Rapid improvement of the Clinical Disease Activity Index (CDAI) at 3 months predicts a preferable CDAI outcome at 1 year in active rheumatoid arthritis patients treated with tocilizumab: results from an observational investigation of daily clinical practice

S. Kawashiri[1,2], A. Nishino[2], T. Suzuki[2], Y. Nakashima[2], Y. Horai[2], Y. Ueki[3], T. Aramaki[3], K. Fujikawa[4], M. Nakashima[5], A. Okada[5], K. Migita[6], A. Mizokami[4], N. Matsuoka[7], M. Mine[8], S. Sakito[9], N. Iwamoto[2], K. Ichinose[2], M. Tamai[2], H. Nakamura[2], T. Origuchi[10], K. Aoyagi[1], K. Eguchi[11], A. Kawakami[2]

[1]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [2]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [3]Sasebo Chuo Hospital, Centre for Rheumatic Disease, Sasebo, Japan; [4]Department of Rheumatology, Isahaya General Hospital, Isahaya, Japan; [5]Department of Internal Medicine, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan; [6]Department of General Internal Medicine, NHO National Nagasaki Medical Centre, Omura, Japan; [7]Nagasaki Medical Hospital of Rheumatology, Nagasaki, Japan; [8]Suga Orthopaedic Hospital, Centre for Rheumatic Disease, Isahaya, Japan; [9]Department of Internal Medicine, Sadamatsu Hospital, Omura, Japan; [10]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [11]Sasebo City General Hospital, Sasebo, Japan.

Abstract

Objective

To investigate whether the Clinical Disease Activity Index (CDAI) at three months predicts a preferable CDAI outcome at one year in patients with active rheumatoid arthritis (RA) treated with tocilizumab (TCZ).

Methods

Seventy-eight RA patients in the Nagasaki Prefecture, Japan, whose disease activities at baseline were moderate to high as estimated by the CDAI and who had received 8 mg/kg of TCZ every four weeks, were consecutively enrolled in this study from April 2008 to March 2011. The association of the CDAI at three months with that at one year was examined by the Cochran-Armitage test. The variables at baseline and at three months that were predictive of remission or low disease activity (LDA) according to the CDAI at one year were assessed by logistic regression analysis.

Results

Most of the patients (40 out of 44: 91%), whose CDAI at three months showed remission or LDA continued to show remission or LDA at one year. Disease activity at three months significantly correlated with the frequency of LDA or remission at one year ($p<0.0001$). Logistic regression analysis revealed that only remission or LDA at three months as determined by the CDAI was predictive of remission or LDA at one year as determined by the CDAI (odds ratio 33.2, $p<0.0001$).

Conclusion

A preferable clinical outcome as estimated by the CDAI at one year in active RA patients treated with TCZ is predicted by the CDAI at three months, suggesting that the treat-to-target strategy carried out using the CDAI can be used in clinical practice in these patients.

Key words

tocilizumab, rheumatoid arthritis, Clinical Disease Activity Index, treat-to-target

Shin-ya Kawashiri, Ayako Nishino, Takahisa Suzuki, Yoshikazu Nakashima, Yoshiro Horai, Yukitaka Ueki, Toshiyuki Aramaki, Keita Fujikawa, Munetoshi Nakashima, Akitomo Okada, Kiyoshi Migita, Akinari Mizokami, Naoki Matsuoka, Masanobu Mine, Soko Sakito, Naoki Iwamoto, Kunihiro Ichinose, Mami Tamai, Hideki Nakamura, Tomoki Origuchi, Kiyoshi Aoyagi, Katsumi Eguchi, Atsushi Kawakami

Please address correspondence to:
Shin-ya Kawashiri, MD, PhD,
Department of Public Health,
Nagasaki University Graduate School of Biomedical Sciences,
1-7-1 Sakamoto,
Nagasaki 852-8501, Japan.
E-mail: shin-ya@hotmail.co.jp

Received on February 24, 2015; accepted in revised form on September 29, 2015.

Competing interests: none declared.

Introduction

It is evident that tocilizumab (TCZ) is effective for treating rheumatoid arthritis (RA), since TCZ significantly inhibits both clinical disease activity and the progression of radiographic damage irrespective of concomitant methotrexate (MTX) treatment (1-10). There are several indices for evaluating the clinical disease activity of RA, including the Disease Activity Score in 28 joints (DAS28), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). With regard to the evaluation of the clinical efficacy of TCZ, indices that do not involve C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR) such as the CDAI would be better than DAS28, since TCZ is able to directly inhibit acute inflammatory reactants (11). In fact, TCZ-treated patients with DAS28 remission but without CDAI remission had significantly higher swollen joint counts compared with patients with SDAI or CDAI remission (12).

A systematic review and expert opinion has raised the recommendations of an international task force to treat RA using a treat-to-target (T2T) strategy (13). This recommendation states that drug therapy should be adjusted at least every three months until the desired treatment target is reached (13). A clinical trial of certolizumab pegol in patients with RA found that improvement of DAS28 at three months predicts preferable clinical and radiographic outcomes at one year (14). In RA patients treated with TCZ in a clinical setting, a normalisation of CRP at three months was associated with the achievement of low disease activity (LDA) or remission as evaluated by the CDAI at one year (15). However, none of the previous investigations tried to determine whether rapid improvement of the CDAI at three months predicts a preferable CDAI state at one year in patients with RA treated with TCZ.

In the present study, we focused on active RA patients in a clinical setting and investigated numerous variables including CDAI at baseline or at three months to determine which is predictive of a preferable CDAI outcome at one year.

Patients and methods

RA patients

All RA patients included in the present study fulfilled the 2010 RA classification criteria (16). After the approval of TCZ in April 2008 in Japan, all patients from nine rheumatology centres in Nagasaki Prefecture (Nagasaki University Graduate School of Biomedical Sciences, Sasebo Chuo Hospital, Isahaya General Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, NHO National Nagasaki Medical Center, Nagasaki Harbor Medical Center City Hospital, Nagasaki Medical Hospital of Rheumatology, Suga Orthopaedic Hospital, and Sadamatsu Hospital) who began treatment with TCZ by March 2011, were consecutively registered in this study and were followed up every four weeks at the time of infusion. A total of 110 RA patients were observed for one year from the initial infusion of TCZ as we recently reported (10). In these 110 patients, we re-analysed 78 patients whose disease activities at baseline were moderate to severe as estimated by the CDAI and continued for 1 year in order to validate the T2T strategy in active RA patients treated with TCZ as stated in Fig. 1 of the manuscript of T2T (13, 17). This study was a retrospective observational study using anonymised information, and it also conformed to the standard TCZ treatment proposed by the Japan College of Rheumatology. Patients gave their informed consent to undergo the protocol, which was approved by the Institutional Review Board of Nagasaki University. TCZ was infused every 4 weeks at a dose of 8 mg/kg body weight.

Clinical and laboratory assessments

Disease activity was evaluated using the CDAI, the SDAI, and the DAS28. Functional assessment was evaluated by the Modified Health Assessment Questionnaire (MHAQ). We followed the criteria set by the EULAR for using the DAS28-ESR and the method recommended by Smolen and colleagues for using the CDAI and SDAI (18). High disease activity (HDA), moderate disease activity (MDA), LDA, and remission were defined in the present study by CDAI scores >22, ≤22, ≤10, and ≤2.8, respectively.

Table I. Demographic and clinical characteristics at baseline of the 78 RA patients.

	n=78
Age (years[a])	59. 6 ± 11.9
Gender (female; %)	87.2
Duration of disease (years [a])	11.0 ± 9.7
Steinblocker classification	
Stage (I/II/III/IV; %)	5 / 17 / 7 / 49
Class (1 / 2 / 3 / 4; %)	9 / 58 / 9 / 2
Concomitant MTX (%)	48.7
Concomitant GCs (%)	66.7
Previous TNF inhibitors (%)	64.1
Tender joint counts (n[a])	12.0 ± 7.6
Swollen joint counts (n[a])	5.9 ± 4.4
PtGA (mm[a])	51.5 ± 23.2
EGA (mm[a])	45.1 ± 21.8
Positivity of RF (%)	90.7
Positivity of ACPA (%)	90.9
CRP (mg/dL[a])	2.8 ± 3.4
ESR (mm/hr[a])	59.0 ± 34.1
DAS28-ESR[a]	5.82 ± 1.11
CDAI[a]	27.1 ± 12.0
SDAI[a]	29.6 ± 13.5
MHAQ[a]	0.8 ± 0.6

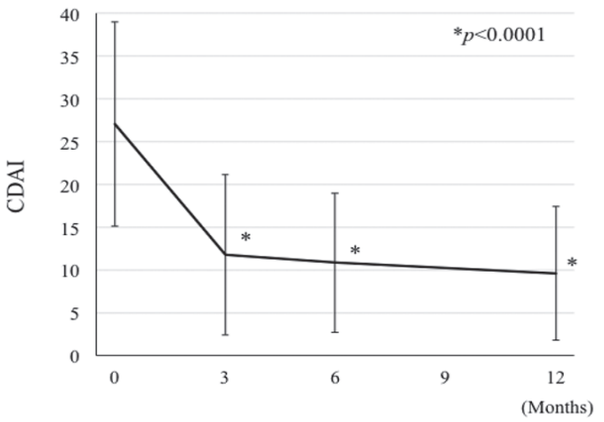
[a]Mean ± SD.
MTX: methotrexate; GCs: glucocorticoids; TNF: tumour necrosis factor; PtGA: patient's global assessment; EGA: evaluator's global assessment; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; DAS28: Disease Activity Score 28; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; MHAQ: Modified Health Assessment Questionnaire.

The following laboratory variables at baseline were assessed: CRP (Eiken Chemical Co. Ltd., Tokyo, Japan), erythrocyte sedimentation rate (ESR), rheumatoid factor (Dade Behring, Marburg, Germany; cut-off value, 14 IU/mL) and anti-cyclic citrullinated peptide antibodies (DIASTAT Anti-CCP, Axis-Shield, Dundee, UK; cut-off value, 4.5 U/mL).

Statistical analyses

The changes from baseline were compared using Wilcoxon's signed rank test. The associations of the CDAI at three months with the CDAI at one year were examined by the Cochran-Armitage test. We performed a logistic regression analysis to investigate the relationships of the variables at baseline and three months with the CDAI state at one year. For logistic regression analysis, we selected the variables p values less than 0.2 in Table II. NPAR-1WAY and REG in the SAS system®, version 9.2 (SAS Institute Inc., Cary, UC, USA) were used for the calculations. The overall significance level for statistical analysis was 5% (two-sided). *p*-values less than 0.05 were considered significant.

Fig. 1. Changes in the Clinical Disease Activity Index (CDAI) over the course of one year after the introduction of TCZ. The changes from baseline were compared using Wilcoxon's signed rank test. *$p<0.0001$.



Results

Demographic and clinical characteristics of 78 RA patients

The demographic and clinical characteristics of the 78 RA patients treated with TCZ are shown in Table I. The mean ± SD of the patients' ages was 59.6±11.9 years, and that of their disease duration was 11.0±9.7 years. Their disease activity was high, as shown by the means ± SD of the DAS28-ESR, SDAI, and CDAI: 5.82±1.11, 27.1±12.0, and 29.6±13.5, respectively. MTX was concomitantly administered in 38 patients (48.7%) with TCZ. Fifty patients (64.1%) had previously received tumour necrosis factor (TNF) inhibitors.

Clinical improvement in one year resulting from TCZ treatment

As shown in Figure 1, the mean of the CDAI values decreased significantly from 27.1 at baseline to 11.7 at three months, 10.8 at six months, and 9.6 at one year ($p<0.0001$ *vs*. baseline). The rates of remission, LDA, MDA, and HDA as defined by CDAI at one year were 10.3, 57.7, 23.0, and 9.0%, respectively.

LDA or remission estimated by the CDAI at three months predicted a preferable outcome at one year as estimated by CDAI

Forty out of the 44 patients (91%) whose CDAI at three months showed LDA or remission remained in LDA or remission at one year. In contrast, about half of the patients whose CDAI at three months showed MDA (12 out of 25: 48%), and only one of the nine patients (11%) whose CDAI at three months showed HDA, achieved remission or LDA at one year. The Cochran-Armitage test revealed significant correlations of the CDAI at three months with the frequency of LDA or remission at one year ($p<0.0001$). Table II shows the distribution of variables between RA patients who achieved LDA/remission at one year and those who remained in MDA/HDA at one year as estimated by the CDAI. As shown in Table II, the most remarkable difference was seen in the achievement of LDA or remission at three months, whereas no difference was observed in the CDAI at baseline, concomitant use of MTX, or previous use of TNF inhibitors. Also, it is interesting to note that there was no difference in CRP or ESR either at baseline or at three months (Table II). Logistic regression analysis revealed that only LDA or remission at three months as estimated by CDAI was predictive of LDA or remission at one year as estimated by CDAI (Table III) (odds ratio 33.2, $p<0.0001$).

Discussion

Our recent study found that low MHAQ at baseline predicted the state of remission estimated by CDAI or MHAQ at one year in TCZ-treated RA patients (10), indicating that baseline clinical indices were associated with the clinical outcome at one year in these patients. We re-analysed the same patient

Table II. Comparison of patient characteristics at baseline and three months between LDA and MDA/HDA patients at one year.

	LDA n=53	MDA/HDA n=25	*p*
Age (years[a])	59 (28-82)	67 (34-77)	0.04
Gender (female; %)	90.6	80.0	0.19
Duration of disease (years[a])	9.8 (0.3-53.0)	8.0 (0.9-29.9)	0.43
Concomitant MTX (%)	43.0	40.0	0.29
Concomitant GCs (%)	60.4	80.0	0.09
Previous TNF inhibitors (%)	62.3	68.0	0.62
Tender joint count (n[a])	11 (2-28)	10 (1-28)	0.72
Swollen joint count (n[a])	6 (0-23)	4 (1-16)	0.55
PtGA (mm[a])	46 (10-100)	60 (10-100)	0.07
EGA (mm[a])	40 (10-96)	50 (10-85)	0.18
Positivity of RF (%)	90.0	92.0	0.78
CRP (mg/dL[a])	1.4 (0-20)	2.5 (0.3-10.7)	0.14
ESR (mm/hr[a])	49 (5-134)	62 (4-116)	0.27
CDAI[a]	25.0 (10.0-58.0)	29.0 (10.5-51.5)	0.55
MHAQ[a]	0.6 (0-2.3)	0.9 (0-2.0)	0.38
CRP at three months (mg/dl[a])	0 (0-6.8)	0 (0-5.1)	0.88
ESR at three months (mm/hr[a])	8 (2-70)	11 (1-61)	0.22
LDA at three months (%)	75.5	16.0	<0.0001

[a]Median (range).
LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; MTX: methotrexate; GCs: glucocorticoids; TNF: tumour necrosis factor; PtGA: patient's global assessment; EGA: evaluator's global assessment; RF: rheumatoid factor; CDAI: Clinical Disease Activity Index; MHAQ: Modified Health Assessment Questionnaire.

Table III. Logistic regression analysis to estimate LDA induction by tocilizumab at one year.

	Odds ratio	95% CI		*p*
Age	0.97	0.92	1.04	0.46
Gender	0.69	0.13	3.65	0.66
Concomitant GCs	0.54	0.11	2.69	0.45
PtGA	0.98	0.94	1.03	0.40
EGA	1.02	0.97	1.07	0.43
CRP	1.06	0.86	1.30	0.60
LDA at three months	33.2	5.50	200	<0.0001

CI: confidence interval; LDA: low disease activity; GCs: glucocorticoids; PtGA: patient's global assessment; EGA: evaluator's global assessment.

population to select the patients whose clinical disease activity was moderate to high at baseline and who were eligible for biologic disease-modifying anti-rheumatic drugs (DMARDs) including TCZ (11).

In addition to the baseline characteristics, another critical clinical question is whether early clinical response predicts further clinical outcomes in active RA patients treated with TCZ. Since remission is sometimes difficult to achieve in clinical practice, the desirable outcome was defined as LDA or remission in the present study. The present study has shown for the first time that LDA or remission at three months is the only predictor of achieving LDA or remission at one year in TCZ-treated RA patients whose baseline disease activity is moderate to high. The present study includes the following important findings.

First, it is very interesting that of the baseline indices assessed, including CDAI, CRP, and ESR, only the CDAI at three months predicts a favourable outcome at one year. This may fit with the T2T strategy (13) and the recent 2013 update of the EULAR recommendations for the management of RA with synthetic and biological disease-modifying anti-rheumatic drugs (19), since the efficacy of TCZ can be predicted in a short period. This 2013 recommendation states that disease activity assessment should initially be done monthly to every three months, aiming at a significant improvement within three months and at achieving LDA or remission within six months.

Secondly, acute phase reactants such as CRP and ESR at three months did not predict the response at one year. Since TCZ significantly inhibited the increment of CRP or ESR, the decrement of CRP or ESR can be profound in TCZ-treated patients despite a lack of clinical improvement. In fact, the median level of CRP in both the LDA/remission group and the HDA/MDA group at three months was 0 mg/dl in the present study; therefore, the estimation of a patient's clinical state using CDAI is considered to be preferable in RA patients treated with TCZ. Kaneko *et al*. have reported an association between the normalisation of CRP at three months and the achievement of LDA or remission as estimated by CDAI at one year; however, they did not perform multivariate analysis (15). Also, the sample size was smaller (n=31) than in the present study (n=78). Recently, Pers *et al*. have reported that a high baseline CRP level is associated with EULAR response at 6 months toward French RA patients treated with TCZ (20), however, we did not find such association in the present study. The difference in baseline CRP level (% of the patients in CRP >1mg/dl: 44.4% in Pers *et al*. *vs*. 59.9% in the present study) might influence the results. The similarities between the two manuscripts are also found since younger age by multiple regression analysis and early EULAR response by univariate analysis are variables to associate with better DAS response at 6 months (20) that is pointed out in the present study (younger age by univariate analysis and early CDAI response by multiple regression analysis).

Thirdly, MTX use did not alter the efficacy of TCZ in clinical practice. Randomised controlled trials have shown that, compared with TCZ monotherapy, combination therapy with MTX failed to convey the superior clinical effects assumed by DAS28 or the American College of Rheumatology response criteria (8, 11). A retrospective study of clinical practice has shown that dose of MTX at baseline involves in DAS28 remission at one year in TCZ-treated patients (9). However, the dose of MTX did not af-

fect either structural remission or HAQ remission (9). French RA observational cohort also showed the similar results of TCZ-treated patients that MTX use did not influence the EULAR response at 6 months (20). Since the CDAI does not include APR, our present study appears to directly reflect the efficacy of TCZ, and the concomitant use of MTX may not influence TCZ efficacy greatly. Also, our present study may strengthen the earlier finding that TCZ should be recommended if the combination with MTX is contraindicated (11). However, we should understand in the present study that the selection bias including concomitant use of other DMARDs and the doses of MTX during the study might affect the results.

In conclusion, a preferable clinical outcome at one year as estimated by the CDAI in active RA patients treated with TCZ can be predicted by CDAI at three months, a finding that indicates the importance of using T2T strategies in these patients. These findings suggest that physicians should apply the CDAI to determine the efficacy of TCZ.

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