Successful extension of tocilizumab infusion intervals from 4 weeks to 5 or 6 weeks in 90% of rheumatoid arthritis patients with good response to 4-week intervals

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Abstract

Objective

A period of 4 weeks (w) has been recommended as the interval between tocilizumab (TCZ) infusions for rheumatoid arthritis (RA). However, treating the patients with TCZ (8 mg/kg), we experienced that longer intervals were also effective. We conducted the study to investigate whether the intervals of TCZ infusions could extend from 4w to 5 or 6w.

Methods

This was a retrospective observational study. RA patients who had shown good response to TCZ infusions at 4w intervals were enrolled, and the intervals of TCZ infusions were extended to 5w. Next, the intervals of TCZ infusion were extended to 6w for the patients who had maintained good response with 5w intervals. The patients who had maintained good response for more than two years were estimated as responders.

Results

One hundred patients were enrolled in the present study, and 62 patients maintained good response with 6w-interval infusions, and 28 patients with 5w-interval infusions, indicating that 90% of patients who had shown good response with 4w intervals could extend the intervals from 4w to 5 or 6w.

Conclusion

The present study provides evidence that most of RA patients who showed good response to TCZ infusions at 4w could extend the intervals to 6w or 5w. This finding should be of great interest for both financial and labour reasons.

Key words
rheumatoid arthritis, tocilizumab, extension of intervals

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterised by joint pain, stiffness and swelling due to synovial inflammation (1). Increased serum and synovial fluid levels of inflammatory cytokines correlate with disease activity in patients with RA (2). Interleukin 6 (IL-6) is one of the pleiotropic proinflammatory cytokines produced by multiple cell types, and it is known to be involved in diverse physiological processes (3). Thus, IL-6 inhibition represents a novel therapeutic approach in the treatment of RA.

Tocilizumab (TCZ) is a humanised anti--IL-6 receptor antibody that inhibits both soluble-expressed and membrane-expressed IL-6 receptors (4). TCZ has been demonstrated to have efficacy in active RA patients showing inadequate responses to oral medicines, such as disease-modifying anti-rheumatic drugs (DMARDs) (5). Several controlled trials employing TCZ infusions at intervals of 4 weeks (w) have provided evidence that TCZ induces a rapid reduction in disease activity, as measured by American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (5-7). All studies were carried out at 4w intervals and a dose of 8 mg/kg provided a marked clinical benefit (8). Therefore, the drug labelling and the therapy guidelines for TCZ recommend infusion every 4 weeks at a dose of 8 mg/kg (9).

However, the cost of biologics, including TCZ, is very high, which makes it difficult for all patients to receive biologics because of the associated expenses.

In our clinical experience, we found that TCZ infusions at longer intervals, especially 6w were also effective in many patients. The aim of the present study was to clarify that the intervals of TCZ infusion could extend from 4w to 5 or 6w.

Methods

This was a retrospective observational study which was conducted in accordance with Declaration of Helsinki and approved by the Ethics Committee of the Higashiosaka City General Hospital.

Patients

Among active RA patients who fulfilled the 2010 ACR/EULAR criteria for RA (10) and were treated at Higashiosaka City General Hospital, those showing inadequate response to DMARDs and/or biologics other than TCZ were infused TCZ 8 mg/kg every 4 weeks. The patients who had shown good response to TCZ infusion with 4w intervals for more than 1 year were enrolled in the present study. In the present study, the patients who have other DMARDs than MTX were excluded. Good response was estimated as DAS28 (Disease Activity Score in 28 joints) -CRP score less than 3.2 and DAS28 improvement over 1.2 (11). In the present study, we evaluated DAS28 by CRP (DAS28-CRP).

Study design

After obtaining consent for TCZ therapy every 5 or 6w intervals from the patients, intervals of TCZ infusions (8 mg/kg) were extended from 4w to 5w, along with prednisone (PSL, less than 5 mg/day) and/or methotrexate (MTX, less than 16 mg/w) without changing the doses. The doses of oral medicines were not changed throughout the observation periods. For the patients who could maintain low disease activity (LDA) with 5w of TCZ infusion for more than 6 month, the intervals were extended from 5 to 6w. The patients who maintained LDA to TCZ infusion at every 6w for more than two years were estimated as responders of 6w intervals (6w-responders). The patients who maintained LDA with 5w intervals but did not maintain LDA with 6w intervals were estimated as 5w-responders. The patients who maintained LDA with only 4w intervals were estimated as 4w-responders.

Collected patients clinical data and assessments

The clinical assessments and blood tests were performed each time at TCZ infusion (12). The following parameters were assessed: tender joint count, swollen joint count, physician and patient global assessments of disease activity, and C-reactive protein (CRP) levels. Disease activity was assessed

by DAS28 score and Clinical Disease Activity Index (CDAI). Radiological stage and functional class are defined by Steinblocker's classification (13).

Once the patients obtained LDA with TCZ infusion at 5w or 6w intervals, they were continued TCZ infusion without changing the intervals and the doses of oral medicines. After a 2-year follow-up study, we performed the clinical assessments, and we categorised the patients into 3 groups according to the intervals of TCZ infusion and the attainment of good response (6w-responders, 5w-responders, and 4w-responders). The patients who could not be followed for more than 2 years were considered as study drop-outs.

Statistical analysis

The association between demographic, clinical, serological and treatment variables was explored by the chi-square or Wilcoxon test based on the variable type.

Results

Successful extension of intervals of TCZ infusion from 4w to 5 or 6w

A total of 100 patients (28 males, 72 females) who had obtained LDA with TCZ (8 mg/kg) infusion at 4w intervals were enrolled in the present study. Initially, TCZ was infused at 8 mg/kg every 5w along with MTX and/or PSL without changing the doses. In 6 months, 93 patients maintained LDA with this protocol (Fig. 1). The rest of 7 patients did not maintain LDA at 5w intervals and were infused TCZ at 4w intervals. Six patients were estimated as 4w-responders and were infused TCZ infusions at 4w intervals, and one patient was dropped out. The 93 patients were infused TCZ at 6w intervals, and 62 patients maintained LDA with TCZ infusion for more than 2 years even at 6w intervals and were estimated as 6w-responders. The rest of 31 patients did not obtain LDA at 6w intervals, but 28 patients obtained LDA at 5w intervals and were estimated as 5w-responders, and three patients were dropped out. In total, four patients were dropped out during the study because of their personal reasons.

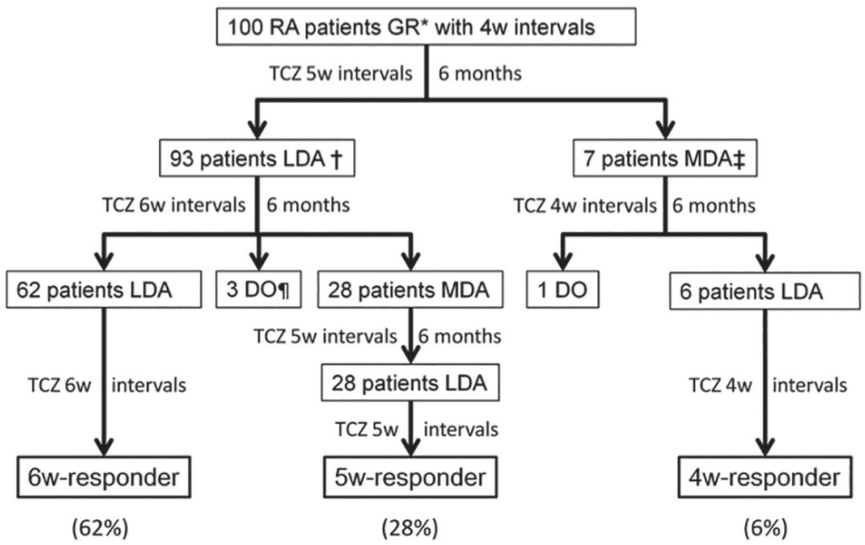

Fig. 1. Patient disposition and flow chart of the study.
The patient disposition and flow chart of the study were summarised. GR*, LDA†, and MDA‡ show EULAR good response, low disease activity, and moderate disease activity, respectively. DO¶ shows dropout patients.

Table I. Patients' baseline characteristics and demographics.

	6w-responders	5w-responders	4w-responders
Number (M/F)	62 (14/48)	28 (7/21)	6 (2/4)
Age (y)	61 ± 19	59 ± 22	63 ± 14
RA duration (y)	6.4 ± 5.6	5.9 ± 6.0	8.4 ± 7.7
BW (kg)	56 ± 12	54 ± 13	58 ± 12
ACPA/RF (%)	68/72	69/75	83/83
Basal DAS28CRP*	5.9 ± 1.6	6.1 ± 1.5	6.5 ± 1.9
Stage (I/II/III/IV)	6/23/15/18	4/7/8/9	1/2/1/2
Class (I/II/III/IV)	31/24/7/0	13/13/2/0	3/2/1/0
PSL (range, mg/day)	2.9 (0~5)	3.8 (0~5)	5.0 (5~5)
MTX (range, mg/w)	4.1 (0~8)	5.0 (0~12)	7.3 (4~16)
History of biologics¶	43/19/0	15/11/2	3/2/1
Time to optimisation†	2.4 ± 1.2	3.8 ± 2.3	6.2 ± 4.5

Values are given as mean ±SD.
*Basal DAS28-CRP was the basal activity data of patients before starting treatment with TCZ.
¶History of biologics was shown as follows, first/second/third, in each responder, and mean previous biologics before TCZ was 0.40.
†The mean months how long patients had been treated with TCZ prior to optimisation were shown. The mean treatment duration of TCZ prior to tapering was 2.2 years.
BW: body weight; ACPA: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; PSL: prednisone; MTX: methotrexate.

Clinical efficacy of TCZ infusion at 5 and 6w intervals

Among 100 patients enrolled, 62 patients were estimated as 6w-responders, 28 patients as 5w-responders, 6 patients as 4w-responders, and four patients dropped out during the study (Fig. 1). The results demonstrated that 96 patients completed the study, and 90 patients maintained LDA with TCZ infusion at 6 and 5w intervals. Moreover, among 100 patients who showed good response to TCZ infusion at 4w intervals, 62 patients could extend the intervals from 4w to 6w. On the other hand, only 6 patients required 4w as the intervals of TCZ infusions. These results suggest that the intervals of TCZ infusions are not always fixed at 4w in these patients.

Patient demographics and characteristics at baseline and after treatment

After we followed up 4, 5, and 6w-responders without changing the intervals

of TCZ infusion and the doses of oral medicines for two years, we compared the baseline demographics and clinical characteristics among them (Table I). The mean age, duration of RA, body weight, radiological stage and functional class were similar among the groups. However, the parameters of baseline disease activity, such as DAS28 and CRP levels, were significantly higher in 4w-responders than in the other groups. These parameters were slightly higher in 5w-responders than in 6w-responders. The mean time prior to optimisation was longer in 4w-responders than in 6 or 5w-responders. Moreover, basal activity data of patients before starting TCZ were higher in 4w-responders than in 5 or 6w-responders (Table I).

When we considered how many patients received TCZ as first biologics, 61 patients received TCZ as the first biologic, and 32 or 3 patients were received as second or third biologic, respectively (Table I). Mean previous biological drug was 0.40.

Next, we carried out clinical assessments before and after the study (Table II), and compared among 4w-, 5w-, and 6w-responders. Throughout the observation period, most patients maintained LDA. At the end of the study, however, DAS28 and CDAI scores and the levels of CRP were elevated slightly in 5w- and 6w-responders. Finally, at the end of the study, DAS28 scores became similar among the 3 groups.

These results suggest that the intervals of TCZ infusions might be extended from 4w to 5 or 6w in the patients who showed rather lower diseases activity at baseline.

Table II. Clinical assessments before and after the extension of TCZ intervals.

	6w-responders		5w-responders		4w-responders	
	baseline	end	baseline	end	baseline	end
CRP (mg/dl)	0.17	0.22	0.20	0.22	0.22	0.21
DAS28CRP	2.1	2.4	2.3	2.4	2.4	2.4
CDAI	4.7	6.4	5.6	6.0	6.8	5.9
VAS (mm)	12.2	18.0	15.0	14.8	19.0	18.8
Tender JC	1.2	1.5	1.4	1.6	1.5	1.5
Swollen JC	1.2	1.5	1.3	1.3	1.7	1.8

Patients' clinical assessments were examined before and after TCZ infusion. Values were given as mean. JC: joint count; VAS: visual analogue scale (0 mm ~ 100 mm) of patient global assessment of disease activity.

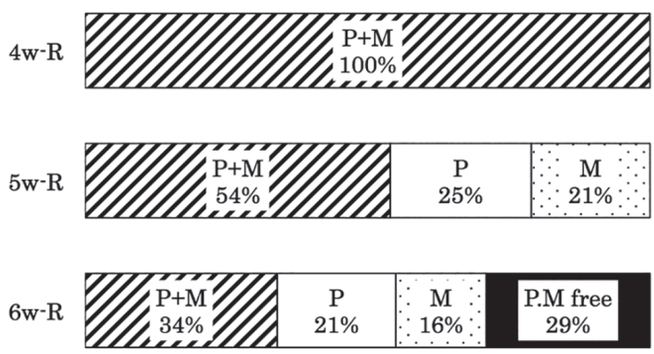

Fig. 2. Comparison of oral medicines (MTX and PSL) among three groups.
After maintaining good response with TCZ infusion for more than 2 years, we compared the number of patients who have no oral medicines (P.M free), PSL alone (P), MTX alone (M), and PSL plus MTX (P+M) among 6w-responders (6w-R), 5w-R, and 4w-R.

Comparison of the doses of oral medicines (MTX and PSL) between the three groups

After we followed up TCZ infusion at 5 and 6w intervals without changing the doses of oral medicines for more than 2 years, comparison of the doses of oral medicines was also carried out. The number of patients who had no oral medicines, PSL alone, MTX alone, and PSL plus MTX were compared between the three groups (Fig. 2). In the 6w-responders, 29% of the patients maintained LDA without oral medicines and 32% of patients with low dose of PSL (less than 5 mg/day) and MTX (less than 8 mg/week). In the 4 or 5w-responders, no patient was maintained LDA without oral medicines. In the 4w-responders, all the patients needed both PSL (5 mg) and MTX (4~16 mg).

These results showed that all patients with 4w-responders needed both PSL and MTX to maintain good response, but 29% of patients with 6w-responders showed LDA without PSL and MTX.

Discussion

Our results show that TCZ infusions at 6w and 5w intervals also maintain LDA in a majority (more than 90%) of RA patients who achieved good response to TCZ infusions at 4w intervals. In addition, more than 60% of the patients maintained LDA even at 6w intervals of TCZ infusion. This finding should be of great interest both for financial and labour reasons.

With regard to the intervals of TCZ infusion, 4w intervals have been recommended by TCZ therapy guidelines (9). However, we found that 5w and 6w intervals were also effective in a majority of the patients. This suggests that intervals for TCZ infusion can be extended to more than 4w.

The reasons why 5 and 6w intervals of TCZ infusion are effective in these patients are not clear at present. But we speculated that the serum TCZ levels increased immediately after TCZ infusion and decreased gradually thereafter. At 4w, TCZ levels were still detectable in the serum, moreover, the trough of serum TCZ levels continued to increase when TCZ was infused at 4w intervals (14). Thus, a period of more than 4w is required for TCZ to disappear from the blood, enabling 5w or 6w intervals of TCZ infusion.

In our preliminary study at more than 7w intervals of TCZ infusion, however, most of the patients could not maintain LDA, because the levels of CRP and DAS28 were elevated significantly at more than 7 weeks after TCZ infusion.

Next, we considered the reasons why the intervals of TCZ infusion to main-

tain good response differed among patients. In 6w-responders, the parameters of disease activity at baseline such as DAS28, CDAI, and the doses of oral medicines were significantly lower than those in 4w-responders, suggesting the intervals of TCZ infusions may depend on disease activity; therefore, we recommend 6w intervals of TCZ infusions to the patients who have rather low disease activity.

The disease activities before starting treatment of TCZ and at baseline of 6w- and 5w-responders were lower than those in 4w-responders. At the end of the study, however, the disease activity did not differ significantly among three groups, because the disease activities of 6w- and 5w-responders were elevated slightly when compared to those of baseline (Table II).

In the present study, the patients who had not maintained LDA were estimated as non-responders, and the dose of oral medicines were not increased throughout the study. In these patients, however, we believe that the dose escalation of oral medicines (PSL and MTX) might extend the intervals from 4w to 5w or 6w, suggesting that more patients could be extended the intervals of TCZ infusion from 4w.

In the present study, the doses of MTX were low, but it has generally been accepted that the effective MTX dose (less than 16 mg/w) in the Japanese population is extremely lower than that in the Caucasian population (15).

During the observation periods, 2 years, our results show that 5w and 6w intervals of TCZ infusion are effective in most of the RA patients. In these patients, however, 5w or 6w intervals of TCZ infusion were still effective in more than 2 years.

We showed hat the interval of TCZ infusion could be extended more than 4w in most patients but clinical evaluation of longer intervals such as radiographical effects remains to be clarified.

Finally, we have provided evidence of the efficacy of TCZ infusions at 5 and 6w intervals, suggesting that all patients may not need to receive TCZ infusions at 4w intervals.

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