were females; the mean age was 54.7 ± 12.1 years, and the mean time

Table 2 Efficacy parameters recorded at different time points during the treatment period with TCZ-SC

Parameter	Week 2		Week 24		Week 52		*P* value*
	Value	Change from BL	Value	Change from BL	Value	Change from BL	
CDAI in patients achieving CDAI remission #	–	–	–	–	1.5 ± 1.4	− 29.3 ± 10.7	0.002
DAS28-ESR	4.4 ± 1.4	− 1.5 ± 1.0	2.6 ± 1.3	− 3.2 ± 1.5	2.2 ± 1.2	− 3.6 ± 1.2	< 0.0001
SDAI	23.1 ± 12.1	− 26.5 ± 44.0	9.7 ± 8.7	− 38.9 ± 48.8	7.3 ± 9.2	− 39.3 ± 26.8	< 0.0001
TJC28	7.6 ± 6.3	− 3.7 ± 5.40	2.6 ± 3.9	− 8.6 ± 6.6	0.8 ± 2.6	− 11.0 ± 6.1	< 0.0001
SJC28	5.0 ± 4.4	− 2.9 ± 3.9	1.2 ± 2.1	− 6.7 ± 5.2	0.4 ± 1.3	− 7.6 ± 4.6	< 0.0001
ESR	18.1 ± 17.9	− 21.8 ± 18.8	8.9 ± 9.6	− 28.9 ± 21.2	10.0 ± 9.4	− 24.0 ± 23.6	–
CRP	1.2 ± 2.0	− 16.9 ± 43.4	0.8 ± 1.9	− 16.9 ± 45.4	1.2 ± 2.4	− 13.8 ± 21.1	–
PtGDA-VAS	50.7 ± 23.1	− 10.6 ± 21.0	31.3 ± 23.0	− 28.4 ± 27.4	23.3 ± 23.0	− 38.4 ± 27.7	< 0.0001
PhGA-VAS	42.0 ± 18.4	− 15.3 ± 17.5	18.4 ± 15.5	− 38.0 ± 25.1	10.2 ± 9.9	− 43.9 ± 17.1	< 0.0001
Pain-VAS	− 7.6 ± 4.6	− 11.4 ± 22.4	30.4 ± 22.5	− 26.5 ± 27.3	21.5 ± 23.1	− 36.0 ± 26.8	< 0.0001
HAQ-DI	0.9 ± 0.7	− 0.2 ± 0.4	0.6 ± 0.6	− 0.4 ± 0.6	0.6 ± 0.7	− 0.5 ± 0.7	< 0.0001
FACIT-F	66.5 ± 15.5	− 5.8 ± 14.1	60.9 ± 17.9	− 11.1 ± 18.6	26.3 ± 32.1	− 43.8 ± 34.9	< 0.0001
PSQI	–	–	10.3 ± 2.60	− 0.7 ± 2.4	10.1 ± 2.7	− 0.9 ± 2.4	0.0045§
Adherence (%)	–	–	94.9 ± 10.2	–	94.7 ± 10.1	–	–

Data are expressed as mean ± standard deviation of the raw values recorded at each time point or of the change from BL, unless specified

BL baseline, *CDAI* Clinical Disease Activity Index, *DAS28-ESR* Disease Activity Score 28 for rheumatoid arthritis with erythrosedimentation rate, *SDAI* Simplified Disease Activity Index, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism, *TJC28* Tender Joint Count 28, *SJC28* Swollen Joint Count 28, *ESR* erythrosedimentation rate, *CRP* C-reactive protein, *PtGDA-VAS* Patient's Global Assessment-Visual Analogue Scale, *PhGA-VAS* Physician's Global Assessment-VAS, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *PSQI* Pittsburgh Sleep Quality Index

* *P* values refer to the difference recorded at each time point vs BL, unless differently stated. The *P* value reported is the same for each time point

Defined as a CDAI ≤ 2.8 during any two consecutive visits, not including the baseline visit

§ Difference between week 24 and BL

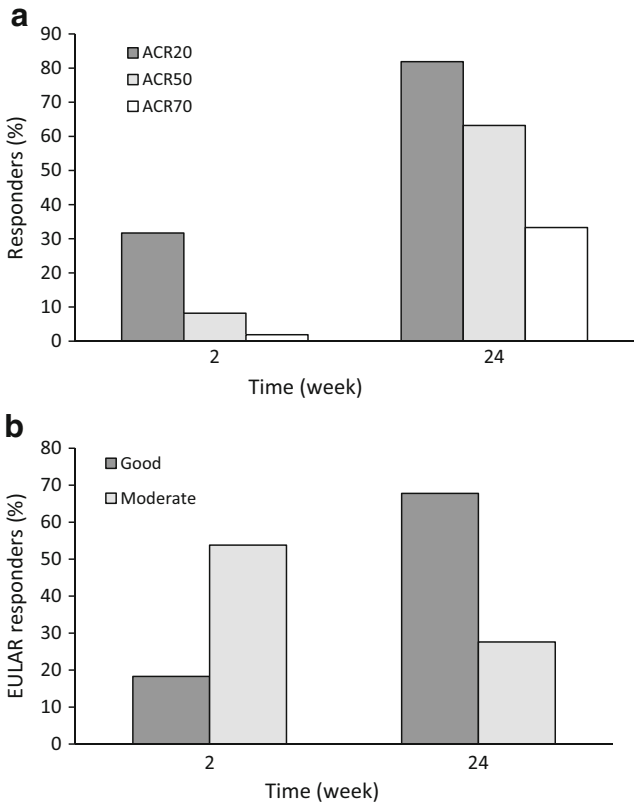

Fig. 3 Rate of ACR20/50/70 responders (**a**) and EULAR good/moderate responders (**b**) after 2 and 24 weeks of TCZ-SC treatment. *ACR*, American College of Rheumatology, *EULAR,* European League Against Rheumatism

from diagnosis was 7.8 ± 7.5 years. DMARD- and anti-TNFα-IRs were 94.7% ($N = 215$) and 5.3% ($N = 12$), respectively. Evidence of structural joint damage was observed in 46.7% ($N = 106$) of cases. TCZ-SC was given as monotherapy in 20.7% ($N = 47$) of cases and with a csDMARD in 79.3% ($N = 180$): concomitant MTX was given to 52.0% ($N = 118$) of patients.

Overall, 34.8% ($N = 79$) and 67.8% ($N = 154$) of patients required DMARD and non-DMARD discontinuation or dose reduction. Furthermore, corticosteroids could be discontinued or reduced in 28.2% ($N = 64$) of cases.

Efficacy of TCZ-SC

The primary study end point was the mean change of CDAI from BL at weeks 2 and 24 (Fig. 2). Treatment with TCZ-SC yielded a significant reduction in the median CDAI, compared to BL, already at week 2, which progressed up to week 24 and remained stable thereafter ($P < 0.0001$ at each time point) (Table 2). Data at week 24 were obtained also for the PPA set, and results were consistent with those observed in the FAS. A significant, rapid and sustained improvement from BL to week 52 was also observed for all the other efficacy variables (Table 2). High ACR20/50/70 and EULAR response rates were reported up to week 24 (ACR70 33.3%, EULAR good response 67.8%), respectively (Fig. 3).

Treatment with TCZ-SC improved patients' health status, as shown by the rapid and sustained improvement in the mean Stanford HAQ-DI total score and individual domains' scores (Table 2 and data not shown, respectively) and in the total score and individual domains' score of the FACIT-F questionnaire (Table 2 and data not shown, respectively). The quality and characteristics of sleep, as determined by PSQI, improved as well during the study (Table 2).

Safety of TCZ-SC

The safety results are summarized in Table 3. AEs and treatment-related AEs were reported in 76.7% (174/227) and in 33.9% (77/227) of patients, respectively. The most commonly reported treatment-related AEs by PT were transaminase increase (4.0%, 9/227), alanine transaminase increase (3.1%, 7/227), and injection site erythema, neutrophil count decrease, neutropenia, and bronchitis (all in 6 patients, 2.6%). The same event has been coded under two different PTs (neutrophil count decrease and neutropenia).

Overall, 18 SAEs (all non fatal) were reported in 7.5% (17/227) of patients and were treatment-related in 7 cases (gastrointestinal perforation, anaphylactic reaction, diverticulitis, *Klebsiella* infection, pneumonia, skin infection, and hepatic enzyme increase).

Treatment discontinuation for AEs (198 events) was reported in 48.9% (111/227) of patients, and it was permanent in 10.6% (24/227 patients). AEs were considered treatment-related in 6.6% (15/227) of cases.

Grade ≥ 3 AEs were reported in 7.0% (16/227) of patients, and AEs of special interest were reported in 7.5% (17/227) of cases.

The changes from BL of hematological parameters and lipids are summarized in Supplementary Table 1.

Finally, TCZ-SC displayed low immunogenicity (Supplementary Table 2). In fact, of the 217 patients for whom the test for anti-TCZ antibodies was available, 2.3% ($N = 5$) only resulted positive, whereas the vast majority of patients had negative results for the presence of anti-TCZ antibodies both at BL and all post-BL visits. Negative results at BL and positive results at post-BL visits were observed in one patient at week 12, one at week 24, one at week 52, and one at withdrawal. Conversely, negativization of positive results at BL was observed in three patients at week 24, three at week 38, four at week 52, and one at the 8-week follow-up visit.

Compliance to study treatment and home administration

The median extent of exposure to TCZ-SC was 11.8 months (range 0–12.1). The median overall compliance to study drug

Table 3 Summary of treatment-emergent adverse events in the FAS population

Categories of AEs	Patients *N* (%)	Events *N*
≥ 1 AE	174 (76.7)	485
≥ 1 SAE	17 (7.5)	18
≥ 1 non-serious AE	36 (15.9)	98
≥ 1 treatment-related AE	77 (33.9)	140
≥ 1 treatment-related SAE	7 (3.1)	7
≥ 1 treatment-related non-serious AE	0 (0.0)	0
Treatment discontinuation for ≥ 1 AE*	111 (48.9)	198
Treatment discontinuation for ≥ 1 SAE*	16 (7.0)	17
Treatment discontinuation for ≥ 1 non-serious AE*	13 (5.7)	21
≥ 1 grade ≥ 3 AE	16 (7.0)	17
≥ 1 grade ≥ 3 SAE	9 (4.0)	9
≥ 1 grade ≥ 3 non-serious AE	0 (0.0)	0
≥ 1 AE of special interest	17 (7.5)	22
≥ 1 SAE of special interest	8 (3.5)	8
≥ 1 non-serious AE of special interest	0 (0.0)	0
Deaths due to any cause	1 (0.4)	1
Fatal SAE	0 (0.0)	0
Fatal treatment-related SAE	0 (0.0)	0

AE adverse event, *SAE* serious AE

*Permanent or temporary

was 100% (range 42–100%) at both week 24 ($N = 221$) and week 52 ($N = 222$).

Patients were deemed as ready for home administration after a median of 2.0 (range 1–8) administrations. The rate of administrations (since the last visit) performed at home was of 80.6% ($N = 191$) at week 2, 61.7% at week 4 ($N = 266$), and of 95.5% ($N = 420$) at week 52.

Discussion

TCZ-SC represents an additional effective and safe therapeutic option for RA patients, with the advantage to be more convenient in terms of ease of administration and costs [22, 23]. Yet, data on its use in a setting close to real life are poor [24, 25]. In the present phase IIIb study, the 52-week treatment with TCZ-SC alone or in combination with a csDMARD yielded a rapid improvement, already by week 2, of all the efficacy parameters assessed in DMARD-IR and anti-TNFα-IR patients with moderate-to-severe active RA. Importantly, the effects were sustained throughout the study period and the safety profile was acceptable and consistent with the known profile of TCZ. Our findings are in line with the results from the phase IIIb/IV umbrella study TOZURA [19] in terms of DAS-28 ESR, trend of CDAI and HAQI change from BL, rate of ACR responders, and safety profile. Notably, this is the first study collecting data on the use of TCZ-SC as monotherapy in Italy, on the quality of sleep and on the rate of home administration (both specific of this Italian subanalysis) and in a setting close to clinical practice.

Since the start of this study, the long-term effects of TCZ-SC were assessed in the extension phases of the SUMMACTA and BREVACTA pivotal trials [24, 25]. Results demonstrated the sustained efficacy and safety of TCZ-SC throughout the study period (i.e., 97 weeks in total for SUMMACTA [25] and 84 weeks for the multicenter phase IIIb extension study including US patients who had completed the SUMMACTA and BREVACTA trials [24]). In both cases, immunogenicity was low (1.6% in the TCZ-SC arm in [25] and < 1% in [24]) and no correlation was observed between the presence of anti-TCZ antibodies and the clinical response or AEs [25]. Although the total length of the present study is shorter than that of the abovementioned trials, our findings show a similar trend of durable efficacy and no new safety concerns. With regard to immunogenicity, in particular, we observed a rate of 2.6%, which further corroborates the low risk of immunogenicity associated with TCZ-SC. It is worth noting that a pooled analysis of data from 8974 patients reported a low immunogenicity risk of TCZ-SC and TCZ-IV, with the proportion of patients who developed anti-TCZ antibodies being 1.5% and 1.2%, respectively. In line with our results, no correlation with TCZ pharmacokinetics, safety events, or loss of efficacy was observed [24–26].

One of the most prevalent complaints of RA patients is poor sleep quality, which has been associated with depression, pain, fatigue, and functional disability [4, 5]. Therefore, addressing sleep disturbances in RA may have a critical impact

on patients' health and QoL. Nonetheless, the quality of sleep is rarely evaluated in clinical trials. In the present analysis, PSQI was employed to assess the sleep quality of RA patients receiving TCZ-SC. Our findings demonstrate a significant reduction from BL of the PSQI total score following 24-week treatment with TCZ-SC.

The advantages of TCZ-SC, compared to TCZ-IV, include the ease of administration, which, in turn, allows home therapy. This has clearly a positive impact on the human and economic burden of the disease and on the patient compliance and satisfaction as well. Results from our study showed that a relevant proportion of patients were able to self-administer the drug after only a median of 2.0 administrations, and the compliance remained high throughout the study period. Of note, a post-marketing surveillance study concluded that patient-reported self-administration of a SC medication led to feelings of independence (89.1%) and improved QoL (83.6%) and may be desirable for many patients with RA [27].

However, some limitations have to be acknowledged, which are mainly linked to the study design.

In conclusion, the 52-week TCZ-SC treatment of moderate-to-severe RA patients with inadequate response to DMARDs or anti-TNFα agents provided rapid and sustained clinical benefit, with a good safety profile. The ease of administration and high compliance observed suggests the feasibility of TCZ-SC in a clinical setting where QoL is of primary importance for many patients.

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Compliance with ethical standards

The study was approved by each institutional ethics committee/review board, and all patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

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