ORIGINAL ARTICLE

Retreatment efficacy and safety of tocilizumab in patients with rheumatoid arthritis in recurrence (RESTORE) study

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Abstract

Objectives To evaluate the safety and efficacy of retreatment with tocilizumab (TCZ) in patients who had participated in the DREAM study (*Drug free* remission/low disease activity after cessation of tocilizumab [Actemar] monotherapy study) and had experienced loss of efficacy.

Methods Patients were retreated with TCZ or other disease modifying antirheumatic drugs (DMARDs). Disease activity was measured using the 28-joint disease activity score (DAS28) for 12 weeks.

Results A total of 164 eligible patients, including 161 who experienced loss of efficacy within 52 weeks of the DREAM study, resumed treatment: 157 with TCZ and 7 with DMARDs and/or infliximab. Of TCZ-treated patients, 88.5 % (139 patients) achieved DAS28 <2.6 within 12 weeks, whereas among patients treated with DMARDs and/or infliximab only 14.3 % (1 patient) achieved DAS28 <2.6. Adverse events were observed in 70 TCZ-treated patients (44.0 %), but no serious infusion reactions were observed.

Conclusions Retreatment with TCZ was well-tolerated and effective in patients who had responded to the preceding TCZ monotherapy but had experienced loss of efficacy after cessation of TCZ.

Keywords Interleukin 6 · Retreatment · *Drug free* · Rheumatoid arthritis · Tocilizumab

For the MRA study group for RA.

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Introduction

Tocilizumab (TCZ) treatment frequently achieves remission in patients with rheumatoid arthritis (RA) as measured by the 28-joint disease activity score (DAS28) [1–12]. We have demonstrated in the DREAM study (*Drug free remission/low disease activity (LDA) after cessation of TCZ [Actemra] monotherapy study*) [13] that in some cases the efficacy of TCZ is sustained for more than 1 year after cessation of TCZ and without the use of other disease modifying antirheumatic drugs (DMARDs). However, the majority of patients experienced loss of efficacy, and needed to restart treatment for RA. In this study we evaluate the safety and efficacy of TCZ retreatment at recurrence of disease activity after cessation of TCZ.

Methods

Patients

All patients who participated in the DREAM study and had experienced loss of efficacy were enrolled. Criteria for loss of efficacy in the DREAM study was defined as DAS28-erythrocyte sedimentation rate (ESR) >3.2 at 2 consecutive observations, initiation of additional RA treatments including increase in oral corticosteroid dose, the patient's request for retreatment, or the treating physician judging that retreatment was necessary.

Study protocol

The study protocol was approved by the Ministry of Health, Labour and Welfare of Japan and by the local ethical committees. This study is registered with http://clinicaltrials.gov (NCT00661284). Patients were treated with biologic DMARDs including TCZ and infliximab (IFX), and/or conventional synthetic DMARDs including methotrexate (MTX). If the patient received TCZ retreatment, TCZ was administered intravenously (8 mg/kg) every 4 weeks. Other biologic DMARDs and/or synthetic DMARDs were administered based on the dosage and regimen in the package insert. The concomitant use of corticosteroids and non-steroidal anti-inflammatory drugs was allowed during the study period.

Anti-tocilizumab antibodies

Serum anti-TCZ antibody levels were determined by ELISA. Serum was added to the wells coated with 100 µl of Fab fragment of TCZ (0.2 µg/ml) and incubated for 2 h. After washing, biotin-conjugated TCZ was added and developed with alkaline phosphatase conjugated to streptavidin.

IgE-type anti-TCZ antibodies were also measured by ELISA. In this case, whole TCZ was used because an antigen coated each cup, and enzyme-linked anti-IgE antibodies were used as second antibodies.

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Statistical analysis

Clinical response was measured by DAS28-ESR. Remission was defined, in accordance with the European League Against Rheumatism (EULAR) definition, as DAS28 <2.6 [14]. The rates of remission under the new EULAR/ American College of Rheumatology (ACR) remission criteria (Boolean definition) were also considered [15]. Adverse events (AEs) and serious adverse events (SAEs) were tabulated after converting the verbatim event names to MedDRA Ver. 8.0 System Organ Class (SOC) terms.

The factors contributing to the resumption of DAS28-ESR remission after retreatment were estimated from univariate and multivariate logistic regression analyses using the following patient baseline data for this study: DAS28-ESR, tender joint count (TJC), swollen joint count (SJC), patient's global assessment (Pt-GA), modified health assessment questionnaire (MHAQ) score, serum C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), serum IL-6 concentration, serum matrix metalloproteinase (MMP)-3 concentration, and the duration of TCZ cessation. In the multivariate logistic analysis, stepwise selection with a level of significance of 0.05 was used for entry or removal of variables. Logistic regression analysis was also conducted to analyse the relationship between the TCZ treatment interval and development of AEs during this study.

Results

Characteristics of patients

In total, 166 patients were enrolled and resumed treatments. Of the patients who received TCZ retreatment, 2 were ineligible and were excluded from the analysis of efficacy. The 164 remaining patients eligible for analysis of efficacy included 161 patients who had experienced loss of efficacy by week 52 of the DREAM study, and 3 patients who had experienced loss of efficacy after completion of the DREAM study (an interval of >1 year).

In the 164 eligible patients, 73 patients (44.5 %) resumed treatment due to DAS28-ESR >3.2 at 2 consecutive visits, 66 patients (40.2 %) to investigator's judgement, 11 patients (6.7 %) to patients' request, and 14 patients (8.5 %) to addition of RA treatments including increase in oral corticosteroid dose. The major reason investigators judged retreatment was necessary was a DAS28-ESR >3.2 score at one visit in 55/66 patients (83.3 %). Four out of eleven patients who requested treatment were also DAS28-ESR >3.2. Therefore, 146/164 patients were DAS28-ESR >3.2 at the baseline of the RESTORE study (the mean DAS28-ESR[95 %CI] was 4.6 [4.5–4.8]).

A total of 159 patients received at least 1 infusion of TCZ (including 2 ineligible patients), and 7 patients received other DMARDs, including MTX, tacrolimus, and/ or IFX. In the TCZ-treated patients, 133 patients received TCZ monotherapy and 26 received TCZ therapy in combination with synthetic DMARDs (25 patients with MTX; 1 patient with salazosulfapyridine). The median treatment interval between the last TCZ infusion and restarting the TCZ treatment in this study was 13.1 weeks (min–max, 6.14–60.4 weeks). Corticosteroids were used concomitantly in 57 of the patients treated with TCZ and in 4 of the patients treated with other DMARDs. The median corticosteroid dose in TCZ-treated patients at baseline of this RESTORE study was 3.0 mg/day, which was comparable with the median dose in patients treated with other DMARDs (2.3 mg/day). Other baseline characteristics of the patients who received TCZ were comparable with those of patients treated with other DMARDs (Table 1).

Efficacy of TCZ retreatment

The mean (±SD) DAS28-ESR before initial treatment using TCZ in the previous clinical studies (i.e. Japanese phase I/II open-label dose escalation study, a phase II double-blind dose finding study, a phase III open-label randomized study (SAMURAI), a phase III double-blind study (SATORI), a drug–drug interaction study, and a renal failure study) was 6.2 (±1.0) and improved with 12 weeks of TCZ treatment to 2.8 (±1.2). The mean (±SD) DAS28-ESR at the last observation point of the previous TCZ treatment studies (i.e., baseline of the DREAM study) was 1.5 (±0.7) (Fig. 1a).

In this study, the mean (±SD) DAS28-ESR in patients who restarted TCZ treatment decreased from 4.4 (±1.1) (95 % CI: 4.2–4.6) before restarting treatment to 1.8 (±0.8) (95 % CI: 1.6–1.9) after 12 weeks of treatment. In contrast, the mean (±SD) DAS28-ESR in patients treated with DMARDs and/or IFX was 4.2 (±1.1) (95 % CI: 3.2–5.2) before restarting treatment and 3.3 (±1.0) (95 % CI: 2.5–4.2) after 12 weeks of treatment (Fig. 1a).

Of the TCZ-retreated patients, 95.5 % (150/157 patients, 95 % CI: 91.0–98.2 %) achieved DAS28-ESR ≤3.2 and 88.5 % (139/157 patients, 95 % CI: 82.5–93.1 %) achieved DAS28-ESR <2.6 within 12 weeks as compared to only 28.6 % of the other DMARD-treated patients (2/7 patients, 95 % CI 3.7–71.0 %) achieving DAS28-ESR ≤3.2 and 14.3 % (1/7 patients, 95 % CI: 0.4–57.9 %) achieving DAS28-ESR <2.6.

The percentage of TCZ-retreated patients who reached DAS28-ESR <2.6 within 12 weeks in the TCZ monotherapy group (87.9 %, 116/132 patients, 95 % CI: 81.1–92.9 %) was comparable to the percentage in the TCZ plus synthetic DMARDs therapy group (92.0 %, 23/25 patients, 95 % CI: 74.0–99.0 %).

Table 1 Demographic and clinical characteristics of patients at baseline of RESTORE study

No. of patients	Total	Patients treated with TCZ	Patients treated with other DMARDs
	166	159[a]	7
Age, years (median [range])	57 (26–78)	56 (26–78)	65 (42–74)
Gender, female (%)	149 (89.8)	144 (90.6)	5 (71.4)
Disease duration, years (median [range])	7.8 (3.7–24.0)	7.7 (3.7–24.0)	8.6 (6.9–18.9)
No. (%) of patients using concomitant corticosteroids	61 (36.7)	57 (35.8)	4 (57.1)
Dose, mg/day (prednisolone equivalent) (median [range])	3.0 (0.5–10.0)	3.0 (0.5–10.0)	2.3 (2.0–7.0)
DAS28-ESR (median [range])	4.3 (0.8–7.8)	4.4 (0.8–7.8)	4.1 (2.9–5.9)
(Mean ± SD)	4.4 ± 1.1	4.4 ± 1.1	4.2 ± 1.1
Tender joint count (28-joint count) (median [range])	3.0 (0–27)	3.0 (0–27)	3.0 (1–5)
(Mean ± SD)	4.3 ± 4.3	4.4 ± 4.4	2.6 ± 1.4
Swollen joint count (28-joint count) (median [range])	2.0 (0–16)	2.0 (0–16)	2.0 (0–7)
(Mean ± SD)	3.3 ± 3.1	3.3 ± 3.2	2.4 ± 2.2
CRP, mg/dl (median [range])	0.8 (0.0–13.5)	0.9 (0.0–13.5)	0.8 (0.1–4.7)
(Mean ± SD)	1.6 ± 2.1	1.6 ± 2.1	1.2 ± 1.6
ESR, mm/h (median [range])	36 (2–115)	37 (2–115)	32 (16–113)
(Mean ± SD)	41 ± 24	40 ± 23	49 ± 39
MHAQ score (median [range])	0.3 (0.0–2.1)	0.4 (0.0–2.1)	0.0 (0.0–0.8)
(Mean ± SD)	0.5 ± 0.5	0.5 ± 0.5	0.2 ± 0.3
MMP-3, ng/ml (median [range])	95 (34–800)	96 (34–800)	77 (44–319)
(Mean ± SD)	167 ± 167	169 ± 169	129 ± 112

DAS28 28-joint disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MHAQ* modified health assessment questionnaire, *MMP-3* matrix metalloproteinase-3, *TCZ* tocilizumab, *DMARDs* disease modifying antirheumatic drugs

[a] Two ineligible patients who did not meet the eligible criteria of DREAM study were included

The mean (±SD) tender joint count (TJC) in 28 joints in TCZ-retreated patients improved from 4.4 (±4.4) before restarting treatment to 0.8 (±1.6) after 12 weeks. The mean (±SD) swollen joint count (SJC) in 28 joints also improved from 3.3 (±3.2) to 0.8 (±1.6) (Fig. 1b). Moreover, 63.1 % of patients (99/157) had no tender and/or swollen joints after 12 weeks retreatment with TCZ (Fig. 1c). Under the Boolean remission criteria, the remission rate by TCZ treatment was 43.9 % (69/157 patients, 95 % CI: 36.0–52.1 %) at week 12 (Fig. 1d). The mean (±SD) MMP-3 values in TCZ-retreated patients improved from 166.5 (±164.5) ng/ml at baseline in this study, i.e. prior to TCZ retreatment, to 77.4 (±64.8) ng/ml at week 12. Univariate logistic regression analysis showed the following variables to be associated with the resumption of DAS28-ESR remission: lower DAS28-ESR, lower TJC, lower SJC and lower MHAQ at baseline. On the other hand, duration of TCZ cessation in the DREAM study was not associated with resumption of DAS28-ESR remission (Fig. 2). Multivariate logistic regression analysis showed that lower DAS28-ESR at baseline was the contribution factor for resumption efficacy.

At baseline, 17 patients had DAS28-ESR ≤3.2. Thus, we further analysed efficacy in the 140 patients who had DAS28-ESR >3.2 at the baseline (the mean DAS28-ESR [95 % CI] was 4.6 [4.5–4.8]) and restarted TCZ in this study. Out of these patients, 87.1 % (122/140 patients, 95 % CI: 80.4–92.2 %) achieved DAS28-ESR <2.6 and 42.9 % (60/140 patients, 95 % CI: 34.5–51.5 %) achieved Boolean remission within 12 weeks. In addition, univariate and multivariate logistic regression analysis also identified lower DAS28-ESR value at baseline to be the factor contributing the resumption of DAS28-ESR remission by 12 weeks of TCZ treatment in these patients. These results are not significantly different from those including the patients with DAS28-ESR ≤ 3.2 at baseline.

Safety of TCZ retreatment

AEs were reported in 44.0 % (70/159) of the patients who were retreated with TCZ and in 42.9 % (3/7) of the patients treated with other DMARDs. All AEs reported in the TCZ-treated group were mild and tolerable relative to the benefit provided. The incidence rate of AEs in the TCZ monotherapy group (42.9 %, 57/133 patients, 95 % CI: 34.3–51.7) was comparable to the incidence rate in the TCZ plus synthetic DMARDs therapy group (50.0 %, 13/26 patients, 95 % CI: 29.9–70.1). There was no
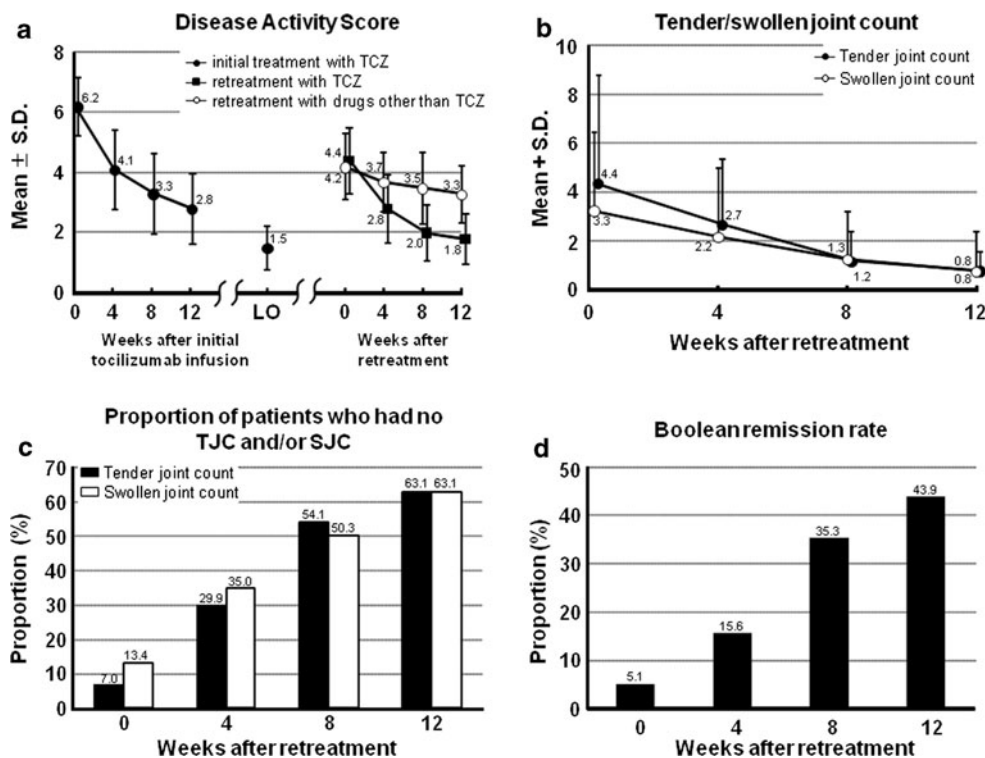
Fig. 1 Changes in DAS28-ESR, tender joint count, swollen joint count, and Boolean remission rate after resumption of treatment. **a** Mean (±SD) change in DAS28-ESR: from baseline of the initial tocilizumab (TCZ) treatment to week 12 and last observation point of the long-term extension studies (*closed circles*), and from the baseline of this study to week 12 in patients retreated with TCZ (*closed squares*) and in patients treated with other DMARDs (*open circles*). *Error bars* show SD. **b** Mean (+SD) tender joint count in 28 joints (*closed circles*), and mean (+SD) swollen joint count in 28 joints in TCZ-retreated patients (*open circles*). *Error bars* show SD. **c** Proportion of TCZ-retreated patients with no tender joints (*solid bars*) and those with no swollen joints (*open bars*). **d** Remission rates under the new EULAR/ACR remission criteria in the TCZ-retreated patients. *TJC* tender joint count, *SJC* swollen joint count, *LO* last observation point

Fig. 2 Factors associated with resumption of DAS28-ESR remission by 12 weeks of TCZ retreatment after cessation of TCZ therapy. Factors contributing to the resumption of DAS28-ESR remission by 12 weeks of TCZ treatment were estimated by univariate and multivariate logistic regression analyses. *OR* odds ratio, *CI* confidence interval, *DAS28* 28-joint disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MHAQ* modified health assessment questionnaire, *IL-6* interleukin 6, *MMP-3* matrix metalloproteinase 3, *TCZ* tocilizumab

relationship between the development of AEs and the duration of TCZ cessation in the DREAM study. Infections were the most common AEs in the TCZ-treated group (27 patients, 17.0 %) (Table 2). None of the patients in this study were positive for anti-TCZ IgE antibodies. Only 1 patient who discontinued TCZ treatment for 35 weeks

Table 2 Adverse events observed after restarting TCZ treatment

Adverse event (SOC)	No. patients (%)
Total	70 (44.0)
Infections and infestations	27 (17.0)
Investigations	17 (10.7)
Gastrointestinal disorders	14 (8.8)
Skin and subcutaneous tissue disorders	12 (7.5)
Injury, poisoning and procedural complications	8 (5.0)
Respiratory, thoracic and mediastinal disorders	5 (3.1)
Nervous system disorders	3 (1.9)
General disorders and administration site conditions	3 (1.9)
Neoplasms benign, malignant and unspecified	2 (1.3)
Eye disorders	2 (1.3)
Vascular disorders	2 (1.3)
Musculoskeletal and connective tissue disorders	2 (1.3)
Blood and lymphatic system disorders	1 (0.6)
Immune system disorders	1 (0.6)
Ear and labyrinth disorders	1 (0.6)
Cardiac disorders	1 (0.6)
Reproductive system and breast disorders	1 (0.6)

SOC MedDRA Ver. 8.0 System Organ Class

became positive for anti-TCZ IgG antibodies 12 weeks after restarting TCZ treatment, and no decrease in the efficacy or any infusion reaction was observed in this patient. Moreover, no serious allergic reactions were reported in any patient.

One patient who discontinued TCZ treatment for 24 weeks experienced an infusion reaction 8 weeks after restarting TCZ therapy. The reactions included eruption, fatigue, and hypertension following the third infusion, but were mild and transient and did not require any treatment.

Three SAEs (1.9 %) were reported during retreatment with TCZ: appendicitis, wrist fracture, and chronic sinusitis. Causal relationships with TCZ were ruled out in the wrist fracture and chronic sinusitis.

Discussion

This study demonstrated that retreatment with TCZ was well-tolerated and effective in patients who had previously withdrawn from TCZ treatment. None of the patients in this study developed anti-TCZ IgE antibodies and only 1 patient tested positive for anti-TCZ IgG antibodies after restarting the TCZ treatment. Moreover, no serious allergic reactions were reported in any patient, including 3 patients retreated with TCZ after a long-term interval of more than 1 year. Our results confirm the results reported by Sagawa [16]. On the other hand, the development of serious

infusion reactions was reported in patients who had restarted IFX treatment after long-term cessation of IFX [17]. This difference between TCZ and IFX can be attributable to the fact that, whereas IFX is a chimeric monoclonal antibody, TCZ is humanised, which reduces the content of foreign protein and thus the potential for the development of neutralising antibodies or IgE antibodies.

Regarding the efficacy of restarting TCZ at recurrence of disease activity after the cessation of TCZ treatment, the DAS28-ESR remission rate at 12 weeks after restarting TCZ was 88.5 %, which is comparable to the remission rate at the last observation point before cessation of initial TCZ treatment in the DREAM study (90.4 %). This improvement in DAS28-ESR was induced not only by improvement in acute-phase reactions, but also by improvement in TJC and SJC: over 60 % of the TCZ-retreated patients had complete improvement in terms of TJC or SJC or both (TJC or SJC or both was zero) within 12 weeks of treatment. Moreover, the Boolean remission rate as newly recommended by ACR/EULAR [15] reached 43.9 % (69/157 patients) at week 12. This value was extremely high.

The ACR/EULAR treatment recommendations state that, in patients who achieve remission with biological products, it may be possible to taper off the biological product after tapering off the corticosteroid [18]. However, in the majority of patients who discontinue treatment with biologics, it is found that efficacy cannot be sustained without use of the biologics and that disease activity may increase [16, 19]. This fact indicates that after attempting discontinuation of treatment with a biologic DMARD, it is necessary to guarantee safety and the ability to resume efficacy when restarting treatment with the same DMARD. Our results clearly indicate that TCZ was well-tolerated and effective in the patients who resumed TCZ treatment.

MMP-3 is deeply involved in cartilage destruction in RA and is also correlated with disease activity [20]. Since normalisation of the MMP-3 level is thought to reflect inhibition of excessive cartilage and bone destruction in the joints, normalisation of the MMP-3 level may indicate an improvement in the underlying cause of RA as well as synovial inflammation. In this study, we did not examine the progression of joint damage by imaging after restarting TCZ. However, since the MMP-3 levels were quickly improved after TCZ retreatment, TCZ retreatment should be considered to control disease activities and potentially prevent joint destruction once disease activity increased after the cessation of TCZ treatment. Further study of changes in radiological progression will be necessary to validate the modality of TCZ treatment investigated in the DREAM/RESTORE studies.

In conclusion, our results indicate that TCZ retreatment was effective and well tolerated in patients in whom disease activity recurred after cessation of TCZ monotherapy. Our

results also indicate that, together with the results of the DREAM study, the treatment interval of TCZ can also be adjusted flexibly without attenuation of efficacy.

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