Original Article

Title:

The efficacy and safety of additional administration of tacrolimus in patients with rheumatoid arthritis who showed an inadequate response to tocilizumab

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Keywords (alphabetical order):

Biologics, Inadequate response, Rheumatoid arthritis, Tacrolimus, Tocilizumab

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This article contains 4 figures and 1 table.

No supports or benefits in any form have been received for this report.

Abstract

Objectives

Tocilizumab (TCZ) shows good retention in patients with rheumatoid arthritis (RA), but no previous reports demonstrated hopeful treatment options against inadequate response to TCZ. Tacrolimus (TAC) has proved to show efficacy against inadequate response to tumor necrosis factor alpha inhibitors, yet its add-on effects on TCZ remain unknown.

Methods

Twenty patients with RA (17 women, age 58.6 y, disease duration 12.1 y, prior TCZ duration 2.6 y, 18 intravenous [8 mg/kg/month] and 2 subcutaneous [324 mg/month] TCZ treatment, methotrexate 6.1mg/week [70.0%]) who showed an inadequate response to TCZ (clinical disease activity index [CDAI] ≥ 5.8, 18 secondary nonresponders) were additionally treated with TAC (1.1 mg/day), and enrolled in this 24-week, prospective study.

Results

Seventeen patients (85.0%) continued the treatment for 24 weeks. Statistically significant decreases in outcome measures were as follows: disease activity score based on 28 joints with C-reactive protein (DAS28-CRP) from 3.3 at baseline to 2.1 at week 24 ($P < 0.001$), CDAI from 17.7 to 7.6 ($P < 0.001$), and serum matrix metalloproteinase-3 levels from 232.8 to 66.2 ng/mL ($P < 0.001$). 15 patients (75%) achieved low disease activity or remission (DAS28-CRP ≤ 2.7 or

CDAI ≤ 10) at week 24.

Conclusions

Adding low-dose TAC to inadequate responders to TCZ may be a promising complementary treatment option.

Introduction

Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody of the IgG1 subclass directed at the IL-6R α chain. It was originally developed in Japan and has been widely used for the treatment of rheumatoid arthritis (RA) [1, 2] in clinical settings since 2008 in Japan, 2009 in Europe, and 2010 in the USA. Recently, the European League against Rheumatism (EULAR) announced a 2013 update to the 2010 recommendations for the management of RA with synthetic and biological DMARDs, in which TCZ is essentially considered to be as efficacious and safe as tumor necrosis factor alpha (TNF-α) inhibitors and should be considered as a first-line biologic agent [3]. In addition, we have previously demonstrated that TCZ therapy is associated with reduced serum oxidative stress levels [4] and may also promote osteoblast differentiation in patients with RA [5].

The EULAR recommendations support the use of all biological agents in combination with methotrexate (MTX) [3]. In patients with MTX contraindications or intolerance, TCZ may be considered as part of the first-line treatment strategy with biological agents [3]. Among all biological agents, only TCZ has been demonstrated to be superior as a monotherapy over MTX or other conventional DMARDs [1, 6]. In addition, TCZ is also effective and safe either with or without low-dose MTX for patients with active RA who inadequately respond to DMARDs and/or TNF-α inhibitors [7]. Therefore, TCZ tends to be chosen for patients who cannot tolerate

MTX in real-world setting.

However, there are some patients who experience lack of efficacy or loss of efficacy with TCZ. In such cases, the EULAR recommendations suggest changing TCZ to another biologic with another mode of action or add-on therapy with conventional DMARDs [3]. To date, however, we lack reliable evidence for choosing alternative treatments for individual patients with RA who previously had an inadequate response to TCZ, and frequent changes of biologics may lead to multiple biologic failures.

Tacrolimus (TAC) is an antibiotic that was isolated from the fungus *Streptomyces tsukubaensis* in Japan in 1984. In 1993, TAC was approved as a rejection inhibitor, and it is the most widely used immunosuppressive drug in the transplantation field globally. In 2005, it was also approved for use in RA, and the clinical efficacy of TAC as a single agent in RA has been reported [8, 9]. Moreover, the concomitant use of small doses of TAC has been shown to be effective when DMARDs [10] and TNF-α inhibitors have resulted in insufficient effects or in cases of secondary failure [11, 12]. Therefore, we hypothesized that adding TAC may be a hopeful complementary therapy for patients with an inadequate response to TCZ and examined the efficacy and safety in this 24-week, prospective study.

Patients and methods

All of the patients with RA included in this study fulfilled the 1987 classification criteria of the American College of Rheumatology [13]. TCZ was infused every 4 weeks at a dose of 8 mg/kg or subcutaneously injected every 2 weeks at a dose of 162 mg in accordance with drug labeling and the TCZ therapy guidelines of the Japan College of Rheumatology (JCR) [14]. Twenty patients who had an inadequate response to TCZ in four hospitals associated with the Osaka University Graduate School of Medicine participated in this prospective study from January 2012 to April 2015. An inadequate response to TCZ was defined as having all of the following conditions met: clinical disease activity index (CDAI) score > 2.8 [15, 16] when TAC was started; both tender joint count and swollen joint count were the same or increased compared to those at 4 to 8 weeks prior to TAC; and TCZ was used at same dose for at least 8 weeks prior to TAC. The patients were treated with TAC combination without changing the dosage of TCZ. Efficacy and safety were evaluated 8 weeks later, 16 weeks later, and 24 weeks later. This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethical review boards of the Osaka University Graduate School of Medicine (approval number, 11258) and informed consent was obtained from patients included in the study.

Evaluation of the activity of RA

Efficacy and safety were assessed by comparing changes in tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease activity (Pt-GA, 100 mm), physician's global assessment of disease activity (Ph-GA, 100 mm), serum C-reactive protein (CRP), serum matrix metalloproteinase-3 (MMP-3), white blood cell (WBC) count, lymphocyte count, and functional assessments according to the modified Health Assessment Questionnaire (mHAQ) scores [17] over time. Disease activity was assessed by measures including: disease activity score on 28 joints (DAS28) alone and with CRP (DAS28-CRP) [19], and CDAI score. DAS28-CRP was divided into four categories: remission ≤ (2.3), low disease activity (> 2.3 and ≤ 2.7), moderate disease activity (> 2.7 and ≤ 4.1), and high disease activity (> 4.1). CDAI was divided into four categories: remission (≤ 2.8), low disease activity (> 2.8 and ≤ 10), moderate disease activity (> 10 and ≤ 22), and high disease activity (> 22) [16]. Observation points were set to the following five time points: 4-8 weeks prior to the start of TAC, at the start of TAC, 8 weeks after the start of TAC (week 8), 16 weeks after the start of TAC (week 16), and 24 weeks after the start of TAC (week 24). Clinical responses were defined by EULAR response criteria [19] and also with the American College of Rheumatology (ACR) 20% improvement criteria [20]. Trough whole-blood TAC concentrations were monitored, and any adverse events during the follow-up period were also examined.

Statistical analysis

Longitudinal changes of each parameter before and after TAC administration for 24 weeks were examined by the Wilcoxon signed-rank test. Differences in variables between the DAS28-CRP moderate- or good-response group and the no-response group after 24 weeks of TAC administration were assessed by the Mann-Whitney U test or chi-square test. Statistical data are expressed as the mean ± standard deviation (SD), and P values of < 0.05 were considered statistically significant. All statistical analyses were carried out with IBM SPSS version 19 software (IBM, Armonk, NY, USA).

Results

Demographic data and drug therapy

Twenty patients (17 women) had inadequate responses to TCZ (2 primary non-responders and 18 secondary non-responders), and were then treated with add-on low-dose TAC (0.5–2 mg/day). Eighteen patients were treated with intravenous TCZ infusion, and two were treated with subcutaneous TCZ injection (Table 1).

Their mean age was 58.6 y (range, 40–73 y), and mean disease duration was 12.1 y (range, 1−25 y). Of all the patients, 80.0% were in Steinbrocker's stage III or IV, and 25.0% were in

functional class 3 or 4. Both the rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody were positive in 17 patients (85.0%). TCZ was introduced as the first biologic in 7 patients, and the remaining 13 were bio-switched. 5 patients were switched from infliximab (IFX) and etanercept (ETN), 2 patients from golimumab (GOL), and 1 patient from adalimumab (ADA). TAC was started at 2.6 years (0.3−5.1) after the initiation of TCZ. The mean dose and usage rates of combined MTX were 6.1 mg/week (0−16) and 70.0% at baseline, and 5.6 mg/week (0−16) and 65.0% at week 24. Likewise, those of PSL were 1.1 mg/day (0–6) and 30.0% at baseline, and 0.7 mg/day (0–5) and 20.0% at week 24, respectively. Only 2 patients (10.0%) received bucillamine (BUC) and 3 patients received salazosulfapyridine (SASP) at baseline. Three patients (15.0 %) were treated without any conventional DMARDs (MTX, BUC, and SASP). No significant changes in the mean dose and prescription rate of MTX, PSL, BUC, and SASP were observed throughout the study.

Retention rate and combined TAC dose

Among all of the patients, 17 (85.0%) continued the combination treatment until week 24. Two patients discontinued for lack of efficacy, and one for digestive symptoms. Mean daily dose of TAC was 1.1 mg/day (0.5−2.0) at baseline and 1.1 mg/day (0.5−2.0) at week 24, which wasn't significantly changed throughout the study.

Adverse effects

During the follow-up period, 1 patient developed leukopenia (< 3500/μL) and 3 patients developed lymphopenia (< 1000/μL), although no apparent signs of infection were observed. Serious adverse events that required medical intervention were not observed during the follow-up period.

Efficacy

Figs. 1, 2, and 3 show changes in clinical variables. The graphs include the data at 4-8 weeks prior to TAC initiation as representative data before an inadequate response to TCZ. The mean scores of DAS28-CRP were 2.6 ± 0.8 at 4−8 weeks prior to the start of TAC, 3.3 ± 0.8 at start of TAC, 2.4 ± 0.7 at week 8, 2.4 ± 0.9 at week 16, and 2.1 ± 0.6 at week 24 (Fig. 1a); the mean scores of CDAI were 11.5 ± 7.8, 17.7 ± 7.6, 9.6 ± 4.6, 8.9 ± 7.3, and 7.6 ± 4.4, for the same periods, respectively (Fig. 1b). The mean serum MMP-3 level was 175.1 ± 203.4 ng/mL, 232.8 ± 241.2 ng/mL, 85.6 ± 70.3 ng/mL, 82.0 ± 98.2 ng/mL, and 66.2 ± 39.7 ng/mL, for the same periods, respectively (Fig. 1c). The mean serum CRP level was 0.16 ± 0.46 mg/dL, 0.27 ± 0.73 mg/dL, 0.05 ± 0.06 mg/dL and 0.05 ± 0.08 mg/dL, 0.05 ± 0.06 mg/dL, for the same periods, respectively (Fig. 1d). All scores were significantly improved from 8 weeks after TAC treatment. The mean serum RF level was 154.5 ± 192.5 at baseline and 173.4 ± 252.0 at week 24, which

didn’t show significant change throughout the study.

The mean SJC was 3.3 ± 3.8 at 4−8 weeks prior to the start of TAC, 5.4 ± 4.0 at the start of TAC, 2.5 ± 2.7 at week 8, 1.6 ± 2.7 at week 16, and 1.4 ± 1.3 at week 24, respectively (Fig. 2a). The mean TJC was 2.2 ± 3.1, 2.7 ± 3.4, 1.4 ± 2.3, 2.2 ± 3.5, 1.2 ± 2.3, for the same periods, respectively (Fig. 2b). The mean Pt-GA was 42.1 ± 19.7, 54.8 ± 19.6, 36.4 ± 20.4, 35.0 ± 22.7, 29.5 ± 16.7, for the same periods, respectively (Fig. 2c). The mean Ph-GA was 31.5 ± 13.5, 45.4 ± 16.4, 24.2 ± 9.7, 19.6 ± 13.6, 18.9 ± 11.2, for the same periods, respectively (Fig. 2d). All of which declined over time after the start of TAC.

No significant differences in changes in the WBC and lymphocyte counts were observed from the initiation of TAC to after the initiation of TAC (Fig. 3a and b). The mean serum trough TAC concentration (ng/ml) was 3.2 ± 3.0 at week 8, 3.7 ± 3.7 at week 16, and 3.2 ± 3.1 at week 24, respectively (Fig. 3c). Only 10.0% (2/20) of patients obtained recommended reference value of serum trough TAC concentration (5.0 - 20.0 ng/ml) at week 24. However, 83.3% (10/12) of patients who showed lower serum trough TAC concentration than 5.0 ng/ml achieved low disease activity (CDAI≦10) at week 24. Improvements were also seen in physical function. The mean mHAQ score was 0.9 ± 0.4 at the start of TAC, which significantly improved to 0.5 ± 0.4 after 24 weeks of TAC therapy (Fig. 3d).

At week 24, 10 patients (50.0%) were in remission, five (25.0%) had low disease activity, and

two (10.0%) had moderate disease activity, except three (15.0%) who discontinued TAC based upon DAS28-CRP disease activity (Fig. 4a). In the same fashion, 14 (70.0%) had low disease activity, and three (15.0%) had moderate disease activity, except three patients (15.0%) who discontinued TAC based upon CDAI disease activity (Fig. 4b). At week 24, 12 of 19 (63.2%) patients achieved more than a moderate response according to the improvement criteria for response to treatment proposed by the EULAR (Fig. 4c). Percentages of patients who attained ACR 20 were 64.7%, 58.8%, and 70.6% at 8 weeks, 16 weeks, and 24 weeks, respectively (Fig. 4d).

Concerning the difference in the response to TAC between primary and secondary non-responders to TCZ, 100% (2/2) primary non-responders and 66.7% (12/18) secondary non-responders achieved low disease activity (CDAI≦10) at week 24. Likewise, difference in the response to TAC between bio-naïve and bio-switched patients, 57.1 % (4/7) bio-naïve and 76.9% (10/13) bio-switched patients achieved low disease activity (CDAI≦10) at week 24. There was no significant difference in the achievement ratio of low disease activity between the groups, respectively.

Discussion

Previously, Mori reported the efficacy of additional use of TAC after switching to TCZ in

patients who showed inadequate response to IFX, although the number of patients was only three, and also prior treatment was limited to IFX [21]. Recently, Ishida et al. reported the add-on effect of TAC in RA who showed inadequate response to biologics, although the ratio of TCZ was only 16.3%, and the clinical results were not distinguished between each biologics [22]. Taken together, this may be the first prospective report that focused on the safety and efficacy of additional treatment with TAC in a constant number of patients with RA, who showed an inadequate response to TCZ.

The efficacy might be explained by several mechanisms. Firstly, TAC forms a complex with FK506 binding protein 12 (FKBP-12), which in turn binds to calcineurin, blocking its activity. This process suppresses T-cell and B-cell activation, the production of antibodies by B cells [23], and also the production of pro-inflammatory cytokines such as TNF-α and IL-6 by activated T cells [24, 25]. This process may synergistically suppress the production of pro-inflammatory cytokines with TCZ and may also inhibit the production of autologous antibodies against biologics, which may lead to loss of efficacy [26]. Secondly, TAC also suppresses IL-6−induced inflammatory processes such as up-regulation of the receptor activator of NF-κB ligand (RANKL) in fibroblast-like synoviocytes, by up-regulation of a suppressor of cytokine (SOCS3) signaling and consequent down-regulation of IL-6/Janus activated kinase (JAK2)/signal transducer and an activator of transcription-3 (STAT3) [27]. Moreover, TAC has

been proved to inhibit nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 (NFATc1) signaling and consequent osteoclasts differentiation [28]. TAC add-on therapy may enhance or restore the anti-inflammatory and anti-bone resorption effects of TCZ through these mechanisms. Thirdly, the long-term use of conventional DMARDs can result in a gradual decrease in their primary effects, such as “escape phenomenon” [29]. It has been reported that P-glycoprotein, which exports steroids and immunosuppressants from inside the target cells and mitigates their therapeutic effects, are induced when the transcription of multidrug resistance-1 is induced [30]. By contrast, calcineurin inhibitors, such as TAC, bind to P-glycoprotein antagonistically, preventing drug export from target cells [30-32]. From these mechanisms, TAC may also restore the effects of other combined conventional DMARDs or glucocorticoids. Concerning the effective dose and serum concentration of TAC, the prescription dose of TAC was relatively small (1.1mg/day; range 0.5-2mg/day), and only 10.0% (2/20) of patients obtained the reference value of serum trough TAC concentration (5.0 - 20.0 ng/ml) at week 24. However, 83.3% (10/12) of patients who showed lower serum trough TAC concentration than 5.0 ng/ml achieved low disease activity (CDAI≦10) at week 24. Taken together, lower serum TAC concentration than reference value may suffice for rescuing inadequate response to TCZ. Naniwa et al. [12] demonstrated the efficacy of additional TAC (1.5–2 mg/day) in patients with RA who were resistant to TNF-α inhibitors in combination with MTX. Recently, the efficacy

and safety of the combination of abatacept and TAC have been reported [33, 34]. Taken together, TAC seems to be a realistic therapeutic option in the treatment of active RA, especially for patients who cannot tolerate MTX and have an inadequate response to biologics.

There are several limitations to this study. First, this study lacks control group such as adding-on other DMARDs and is not a randomized comparative study. Second, leukopenia, lymphopenia, and consequent infection is major concerns when combining immunosuppressive agents, and the rates of these adverse effects might have been underestimated due to the small numbers of patients and short durations of follow-up. Third, precise mechanisms explaining how add-on TAC restores the efficacy of TCZ, even in low serum concentration, could not be specifically elucidated and should be evaluated in further studies. Fourth, whether this combination therapy consequently protects the joints from radiographic damage should be evaluated in large-cohort, longer-duration, randomized studies.

In conclusion, the results of this prospective study demonstrate that additional use of TAC can be considered as an effective complementary therapy for TCZ-refractory RA patients, especially those with intolerance to MTX.

Conflict of interest

No authors have any conflicts of interest.

Figure Legends

Figure 1. Changes in clinical variables for all patients

Mean values of (a) DAS28-CRP, (b) CDAI, (c) MMP-3, (d) CRP; *bars* indicate SD.

* P < 0.05, ** P < 0.01, *** P < 0.001

IR, inadequate response; TCZ, tocilizumab; DAS28-CRP, disease activity score assessing 28 joints with CRP; CDAI, clinical disease activity index; MMP-3, matrix metalloproteinase-3; CRP, C-reactive protein

Figure 2. Changes in clinical variables for all patients

Mean values of (a) SJC, (b) TJC, (c) Pt-GA, (d) Ph-GA; b*ars* indicate SD.

* P < 0.05, ** P < 0.01, *** P < 0.001

IR, inadequate response; TCZ, tocilizumab; SJC, swollen joint count; TJC, tender joint count; Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's global assessment of disease activity

Figure 3. Changes in clinical variables for all patients

Mean values of (a) WBC count (cells/μl), (b) lymphocyte count (cells/μl), (c) serum trough

TAC concentration (ng/ml), and (d) mHAQ; *bars* indicate SD.

* P < 0.05, ** P < 0.01, *** P < 0.001

IR, inadequate response; TCZ, tocilizumab; WBC, white blood cell; TAC, tacrolimus; mHAQ, modified Health Assessment Questionnaire

Figure 4. Changes in distribution of disease activity and clinical responses

(a) Distribution of disease activity at the time of TAC initiation, 8 weeks, 16 weeks, and 24 weeks after TAC initiation; disease activity was defined using DAS28-CRP scores as follows: remission, DAS28-CRP ≤ 2.3; low disease activity, 2.3 < DAS28-CRP ≤ 2.7; moderate disease activity, 2.7 < DAS28-CRP ≤ 4.1; high disease activity, 4.1 < DAS28-CRP.

(b) Distribution of disease activity at the time of TAC initiation, 8 weeks, 16 weeks, and 24 weeks after TAC initiation; disease activity was defined using CDAI scores as follows: remission, CDAI ≤ 2.8; low disease activity, 2.8 < CDAI ≤ 10; moderate disease activity, 10 < CDAI ≤ 22; high disease activity, 22 < CDAI.

(c) Response to treatment according to the EULAR criteria at the time of TAC initiation, 8 weeks, 16 weeks, and 24 weeks after TAC initiation.

(d) Response to treatment according to the ACR 20% criteria at the time of TAC initiation, 8 weeks, 16 weeks, and 24 weeks after TAC initiation.

TAC, tacrolimus; DAS28-CRP, disease activity score assessing 28 joints with CRP; CDAI, clinical disease activity index; ACR20, American College of Rheumatology 20% improvement criteria

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Table

Table 1. Baseline characteristics of 20 patients

Gender	17 females, 3 males
Age (years)	58.6 ± 9.3 (40-73)
Body weight (kg)	53.3 ± 5.8 (42.8-63)
Steinbrocker' s stage (n)	Stage Ⅰ 1 Ⅱ 3 Ⅲ 5 Ⅳ 11
Steinbrocker' s functional class (n)	Class Ⅰ 5 Ⅱ 10 Ⅲ 5 Ⅳ 0
Duration of disease (years)	12.1± 6.9 (1-25)
Duration of TCZ treatment (years)	2.6 ± 1.6 (0.3-5.1)
Formulation of TCZ	i.v. 18, s.c. 2
Type of TCZ failure (n)	2 primary non-responders, 18 secondary non-responders
Prior use of biologics (n)	7 bio-naïve, 13 bio-switched IFX(5) ETN (5) GOL (2) ADA (1)
MTX dose (mg/week), usage (% patients)	6.1 ± 5.0 (0-16), 70.0%
PSL dose (mg/day), usage (% patients)	1.1 ± 2.0 (0-6), 30.0%
BUC dose (mg/day), usage (% patients)	22.2 ± 64.7 (0-200), 10.0%
SASP dose (mg/day), usage (% patients)	147.1 ± 343.0 (0-1000), 15.0%
RF positivity, n/N (%)	17/20, 85.0%
ACPA positivity, n/N (%)	17/20, 85.0%
DAS28-CRP	3.2 ± 0.8 (1.8-4.8)
SJC (swollen joint count), 0-28	4.8 ± 3.9 (1-16)
TJC (tender joint count), 0-28	2.6 ± 3.2 (0-14)
CRP (mg/dL)	0.26 ± 0.71 (0.01-2.92)
Pt-GA (0-100 mm)	54.9 ± 22.0 (10-95)
Ph-GA (0-100 mm)	44.1 ± 18.2 (8-85)
CDAI	17.2 ± 7.5 (5.8-38.5)
MMP-3 (ng/mL)	215.1 ± 226.1 (24.6-771)
WBC count (cells/μl)	6799 ± 3559 (2840-17700)
Lymphocyte count (cells/μl)	1418 ± 608 (621.6-2534.4)

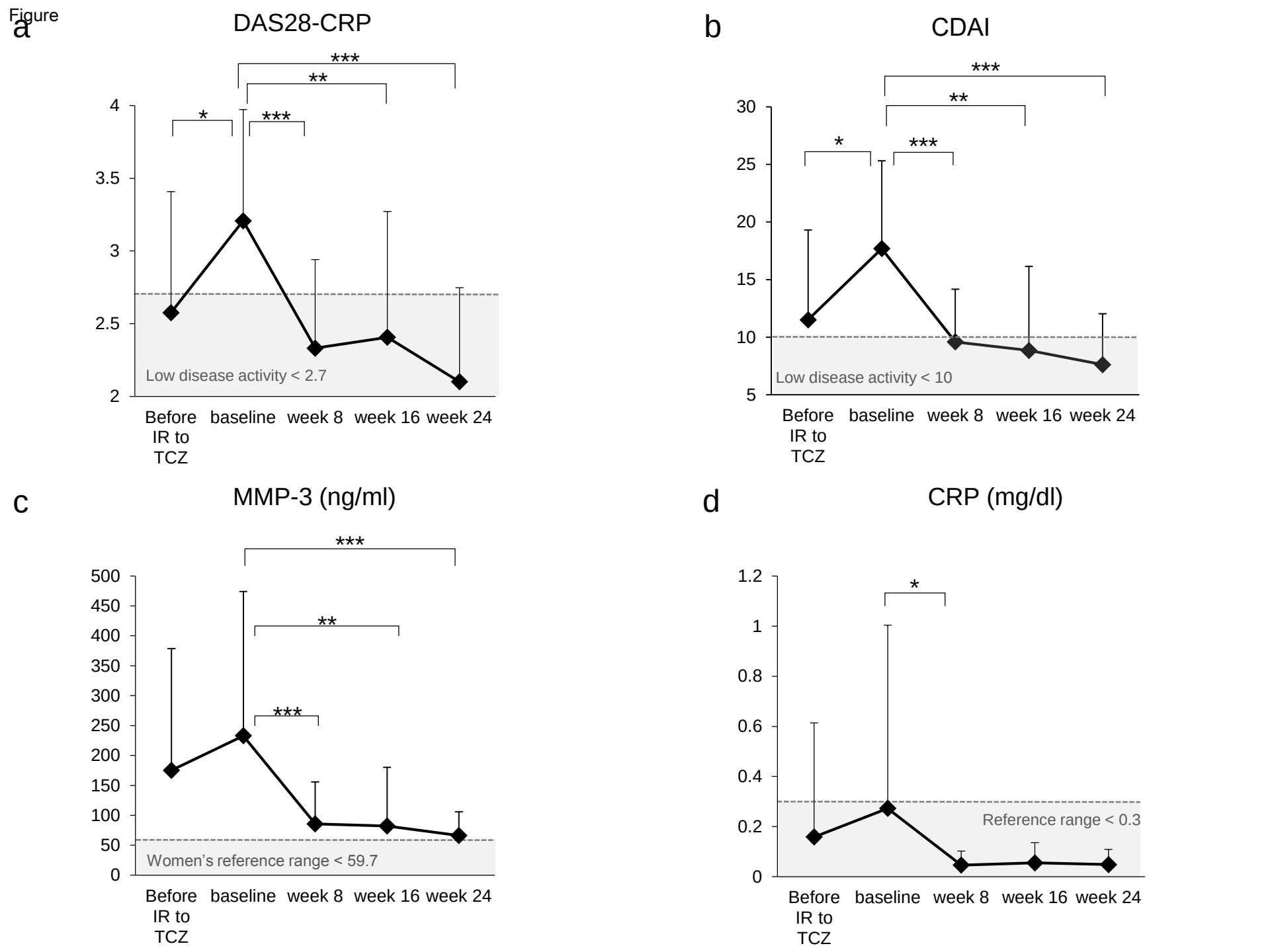
Data are expressed as mean ± SD.

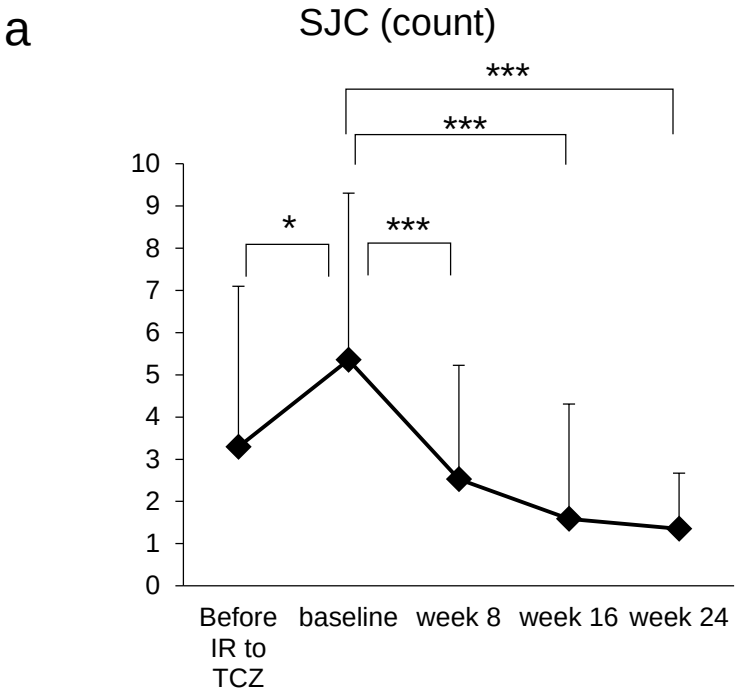
TCZ, tocilizumab; i.v., intravenous; s.c., subcutaneous; IFX, infliximab; ETN, etanercept; GOL,

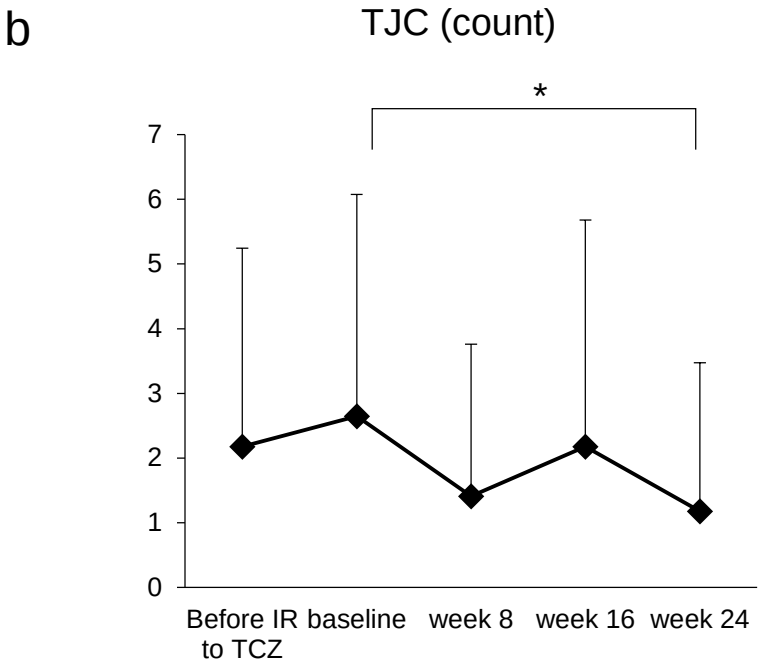
golimumab; ADA, adalimumab; MTX, methotrexate; PSL, prednisolone; BUC, bucillamine; SASP, salazosulfapyridine; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide (anti-CCP) antibody; CRP, C-reactive protein; DAS28-CRP, disease activity score assessing 28 joints with CRP, SJC, swollen joint count; TJC, tender joint count; Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's global assessment of disease activity; CDAI, clinical disease activity index; MMP-3, matrix metalloproteinase-3; WBC, white blood cell

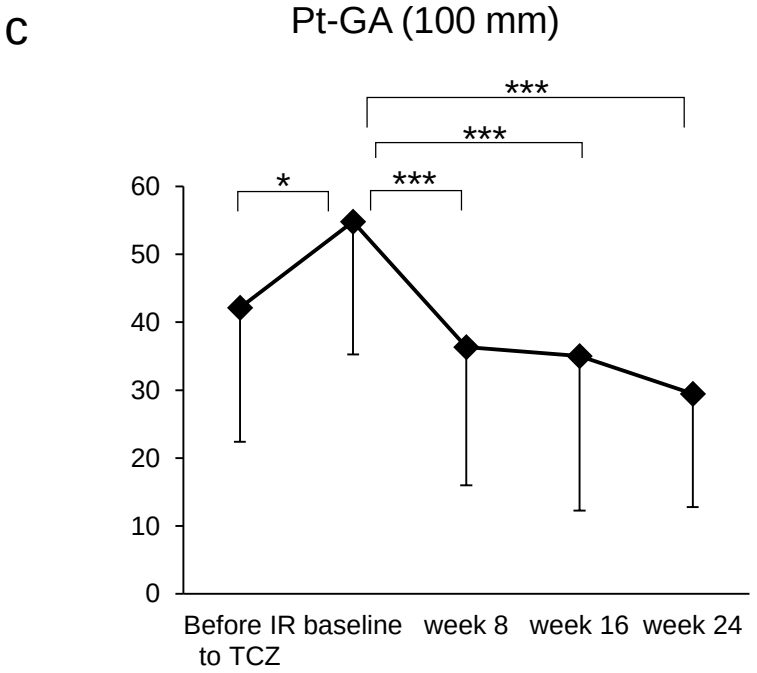
n/*N* (%) = number of patients with measurements/total number of patients (%)

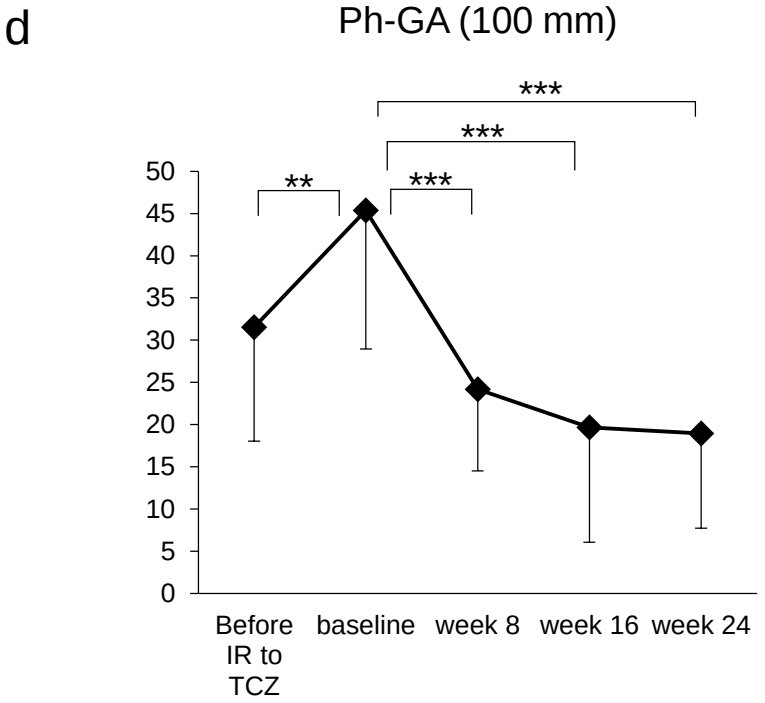
Figure


a
DAS28-CRP
***
**
*
***
4
3.5
3
2.5
2
Low disease activity < 2.7
Before IR to TCZ
baseline
week 8
week 16
week 24
b
CDAI
***
**
*
***
30
25
20
15
10
5
Low disease activity < 10
Before IR to TCZ
baseline
week 8
week 16
week 24
c
MMP-3 (ng/ml)
***
**
***
500
450
400
350
300
250
200
150
100
50
0
Women's reference range < 59.7
Before IR to TCZ
baseline
week 8
week 16
week 24
d
CRP (mg/dl)
*
1.2
1
0.8
0.6
0.4
0.2
0
Reference range < 0.3
Before IR to TCZ
baseline
week 8
week 16
week 24

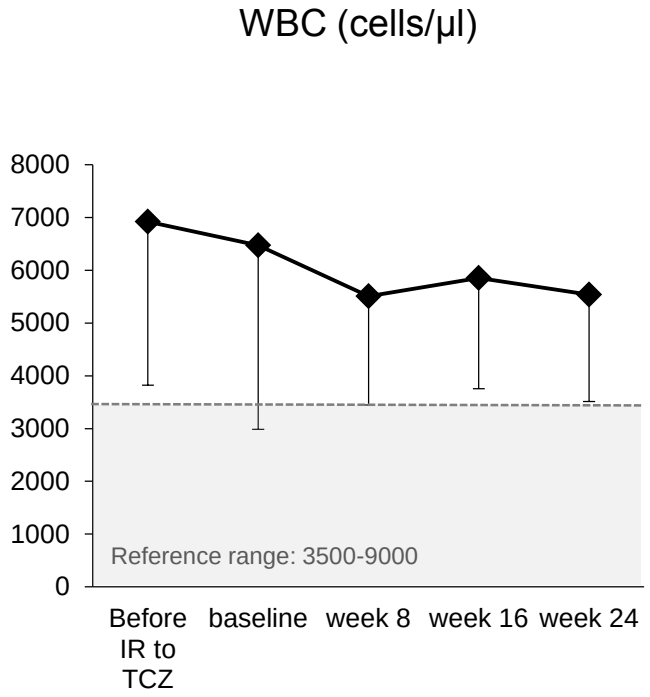

a
SJC (count)
***
***
*
***
10
9
8
7
6
5
4
3
2
1
0
Before IR to TCZ
baseline
week 8
week 16
week 24


b
TJC (count)
*
7
6
5
4
3
2
1
0
Before IR to TCZ
baseline
week 8
week 16
week 24

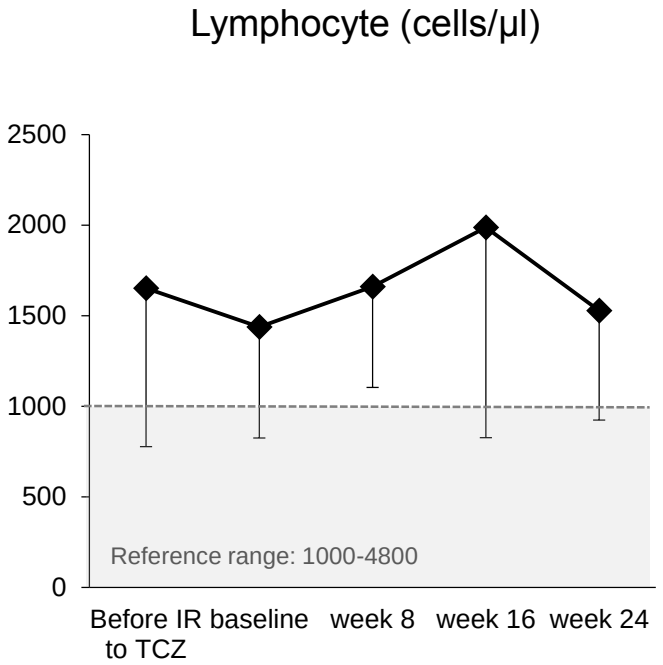

c
Pt-GA (100 mm)
***
***
*
***
60
50
40
30
20
10
0
Before IR to TCZ
baseline
week 8
week 16
week 24


d
Ph-GA (100 mm)
***
***
**
***
50
45
40
35
30
25
20
15
10
5
0
Before IR to TCZ
baseline
week 8
week 16
week 24

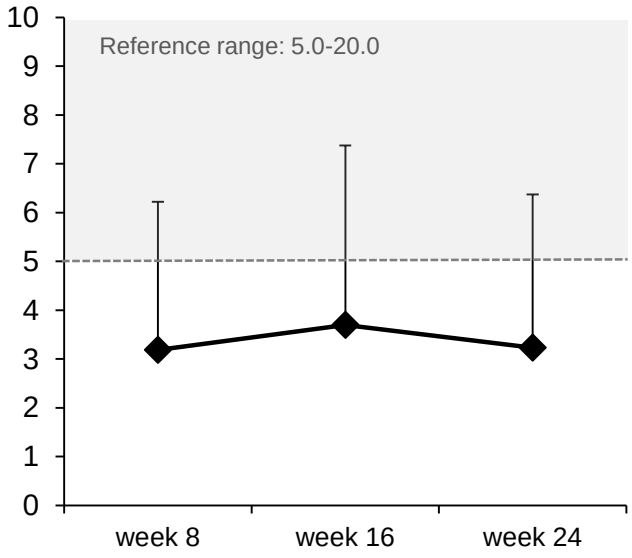
a


WBC (cells/μl)
8000
7000
6000
5000
4000
3000
2000
1000
0
Reference range: 3500-9000
Before IR to TCZ
baseline
week 8
week 16
week 24

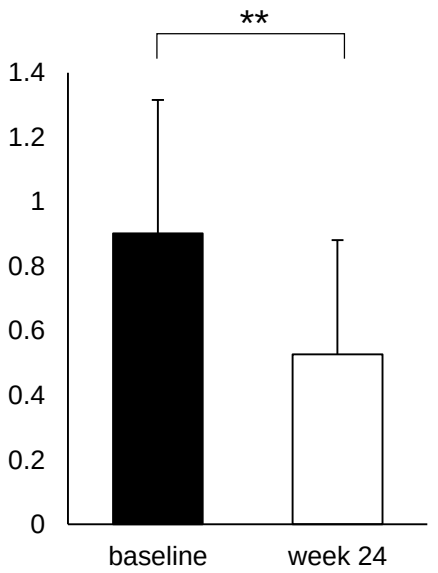
b


Lymphocyte (cells/μl)
2500
2000
1500
1000
500
0
Reference range: 1000-4800
Before IR to TCZ
baseline
week 8
week 16
week 24

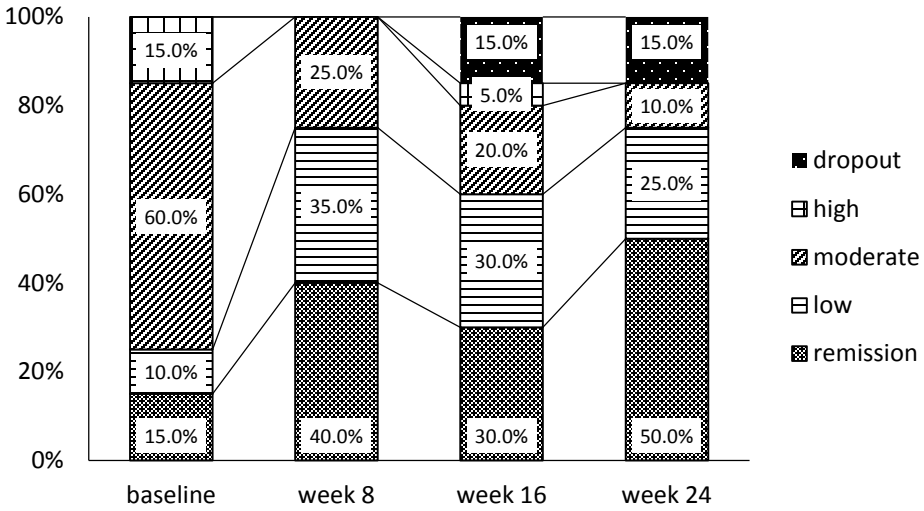
c


Trough TAC concentration (ng/ml)
10
9
8
7
6
5
4
3
2
1
0
Reference range: 5.0-20.0
week 8
week 16
week 24

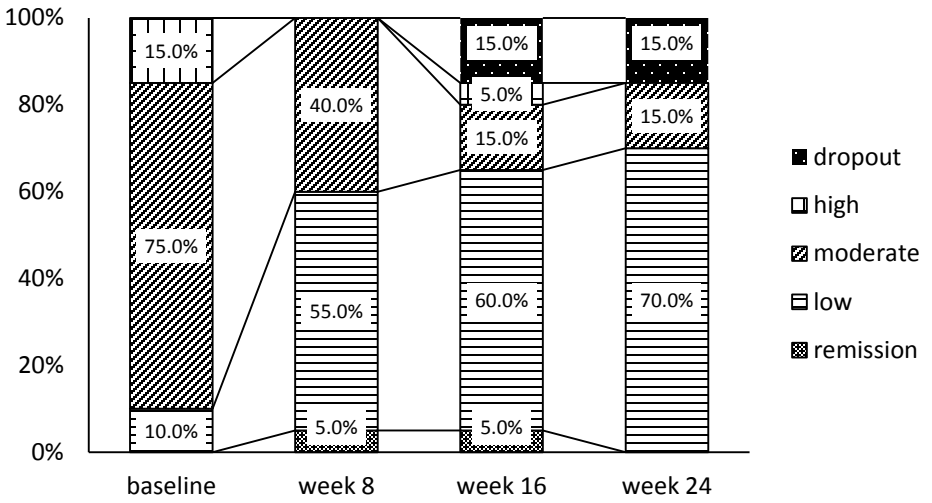
d


mHAQ
**
1.4
1.2
1
0.8
0.6
0.4
0.2
0
baseline
week 24

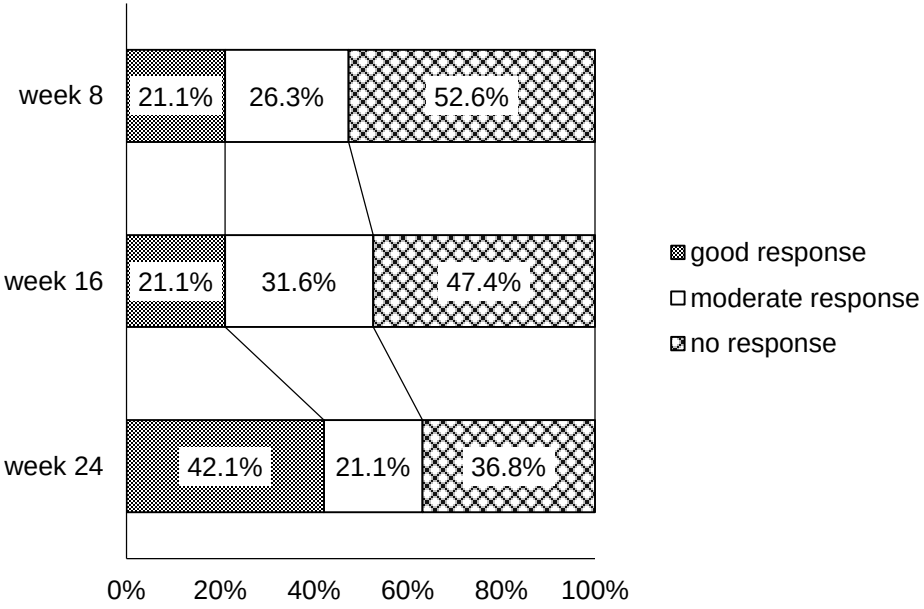
a Distribution of DAS28-CRP disease activity



b Distribution of CDAI disease activity



c Response to treatment according to the EULAR criteria



d ACR 20 response rate