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Effects of concomitant glucocorticoids in TOZURA, a common-framework study programme of subcutaneous tocilizumab in rheumatoid arthritis

Ernest Choy[1], Roberto Caporali[2], Ricardo Xavier[3], Bruno Fautrel[4], Raimon Sanmarti[5], Min Bao[6], Jenny Devenport[6] and Attila Pethö-Schramm[7]

Abstract

Objectives. This *post hoc* analysis of the TOZURA study programme evaluated the efficacy and safety of subcutaneous tocilizumab (TCZ-SC) as monotherapy or with concomitant conventional synthetic DMARDs (csDMARDs) in patients with RA categorized by baseline glucocorticoid (GC) use.

Methods. TOZURA was a multinational, open-label, single-arm, common-framework study programme (11 protocols, 22 countries) in patients with moderate to severe RA in whom csDMARDs or biologic therapies had failed or who were MTX naïve. Patients received once-weekly TCZ-SC 162 mg for $\geqslant$24 weeks as monotherapy or in combination with csDMARDs and/or oral GC use ($\leqslant$10 mg/day prednisone or equivalent), which was to be continued unchanged for 24 weeks. Treatment subgroups were defined by baseline GC use and analysed for efficacy and safety.

Results. Of 1804 patients who received TCZ-SC, 145 received monotherapy + GC, 208 received monotherapy without GC, 730 received combination therapy + GC and 721 received combination therapy without GC. The median GC dose in both GC subgroups was 5 mg/day. The proportion of patients who achieved clinical remission, defined as DAS in 28 joints using ESR $<$2.6, increased similarly from baseline to week 24 in all subgroups. Improvements in patient-reported outcomes were similar in all subgroups. Overall adverse event profiles were generally similar between subgroups, with some slight numerical differences between GC and non-GC subgroups.

Conclusion. The incremental efficacy benefits of TCZ-SC as monotherapy and in combination with csDMARDs were similar between patients with and without previous and continued oral GC treatment, with generally similar safety profiles.

Trial Registration. ClinicalTrials.gov, http://www.clinicaltrials.gov, NCT01941940, NCT01941095, NCT01951170, NCT01987479, NCT01988012, NCT01995201, NCT02001987, NCT02011334, NCT02031471, NCT02046603, NCT02046616.

Key words: RA, biologic therapies, csDMARDs, tocilizumab, glucocorticoid

Rheumatology key messages

- The impact of glucocorticoid use was analysed in RA patients treated with open-label subcutaneous tocilizumab.
- Similar effective disease control with tocilizumab monotherapy or combined with csDMARD, irrespective of glucocorticoid use.
- Tocilizumab's safety was similar across glucocorticoid treatment subgroups and consistent with its known profile.

Introduction

RA is a chronic autoimmune disease characterized by systemic inflammation, autoantibodies, persistent synovitis and joint destruction [1]. RA significantly impacts a patient's physical function and reduces quality of life, work productivity and social participation [2]. Oral glucocorticoid (GC) therapy is initiated in the majority of patients with RA

[1]Division of Infection and Immunity, CREATE Centre, Cardiff University, Cardiff, UK, [2]Division of Rheumatology, University of Pavia and Fondazione IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [3]Department of Medicine, Universidade Federal do Rio Grande do Sul Porto Alegre, Rio Grande do Sul, Brazil, [4]Department of Rheumatology, AP-HP, Pitié-Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France, [5]Department of Rheumatology, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain and [6]Genentech, Inc., South San Francisco, CA, USA and [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland

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Correspondence to: Ernest Choy, UK CREATE Centre and Welsh Arthritis Research Network, Cardiff University School of Medicine, Tenovus Building, Health Park Campus, Cardiff CF14 4XN, UK.
E-mail: choyeh@cardiff.ac.uk

CLINICAL SCIENCE

to rapidly control symptoms of pain and inflammation at the same time that DMARD therapy is initiated [3,4]. In clinical trials in RA, these patients are generally not excluded from participation if they are receiving a stable GC dose at baseline, and they often comprise 40–60% of the study population. GC therapy in patients with RA is well known both for its DMARD effects and for increased risk of its own adverse events (AEs) [3–5]. Nevertheless, the effect of concomitant GCs on the efficacy, patient-reported outcomes and safety of the biologic DMARDs (bDMARDs) or targeted conventional synthetic DMARDs (csDMARDs) in a clinical trial has not been evaluated in detail, except for in a report on a *post hoc* pooled analysis of the effects of GC use in tofacitinib trials [6].

Tocilizumab (TCZ) is a humanized monoclonal antibody that blocks interleukin 6 signalling and has been approved worldwide for the treatment of RA as monotherapy and in combination with csDMARDs [7]. The efficacy and safety of TCZ was first established in its intravenous formulation (TCZ-IV) in clinical trials in patients with RA who had an inadequate response to csDMARDs or anti-TNF agents [8–12]. The efficacy and safety of the subcutaneous formulation of TCZ (TCZ-SC) was established in the phase 3 SUMMACTA, BREVACTA and MUSASHI trials [13–15]. Each of these trials had a long-term extension of $\leqslant$2 years that demonstrated that efficacy and safety with TCZ-SC were consistent with the established profile of TCZ-IV [16–19]. The common-framework TOZURA study programme comprised 11 separate protocols that enrolled patients with RA in 22 countries [20]. TOZURA confirmed the known efficacy and safety profile of TCZ-SC as monotherapy and in combination therapy in a pragmatic, phase 4 clinical setting [20].

Although GC therapy was permitted in the TCZ clinical trials, data on the impact of GC use on the efficacy and safety of TCZ-SC are limited. This *post hoc* analysis of data from the TOZURA study programme evaluated the efficacy and safety of TCZ-SC as monotherapy or in combination with csDMARDs in subgroups of patients with RA defined by baseline oral GC use.

Methods

Source data and study population

This *post hoc* analysis of data from TOZURA, a multinational, open-label, single-arm, common-framework study programme, comprised 11 protocols across 22 countries (NCT01941940, NCT01941095, NCT01951170, NCT01987479, NCT01988012, NCT01995201, NCT02001987, NCT02011334, NCT02031471, NCT02046603, NCT02046616). The common-framework study design ensured that data collection methods and frequency were similar for the first 24 weeks of each individual study. Eligibility criteria, study design and assessments for the TOZURA programme have been previously described [20]. Briefly, the study population comprised adult (aged $\geqslant$18 years) patients with active RA as per the revised 1987 ACR or 2010 EULAR/ACR criteria. Patients had an inadequate response to $\geqslant$1 csDMARD or $\geqslant$1 anti-TNF agent or were MTX naïve. All patients were TCZ naïve at enrolment. Previous bDMARD exposure was permitted, but bDMARDs were prohibited during the study and were discontinued before TCZ-SC initiation. Patients received TCZ-SC 162 mg once weekly (qw) for 24 weeks, administered at investigator discretion as monotherapy or in combination with a csDMARD. Stable concomitant csDMARDs (AZA, chloroquine, HCQ, LEF, MTX or SSZ) were permitted ($\geqslant$4 weeks before baseline) either alone or in combination, except for the combination of MTX and LEF. Oral NSAIDs and GCs ($\leqslant$10 mg/day prednisone or equivalent) were permitted at a stable dose ($\geqslant$4 weeks before baseline). As per the protocol, the GC dose was required to be stable during the 24-week core study period and could be reduced only for safety reasons. Efficacy and safety were evaluated during the 24-week study period.

The TOZURA study protocols, amendments and informed consent documentation were approved by the respective local institutional review boards or independent ethics committees of the investigational centres. All patients provided written, informed consent in accordance with the Declaration of Helsinki.

Statistical analysis

Patients were categorized into four treatment subgroups based on oral GC use at baseline: group 1—patients who received TCZ-SC monotherapy and continued stable baseline oral GC (monotherapy + GC subgroup); group 2—patients who received TCZ-SC monotherapy but no oral GC (monotherapy without GC subgroup); group 3—patients who received TCZ-SC + csDMARD combination therapy and continued stable baseline oral GC (combination therapy + GC subgroup) and group 4—patients who received TCZ-SC + csDMARD combination therapy but no oral GC (combination therapy without GC subgroup). Descriptive statistical methods were used to summarize baseline characteristics, efficacy and safety in treatment subgroups.

Assessments and outcomes

Efficacy end points were analysed over 24 weeks in each subgroup, including the proportion of patients achieving clinical remission based on DAS in 28 joints using ESR (DAS28-ESR), change in DAS28-ESR, Functional Assessment of Chronic Illness Therapy-Fatigue score, HAQ-Disability Index (HAQ-DI), tender joint count in 28 joints, swollen joint count in 28 joints, patient global assessment (PGA) of pain visual analogue scale (VAS) score and PGA of disease activity VAS score. AEs and serious AEs (SAEs) occurring during the 24-week study period were analysed in each subgroup and classified by the Medical Dictionary for Regulatory Activities system organ class terms.

Results

Baseline characteristics in glucocorticoid treatment subgroups

A total of 1804 patients were enrolled in the TOZURA study programme. Of the 353 patients who received

TCZ-SC monotherapy qw, 145 (41.1%) received oral GC at baseline and 208 (58.9%) did not. Of the 1451 patients who received TCZ-SC qw with a concomitant csDMARD, 730 (50.3%) had baseline GC use and 721 (49.7%) did not.

Baseline demographics and disease characteristics were generally balanced between treatment subgroups, except for exposure to previous RA treatments (Table 1). Previous csDMARD exposure was less frequent and previous bDMARD exposure was more frequent in the monotherapy subgroups than in the combination therapy subgroups. In patients who received TCZ-SC monotherapy, prior MTX exposure was more frequent in the monotherapy + GC subgroup than in the monotherapy without GC subgroup (37.9% *vs* 1.9%); however, MTX exposure at baseline was more frequent in both combination therapy treatment subgroups (⩾61.7%) than in the monotherapy groups. Patients in the monotherapy subgroups had numerically longer mean RA duration compared with patients in the combination therapy subgroups, and numerically higher proportions of patients in the subgroups receiving GCs were seropositive for either RF or ACPA compared with patients in the subgroups not receiving GCs. RA disease severity as measured by DAS28-ESR was comparable at initial diagnosis and at the week 1 visit (range of mean DAS28-ESR across subgroups, 5.10–5.43 *vs* 5.57–5.92).

Baseline daily GC doses were similar between the monotherapy + GC and combination therapy + GC subgroups (mean, 6.6 mg *vs* 6.5 mg; median, 5 mg in both subgroups), with 57.2% and 61.8% of patients receiving ⩽5 mg daily in the monotherapy + GC and combination therapy + GC subgroups, respectively (Table 1). As required by the protocol, the majority (>96%) of patients in the subgroups receiving GC remained on their baseline GC dose during the 24-week study period.

Table 1 Baseline demographics and disease characteristics

Characteristics	TCZ-SC monotherapy		TCZ-SC + csDMARD	
	GC use (*n* = 145)	No GC use (*n* = 208)	GC use (*n* = 730)	No GC use (*n* = 721)
Age, mean (S.D.), years	55.0 (12.7)	54.9 (12.7)	53.5 (12.7)	54.3 (11.6)
Sex, *n* (%)				
Male	26 (17.9)	32 (15.4)	138 (18.9)	136 (18.9)
Female	119 (82.1)	176 (84.6)	592 (81.1)	858 (81.1)
Race, *n* (%)[a]				
White	139 (95.9)	203 (97.6)	647 (88.6)	664 (92.1)
Black	3 (2.1)	1 (0.5)	27 (3.7)	26 (3.6)
Asian	0	1 (0.5)	8 (1.1)	6 (0.8)
American Indian or Alaska Native	0	1 (0.5)	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	2 (1.4)	1 (0.5)	43 (5.9)	24 (3.3)
Weight, mean (S.D.), kg	69.2 (14.5)	74.1 (18.1)	71.6 (15.5)	74.4 (16.6)
RA duration, mean (S.D.), years	8.7 (8.0)	8.2 (8.4)	7.4 (7.6)	7.8 (8.3)
Seropositivity, *n* (%)				
RF[b]	104 (77.6)	133 (68.9)	506 (74.6)	465 (70.7)
ACPA[c]	93 (77.5)	106 (63.5)	454 (73.9)	399 (68.2)
Evidence of structural joint damage, *n* (%)[d]	81 (61.4)	91 (52.6)	275 (43.7)	276 (45.0)
CRP, mean (S.D.), mg/l	21.0 (24.6)	15.3 (24.7)	16.1 (21.6)	12.6 (20.1)
DAS28-ESR at time of initial RA diagnosis, mean (S.D.)	5.39 (1.30)	5.34 (1.25)	5.43 (1.29)	5.10 (1.17)
DAS28-ESR at week 1 (baseline) visit, mean (S.D.)	5.92 (1.12)	5.79 (1.11)	5.93 (1.16)	5.57 (1.17)
Prednisone equivalent daily dose, mean (S.D.) [median], mg	6.6 (2.9) [5]	0	6.5 (4.2) [5][e]	0
Previous RA treatment exposure, *n* (%)				
MTX	55 (37.9)	4 (1.9)	487 (66.7)	445 (61.7)
csDMARD (excluding MTX)	2 (1.4)	3 (1.4)	88 (12.1)	113 (15.7)
bDMARD	51 (35.2)	60 (28.8)	117 (16.0)	120 (16.6)
Medical history, any disease, *n* (%)	127 (87.6)	171 (82.2)	587 (80.4)	582 (80.7)
Vascular disorders	44 (30.3)	62 (29.8)	246 (33.7)	201 (27.9)
Musculoskeletal and connective tissue disorders	44 (30.3)	16 (7.7)	198 (27.1)	61 (8.5)
Gastrointestinal disorders	34 (23.4)	27 (13.0)	121 (16.6)	135 (18.7)
Infections and infestations	25 (17.2)	26 (12.5)	113 (15.5)	106 (14.7)

[a]*n* = 144, 207, 726 and 720, respectively. [b]*n* = 134, 193, 678 and 658, respectively. [c]*n* = 120, 167, 614 and 585, respectively. [d]*n* = 132, 173, 629 and 614, respectively. [e]*n* = 725. In the combination therapy group, five patients were receiving GC at baseline, but dose information was not available. bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS28-ESR: DAS in 28 joints using ESR; GC: glucocorticoid; TCZ-SC: subcutaneous tocilizumab.

Some expected differences between the GC and non-GC subgroups were seen in baseline comorbidities (Table 1). A history of vascular disorders, musculoskeletal and CTDs or gastrointestinal disorders was more frequent in the GC-exposed patients than in patients without GC use, with the largest apparent differences in the prevalence of hypertension, osteoporosis and gastritis. A history of infections and infestations was found in similar proportions of patients across treatment subgroups; the most frequently reported types were latent tuberculosis, herpes zoster, pneumonia and urinary tract infection.

Efficacy by treatment subgroups

The proportion of patients in DAS28-ESR–defined clinical remission (DAS28-ESR <2.6) increased over 24 weeks of TCZ-SC treatment, with similar trends observed across all four treatment subgroups (Fig. 1A and B). The proportion of patients in clinical remission in the monotherapy without GC subgroup was slightly lower across visits compared with the monotherapy + GC subgroup. In each treatment subgroup, the majority of patients had achieved clinical remission at week 24. The reduction in mean DAS28-ESR (Supplementary Fig. S1, available at *Rheumatology* online) over 24 weeks reflected these trends. Upon evaluation of the impact of GC use on the DAS28 domains, a trend towards a slightly greater numerical decrease from baseline was apparent only for tender joint count in 28 joints and swollen joint count in 28 joints with GC use in both TCZ-SC groups (Fig. 1C–F).

In all treatment subgroups, the mean Functional Assessment of Chronic Illness Therapy-Fatigue score improved over the first 8 weeks of TCZ-SC treatment and remained stable through the week 24 visit (Fig. 2). Mean HAQ-DI scores decreased over 24 weeks of TCZ-SC treatment, with similar trends across subgroups; the largest improvement was observed in the weeks following treatment initiation (Fig. 3). Mean PGA of pain and PGA of disease activity VAS scores also decreased similarly in all treatment groups from week 1 to week 12 and remained stable through week 24 in all treatment subgroups (Supplementary Figs S2 and S3, available at *Rheumatology* online).

Safety by treatment subgroups

AEs were reported in 75.9–86.3% of patients with RA who received TCZ-SC across treatment subgroups (Table 2), with AEs reported in 81.6% and 85.5% of patients in the GC and non-GC subgroups, respectively. The AE profiles across treatment subgroups were largely similar, but had some minor numerical differences. The most common AEs by the Medical Dictionary for Regulatory Activities system organ class terms were infections and infestations (range across subgroups, 40.0-45.2%), investigations (primarily laboratory investigations; 14.5–27.6%), gastrointestinal disorders (18.6–26.2%) and musculoskeletal and CTDs (18.3–22.3%) (Table 2). Laboratory abnormalities were more frequent in the combination therapy subgroups than in the monotherapy subgroups. Gastrointestinal disorders, skin and subcutaneous tissue disorders and general disorders and administration site conditions were less frequent, and metabolism and nutrition disorders were more frequent, in the GC subgroups than in the non-GC subgroups.

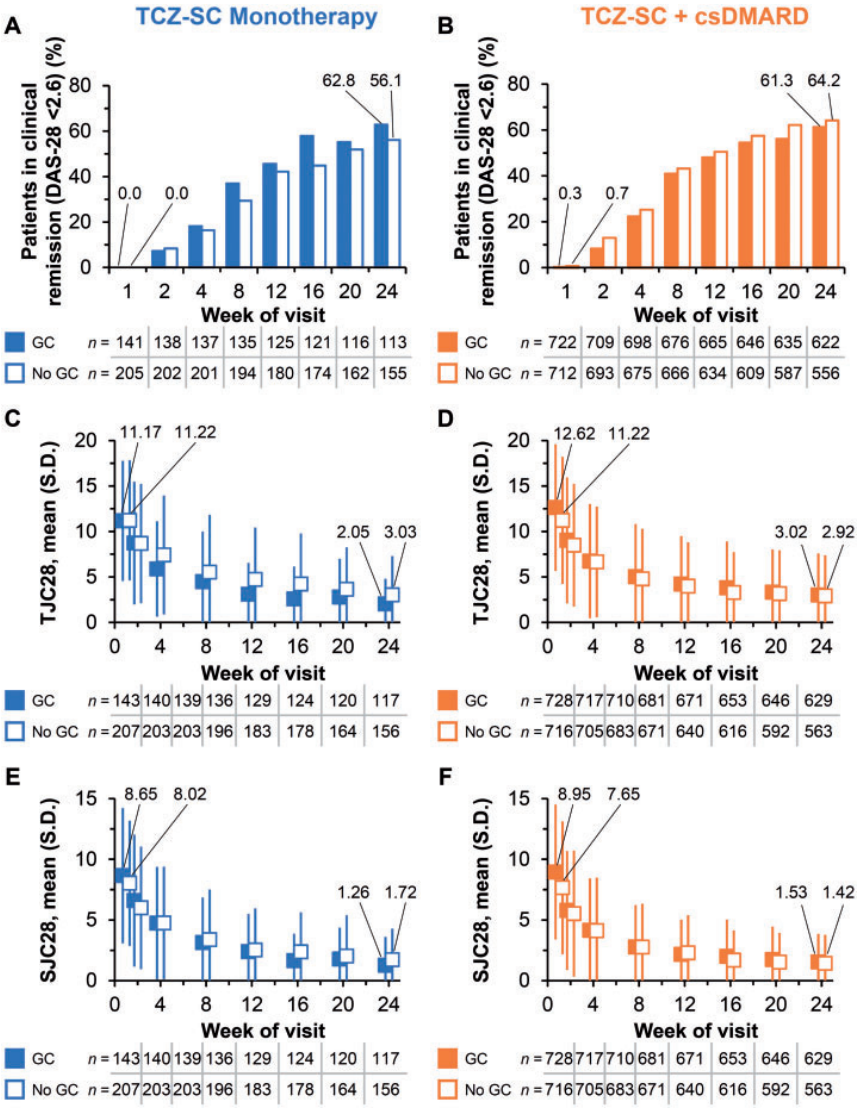
Compared with patients experiencing any AE, only a minor proportion of all patients experienced SAEs. SAEs were reported in the monotherapy group in 13 patients (9.0%) with GC use and in 16 (7.7%) without GC use; in the combination therapy group, SAEs were reported in 42 patients (5.8%) with GC use and in 34 (4.7%) without GC use (Supplementary Table S1, available at *Rheumatology* online). The most frequently reported SAEs by body system were infections and infestations (range across subgroups, 1.1–2.1%), gastrointestinal disorders (0.5–1.4%) and vascular disorders (0.1–2.1%). The frequency of SAEs by body system was generally similar across treatment subgroups with some slight numerical differences between the combined GC use subgroups [55 of 875 patients (6.3%)] *vs* the combined non-GC subgroups [50 of 929 patients (5.4%)]. These slight differences appear to be driven by differences in the number of SAE infections (7 patients *vs* 2) and vascular disorders (8 *vs* 2) in the combined GC use *vs* non-GC subgroups.

Discussion

This *post hoc* analysis of data from the phase 4 TOZURA study programme examined the efficacy and safety of TCZ-SC monotherapy and TCZ-SC in combination with csDMARDs in subgroups of patients defined by baseline GC use. The proportions of TCZ-SC–treated patients who achieved clinical remission (DAS28-ESR < 2.6) were comparable across treatment subgroups. The AE profiles were generally similar between treatment subgroups.

In the only similar study of another targeted DMARD published to date, pooled data from six clinical trials of tofacitinib in RA found no significant effect on the efficacy of tofacitinib in patients with GC use compared with patients without GC use, with some slight differences between patients with and without concomitant csDMARD use [6]. Consistent with the findings of the current evaluation, an analysis of pooled data from four clinical trials of TCZ-IV in patients with RA found no evidence that concomitant GC therapy affected the proportion of patients who achieved DAS28-ESR–defined remission [21]. Although concomitant GC use did not appear to affect the efficacy of TCZ-SC, a slight numerical trend toward better control of disease activity by DAS28-ESR composite score was observed with GC use in patients who received TCZ-SC monotherapy, but this trend was not visible in the TCZ-SC + csDMARD subgroups, possibly due to overlapping effects of csDMARDs and GCs. When evaluating the impact of GC use on the DAS28 domains, a trend toward a slightly higher numerical decrease (1 joint) from baseline was apparent only for tender joint count in 28 joints and swollen joint count in 28 joints with GC use in both TCZ-SC groups. One could hypothesize that, in line with the suggestions published recently, the clinical domains of the DAS28 composite score are more sensitive to detecting anti-inflammatory DMARD effects

FIG. 1 Efficacy of TCZ-SC over 24 weeks in subgroups of patients with RA treated with TCZ-SC

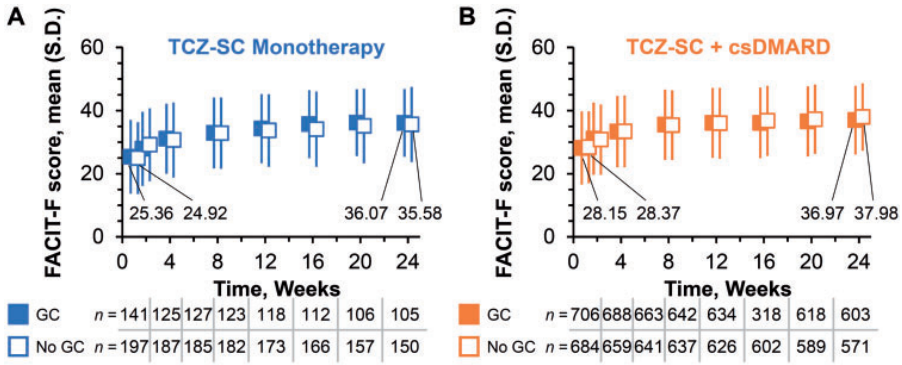


Percentage of patients in clinical remission (DAS28-ESR <2.6) over 24 weeks in subgroups of patients with RA treated with (**A**) TCZ-SC monotherapy or (**B**) TCZ-SC + csDMARD. TJC28 over 24 weeks in subgroups of patients with RA treated with TCZ-SC in subgroups of patients with RA treated with (**C**) TCZ-SC monotherapy or (**D**) TCZ-SC + csDMARD. SJC28 over 24 weeks in subgroups of patients with RA treated with (**E**) TCZ-SC monotherapy or (**F**) TCZ-SC + csDMARD.
csDMARD: conventional synthetic DMARD; DAS28-ESR: DAS in 28 joints using ESR; GC: glucocorticoid; SJC28: swollen joint count in 28 joints; TCZ-SC: subcutaneous tocilizumab; TJC28: tender joint count in 28 joints.

compared with the overall composite score, which includes psychological determinants of PGA [22].

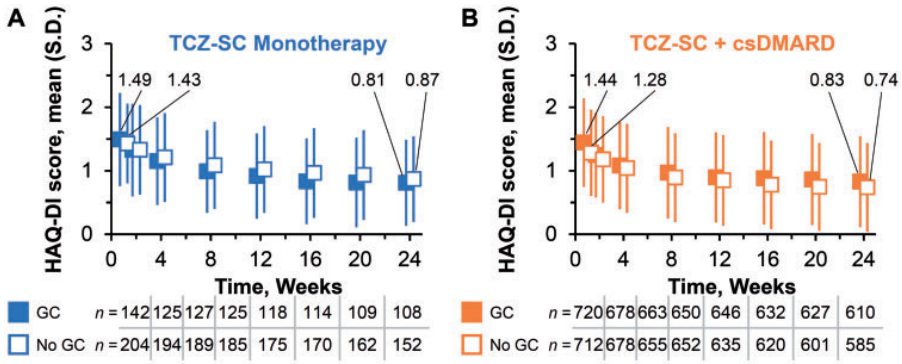
The patient-reported outcomes were largely similar between the GC and non-GC subgroups; only HAQ-DI, PGA of disease activity VAS and, to a lesser degree, PGA of pain VAS appeared to reflect the subtle numerical trends in disease activity and inflammation control observed between these subgroups, with no apparent difference in Functional Assessment of Chronic Illness Therapy-Fatigue scores. These findings should be interpreted cautiously due to the known—and probably unknown—differences in disease characteristics between patients with and without GC use. Of note, patients who received GC treatment in TOZURA had longer duration of

FIG. 2 FACIT-F score over 24 weeks in subgroups of patients with RA treated with (**A**) TCZ-SC monotherapy or (**B**) TCZ-SC + csDMARD



csDMARD: conventional synthetic DMARD; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; GC: glucocorticoid; TCZ-SC: subcutaneous tocilizumab.

FIG. 3 HAQ-DI score over 24 weeks in subgroups of patients with RA treated with (**A**) TCZ-SC monotherapy or (**B**) TCZ-SC + csDMARD



csDMARD: conventional synthetic DMARD; GC: glucocorticoid; HAQ-DI: HAQ-Disability Index; TCZ-SC: subcutaneous tocilizumab.

RA and slightly higher disease activity, and a greater proportion of GC-treated patients were RF or ACPA seropositive compared with patients in the non-GC subgroups.

Somewhat more patients in the non-GC subgroups experienced non-serious AEs than patients in the GC subgroups. Similarly, some slight numerical differences were observed between GC and non-GC subgroups in SAEs, particularly infections and vascular disorders. On the basis of the available information, these minor differences cannot be explained in a robust scientific way, but a slightly increased risk of GC-associated AEs cannot be excluded. However, notably, in CAPRA-2, a 12-week randomized, double-blind, placebo-controlled study of prednisone 5 mg/day in patients with RA, the frequency of any AE was somewhat lower in 231 patients treated with prednisone than in 119 patients who received placebo (42.9% *vs* 48.7%) [23].

This analysis has several limitations. This was a *post hoc* analysis of the TOZURA study programme, which was not designed to compare the efficacy and safety in subgroups based on GC use; hence, any conclusions should be treated as exploratory. This analysis does not allow for any conclusions regarding the efficacy of GCs in RA; it allows for the generation of hypotheses regarding whether prior and continuing stable concomitant low-dose GC use is associated with any impact on the efficacy and safety of TCZ-SC in patients with active RA. This study only included patients who received TCZ-SC weekly; patients receiving TCZ-SC every 2 weeks or TCZ-IV once every 4 weeks may not exhibit the same trends in efficacy and safety with GC use *vs* without GC use. Also, potential effects arising from differences in GC dose were not evaluated. Additionally, patients in the GC subgroups had prior exposure to GC; thus,

Table 2 Summary of AEs over 24 weeks in subgroups of patients with RA treated with TCZ-SC

Patients with ⩾1 AE by body system, *n* (%)	TCZ-SC monotherapy		TCZ-SC + csDMARD	
	GC use (*n* = 145)	No GC use (*n* = 208)	GC use (*n* = 730)	No GC use (*n* = 721)
Any event	110 (75.9)	172 (82.7)	604 (82.7)	622 (86.3)
Infections and infestations	58 (40)	94 (45.2)	292 (40.0)	314 (43.6)
Investigations[a]	21 (14.5)	32 (15.4)	174 (23.8)	199 (27.6)
Gastrointestinal disorders	27 (18.6)	53 (25.5)	143 (19.6)	189 (26.2)
Musculoskeletal and connective tissue disorders	27 (18.6)	38 (18.3)	142 (19.5)	161 (22.3)
General disorders and administration site conditions	20 (13.8)	44 (21.2)	110 (15.1)	152 (21.1)
Skin and subcutaneous tissue disorders	25 (17.2)	41 (19.7)	98 (13.4)	146 (20.2)
Nervous system disorders	17 (11.7)	23 (11.1)	70 (9.6)	113 (15.7)
Respiratory, thoracic and mediastinal disorders	21 (14.5)	26 (12.5)	78 (10.7)	98 (13.6)
Blood and lymphatic system disorders	9 (6.2)	19 (9.1)	77 (10.5)	93 (12.9)
Injury, poisoning and procedural complications	12 (8.3)	15 (7.2)	68 (9.3)	76 (10.5)
Vascular disorders	8 (5.5)	19 (9.1)	57 (7.8)	51 (7.1)
Metabolism and nutrition disorders	10 (6.9)	10 (4.8)	52 (7.1)	32 (4.4)
Eye disorders	9 (6.2)	11 (5.3)	18 (2.5)	34 (4.7)
Psychiatric disorders	6 (4.1)	9 (4.3)	30 (4.1)	21 (2.9)
Reproductive system and breast disorders	0	5 (2.4)	15 (2.1)	25 (3.5)
Renal and urinary disorders	2 (1.4)	1 (0.5)	21 (2.9)	18 (2.5)
Cardiac disorders	5 (3.4)	8 (3.8)	15 (2.1)	13 (1.8)
Hepatobiliary disorders	1 (0.7)	5 (2.4)	17 (2.3)	16 (2.2)
Surgical and medical procedures	5 (3.4)	8 (3.8)	14 (1.9)	6 (0.8)
Ear and labyrinth disorders	3 (2.1)	3 (1.4)	7 (1.0)	18 (2.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	2 (1)	9 (1.2)	16 (2.2)
Immune system disorders	0	0	11 (1.5)	13 (1.8)
Endocrine disorders	1 (0.7)	1 (0.5)	1 (0.1)	2 (0.3)
Congenital, familial and genetic disorders	0	0	4 (0.5)	0

[a]Of the 508 investigations AEs reported, 501 were laboratory investigations and 7 were not; these exceptions included cardiac murmur (3 events), colposcopy (1), breath sounds (1), heart rate irregular (1) and heart rate increased (1). AE: adverse event; csDMARD: conventional synthetic DMARD; GC: glucocorticoid; TCZ-SC: subcutaneous tocilizumab.

these patients were less likely to experience an AE due to GC use. Further, the follow-up was limited to 24 weeks as per the common-framework protocol used across substudies and did not permit the observation of long-term effects in this pooled analysis. This limitation is notable when considering the burden of comorbidities associated with long-term GC use, including infections, cardiovascular disease, osteoporosis and diabetes, in patients with RA [3,24]. Potential effects of concomitant medications used to treat comorbid conditions were not evaluated. Despite a large sample size in the phase 4 setting, the population of the common-framework TOZURA study programme was likely less heterogeneous than the populations of pooled analyses of multiple clinical trials [6,21].

In this *post hoc* analysis of a large RA cohort treated with TCZ-SC in a phase 4 clinical setting, GC use did not appear to impact the efficacy of introducing TCZ-SC as monotherapy or in combination with concomitant csDMARDs. Similar safety profiles for TCZ-SC as monotherapy and in combination with csDMARDs were observed over 24 weeks in patients with or without background GC treatment, though some slight numerical differences were observed between patients receiving GC and those without.

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Data sharing statement: Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094–108.

2 Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. Clin Exp Rheumatol 2010;28:S32–40.

3 Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696–705.

4 Best JH, Kong AM, Lenhart GM *et al*. Association between glucocorticoid exposure and healthcare expenditures for potential glucocorticoid-related adverse events in patients with rheumatoid arthritis. J Rheumatol 2018;45:320–8.

5 Wilson JC, Sarsour K, Gale S *et al*. Incidence and risk of glucocorticoid-associated adverse effects in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018; Advance Access published 1 June 2018, doi: 10.1002/acr.23611.

6 Charles-Schoeman C, van der Heijde D, Burmester GR *et al*. Effect of glucocorticoids on the clinical and radiographic efficacy of tofacitinib in patients with rheumatoid arthritis: a posthoc analysis of data from 6 phase III studies. J Rheumatol 2018;45:177–87.

7 Eulenfeld R, Dittrich A, Khouri C *et al*. Interleukin-6 signalling: more than Jaks and STATs. Eur J Cell Biol 2012;91:486–95.

8 Smolen JS, Beaulieu A, Rubbert-Roth A *et al*. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371:987–97.

9 Genovese MC, McKay JD, Nasonov EL *et al*. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2008;58:2968–80.

10 Emery P, Keystone E, Tony HP *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516–23.

11 Jones G, Sebba A, Gu J *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88–96.

12 Kremer JM, Blanco R, Brzosko M *et al*. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum 2011;63:609–21.

13 Burmester GR, Rubbert-Roth A, Cantagrel A *et al*. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis 2014;73:69–74.

14 Kivitz A, Olech E, Borofsky M *et al*. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:1653–61.

15 Ogata A, Tanimura K, Sugimoto T *et al*. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:344–54.

16 Burmester GR, Rubbert-Roth A, Cantagrel A *et al*. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). Ann Rheum Dis 2016;75:68–74.

17 Kivitz A, Olech E, Borofsky MA *et al*. The efficacy and safety of tocilizumab subcutaneous Q2W and following escalation from Q2W to QW therapy in combination with traditional Dmards in patients with moderate to severe rheumatoid arthritis at 96 weeks. Arthritis Rheumatol 2014;66:S1076–7.

18 Ogata A, Amano K, Dobashi H *et al*. Longterm safety and efficacy of subcutaneous tocilizumab monotherapy: results from the 2-year open-label extension of the MUSASHI study. J Rheumatol 2015;42:799–809.

19 Kivitz A, Wallace T, Olech E *et al*. Long-term safety and efficacy of subcutaneously administered tocilizumab for adult rheumatoid arthritis: a multicenter phase 3b long-term extension study. Rheumatol Ther 2016;3:291–304.

20 Choy E, Caporali R, Xavier R *et al*. Subcutaneous tocilizumab in rheumatoid arthritis: findings from the common-framework phase 4 study programme TOZURA conducted in 22 countries. Rheumatology 2018;57:499–507.

21 Safy M, Jacobs JWG, Edwardes M *et al*. SAT0169 No evidence that concomitant glucocorticoid therapy affects efficacy and safety of tocilizumab monotherapy in rheumatoid arthritis clinical trials. Ann Rheum Dis 2018;77(Suppl 2):945.

22 Ferreira RJO, Duarte C, Ndosi M *et al*. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. Arthritis Care Res (Hoboken) 2018;70:369–78.

23 Buttgereit F, Mehta D, Kirwan J *et al*. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis 2013;72:204–10.

24 De Vries F, Bracke M, Leufkens HG *et al*. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum 2007;56:208–14.