Original Article

Title:

The add-on effectiveness and safety of iguratimod in patients with rheumatoid arthritis who showed an inadequate response to tocilizumab

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__This article contains 4 figures and 1 table.__

__Funding:__

The authors declare they have no specific funding for this study.

Abstract

Objectives

To evaluate the effectiveness of add-on iguratimod (IGU) in patients with rheumatoid arthritis (RA) who showed an inadequate response to tocilizumab (TCZ), especially patients who were intolerant of an effective dose of methotrexate (MTX).

Methods

Thirty-one patients with RA (22 women, age 62.4 years, disease duration 13.8 years, prior TCZ duration 35.7 months, 25 intravenous [8 mg/kg/4 weeks] and 6 subcutaneous [162 mg/2 weeks] TCZ treatments, concomitant MTX 8.5 mg/week [35.5%], and prednisolone (PSL) 4.3 mg/day [25.8%]) who showed an inadequate response to TCZ (disease activity score assessing 28 joints with C-reactive protein [DAS28-CRP] 2.9, clinical disease activity index [CDAI] 15.0, 28 secondary inadequate responders) were treated with additional IGU (final dose 41.7 mg/day) and enrolled in this 24-week, multicenter, retrospective study.

Results

Twenty-nine patients (93.5%) continued the treatment for 24 weeks (1 dropped out for pneumonia and 1 for digestive symptoms). TCZ and the concomitant dose and rate of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (MTX, salazosulfapyridine, and tacrolimus) were not significantly changed during this period. Outcome

measures improved significantly, as follows: DAS28-CRP from 2.9 to 1.7 ($P < 0.001$); CDAI from 15.0 to 6.0 ($P < 0.001$); modified Health Assessment Questionnaire from 0.8 to 0.6 ($P < 0.05$); and rheumatoid factor from 382.1 to 240.3 IU/mL ($P < 0.001$). Using the EULAR criteria, 64.5% achieved a moderate response, and 51.6% achieved ACR 20 at 24 weeks.

Conclusions

Adding IGU to inadequate responders to TCZ may be a promising and safe complementary treatment option.

Keywords:

Iguratimod, Inadequate response, Rheumatoid arthritis, Tocilizumab

Introduction

Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that has been widely used for the treatment of rheumatoid arthritis (RA) [1, 2]. The European League against Rheumatism (EULAR) announced a 2016 update to the 2013 recommendations for the management of RA, in which TCZ is considered as efficacious and safe as tumor necrosis factor alpha (TNF-α) inhibitors, and it should be considered as a first-line biological disease-modifying antirheumatic drug (bDMARD) [3]. Although the EULAR recommendations support the use of all bDMARDs in combination with methotrexate (MTX), TCZ is recommended as one of the first-line bDMARDs in patients with contraindications or intolerance to MTX [3, 4]. This depends on the evidence that, among all bDMARDs, only TCZ was shown to be superior as monotherapy over MTX or other conventional synthetic DMARDs (csDMARDs) [1, 5]. In addition, TCZ also showed good efficacy and retention either with or without MTX for RA patients who responded inadequately to csDMARDs and/or TNF-α inhibitors [6].

However, some patients show an inadequate response to TCZ. In such cases, the EULAR recommendations indicate changing TCZ to another bDMARD with another mode of action or add-on therapy with csDMARDs [3, 4]. To date, however, there is no reliable evidence for choosing alternative bDMARDs or adding-on specific csDMARDs other than MTX for patients

who previously had an inadequate response to TCZ.

Iguratimod (IGU), also known as T-614, is a novel csDMARD that was introduced in clinical settings in 2012 in Japan. Via inhibition of nuclear factor-kappa B (NF-κB), IGU inhibits the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, IL-17, TNF-α, and interferon-γ, in vitro (in synovial cells and monocytic cell lines) and in vivo [7-12]. In addition, IGU inhibits IL-6-induced IL-17 and matrix-metalloprotease 3 (MMP-3) expressions in human synovial fibroblasts from patients with RA [13], and also reduces immunoglobulin (Ig) production by human B lymphocytes [14]. Concerning combination therapy with bDMARDs, only one study demonstrated the effects of add-on IGU in patients who showed inadequate responses to bDMARDs, mainly TNF-inhibitors [15].

Thus, we hypothesized that adding IGU may be a promising complementary therapy for patients with an inadequate response to TCZ, especially in patients who are intolerant to an adequate dose of MTX, and the effectiveness and safety of this combination therapy were examined in this 24-week, multicenter, retrospective study.

Methods

Patients

All of the patients participated in this study fulfilled the following criteria; 1) meet the 1987 RA

classification criteria of the American College of Rheumatology [16]; 2) patients who showed an inadequate response to TCZ followed by additional administration of IGU from February 2014 to August 2017 in four hospitals associated with the Osaka University Graduate School of Medicine; 3) patients who could follow up at least 24 weeks after IGU administration, were retrospectively selected without any other selection bias. Finally, thirty-one patients participated in this retrospective study. TCZ was injected subcutaneously every 2 weeks at a dose of 162 mg or infused every 4 weeks at a dose of 8 mg/kg in accordance with drug labeling and the TCZ therapy guidelines of the Japan College of Rheumatology (JCR) [17]. An inadequate response to TCZ was defined as having all of the following conditions, according to the previous report [18]; 1) TCZ was used at the same dose for at least 8 weeks prior to IGU induction; 2) clinical disease activity index (CDAI) score > 2.8 (more than low disease activity) [19, 20] at IGU induction; 3) either tender joint count and swollen joint count more than 6, or the same or increased compared to those at 4 to 8 weeks prior to IGU induction. Primary non-responder was defined as patients who showed inadequate response to TCZ within 3 months after initiation, and secondary non-responder as more than 3 months after initiation. The patients were treated with IGU 25 mg/day at baseline, and it was then increased to 50 mg/day depending on each physician's decision, without changing the dosage of TCZ. Effectiveness and safety were evaluated at 8, 16, and 24 weeks after IGU induction.

Main outcome variable and study factors

Disease activity was assessed by monitoring serum C-reactive protein (CRP), serum matrix metalloproteinase-3 (MMP-3), rheumatoid factor (RF). Other parameters such as white blood cell (WBC) count, lymphocyte count, estimated glomerular filtration rate (eGFR), and liver function parameters (AST and ALT) were also monitored. As for composite measures, the 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), disease activity score of 28 joints (DAS28) with CRP (DAS28-CRP) [21], and the clinical disease activity index (CDAI) score were evaluated over time. As for physical disability, the modified Health Assessment Questionnaire (mHAQ) scores [22] were also monitored. The missing data was less than 2.6% for all parameters, respectively.

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) [20]. Observation points were set to the following five time points: 4-8 weeks prior to the start of IGU (before IR); at the start of IGU (baseline); 8, 16, and 24 weeks after the start of IGU. Clinical responses were defined by

the American College of Rheumatology (ACR) 20% improvement criteria [23] and EULAR response criteria [21]. All adverse events occurring during the follow-up period were also examined.

Procedures

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethical review board of the Osaka University Graduate School of Medicine (approval number, 15300). The board waived the requirement for patients' informed consent by showing the information on the homepage of the institute and also because of the anonymous nature of the data.

Statistical analysis

Longitudinal changes of each parameter before and after IGU administration at each time point were examined by the Wilcoxon signed-rank test or chi-squared test. The data of patients who dropped out from this combination therapy was calculated as missing value. Statistical data are expressed as means ± standard error (SE), and P values < 0.05 were considered significant. All statistical analyses were carried out with IBM SPSS version 19 software (IBM, Armonk, NY, USA).

Results

Demographic data and concomitant medications

Patients' clinical characteristics at baseline and 24 weeks are shown in Table 1. Thirty-one patients (22 women) had inadequate responses to TCZ, and they were then treated with add-on IGU [mean dose 25 mg/day at baseline and 41.7 mg/day (20 patients were treated by 50 mg/day) at 24 weeks. Their mean age was 62.4 years, and disease duration was 13.8 years. IGU was started at 35.7 months after the initiation of TCZ. Twenty-five patients were treated with intravenous TCZ infusion (8 mg/kg/month), and 6 were treated with subcutaneous TCZ injection (162 mg/2 weeks). TCZ was introduced as the first biologic in 14 patients, and 17 were bio-switched. With respect to concomitant csDMARDs, mean dose and usage rates of combined MTX were 8.5 mg/week (0-12) and 35.5% at baseline, and 8.0 mg/week (0-12) and 35.5% at 24 weeks, respectively. There were 20 patients without MTX combination, and the reasons assessed by each attending physician were history of interstitial pneumonia (n=7), renal dysfunction (n=3), digestive symptom by MTX (n=3), history of malignancy (n=3), liver dysfunction (n=2), history of MTX-associated lymphoproliferative disorders (n=1), and allergic to MTX (n=1), respectively. Likewise, 4 patients (12.9%) received tacrolimus (TAC), and 3 patients (9.7%) received salazosulfapyridine (SASP). No significant changes in the mean doses

and prescription rates of MTX, TAC, and SASP were observed throughout the study. No patients were treated by other csDMARDs. On the other hand, the mean dose of PSL (usage rate of 25.8% throughout this period) was significantly decreased from 4.3 mg/day (0-5) at baseline to 2.3 mg/day (0-5) (P = 0.036) at 24 weeks.

Adverse events

Of all of the patients, 29 (87.1%) continued the combination treatment until 24 weeks. One patient discontinued due to pneumonia, and 1 discontinued for digestive symptoms. During the follow-up period, 2 patients (6.5%) developed leukopenia (< 3500/μL) and lymphopenia (< 1000/μL), and 3 patients (9.7%) showed levels of AST (maximum 71 U/L) and ALT (maximum 149 U/L) exceeding the reference values, although these patients could continue the combination treatment by decreasing IGU or other concomitant csDMARDs or PSL. No significant changes were observed in the mean WBC, lymphocyte count, eGFR, and liver function parameters (AST and ALT) throughout the study.

Effectiveness

Fig. 1 shows the longitudinal changes in laboratory parameters. The data at 4-8 weeks prior to IGU initiation are shown as representative data before an inadequate response (IR) to TCZ. The

mean serum CRP level (mg/dL) (Fig. 1a), MMP-3 level (ng/mL) (Fig. 1b), and RF level (IU/mL) (Fig. 1c) significantly improved from 8-16 weeks after IGU treatment.

Fig. 2 shows longitudinal changes in clinical variables associated with disease activity. The mean TJC (Fig. 2a), SJC (Fig. 2b), Pt-GA (Fig. 2c), and Ph-GA (Fig. 2d) significantly improved from 8 weeks after IGU treatment.

Fig. 3 a-b shows longitudinal changes in composite measures of disease activity. The mean DAS28-CRP (Fig. 3a) and CDAI (Fig. 3b) significantly improved from 8 weeks after IGU treatment. As for physical function, the mean mHAQ score significantly improved after 24 weeks of IGU therapy (Fig. 3c).

Fig. 4 shows longitudinal changes in disease activity distribution and treatment response. Based on DAS28-CRP, 58.1% of patients had moderate or high disease activity at baseline, which decreased to 6.5% at 24 weeks (Fig. 4a). With the CDAI, 67.7% of patients had moderate or high disease activity at baseline, which decreased to 12.9% at 24 weeks (Fig. 4b). The patients with high disease activity (CDAI>22) at baseline tended to achieve lower rate of low disease activity (CDAI≤10) at 24 weeks compared to the patients with lower than moderate disease activity (CDAI≤22) at baseline (60.0 vs. 84.6%; P=0.20), although didn't reach statistical significance.

Concerning the EULAR treatment response, 51.6% of patients showed a moderate response at 8

weeks, which increased to 64.5% at 24 weeks, although no patients reached good response during this period (Fig. 4c). Finally, the percentages of patients who achieved ACR 20 were 32.3%, 45.2%, and 51.6% at 8 weeks, 16 weeks, and 24 weeks, respectively (Fig. 4d).

With respect to the difference in baseline backgrounds between EULAR moderate responder (n=20) and non-responder (n=9), responder group showed higher baseline DAS28-CRP (3.2 vs. 2.1; P<0.001) and CDAI (18.0 vs. 9.0; P<0.001) compared to non-responder group. This may be partially because EULAR treatment response correlates with the decreased amount of DAS28-CRP. Of note, responder group was treated with higher dose of TCZ compared to non-responder group (447.0 vs. 375.3 mg/4 weeks; P=0.01), suggesting add-on IGU may be more effective when combined with higher dose of TCZ.

In regards to the response to IGU between with and without MTX combination, MTX-combination group (n=11) tended to show higher rate of low disease activity (CDAI≤10) (90.9 vs. 75.0%; P=0.28), EULAR moderate response (72.7 vs. 60.0%; P=0.48), and ACR20 (54.5 vs. 45.0%; P=0.61) compared to non-MTX-combination group (n=20) at 24 weeks, although didn't reach statistical significance.

Concerning the difference in the response to IGU between primary and secondary non-responders to TCZ, 100.0% (3/3) of primary non-responders and 78.6% (22/28) of secondary non-responders achieved low disease activity (CDAI≤10) at 24 weeks. Likewise,

85.7% (12/14) of bio-naïve and 76.5% (13/17) of bio-switched patients achieved low disease activity (CDAI≤10) at 24 weeks. There was no significant difference in the rate of achieving low disease activity between the groups.

Discussion

To the best of our knowledge, this is the first study to investigate the efficacy and safety of adding IGU to RA patients who showed an inadequate response to TCZ. It has been reported that formation of anti-drug antibodies (ADAs) against bDMARDs is strongly linked to subtherapeutic serum drug levels and lack of clinical response [24]. To minimize the immunogenicity and likelihood of ADA formation of bDMARDs, high drug dosing, short interval administration, and combination with csDMARDs are advocated [24]. However, concerning TCZ, the proportion of ADA development following TCZ-SC or TCZ-IV treatment was relatively low (1.5% and 1.2%, respectively), and ADA development was not associated with loss of efficacy, suggesting the low immunogenicity of TCZ [25]. From these observations, the precise mechanisms of the inadequate response to TCZ still remain unclear, unlike for TNF-inhibitors. However, a recent study demonstrated that, in patients with an inadequate response to TCZ-SC every other week, shortening the dosing interval to every week improved efficacy with acceptable tolerability, suggesting that inadequate response to TCZ may be

partially due to a lack of drug dosing [26], although adding doses and shortening intervals of TCZ is sometimes associated with an increased risk of infection, as well as the economic burden [26].

Concerning concomitant csDMARD medications with TCZ, post-marketing surveillance demonstrated that the combination with MTX was a positive indicator, while the combination with PSL was a negative indicator of EULAR good response achievement [27]. In addition, we have previously reported the efficacy and safety of adding low-dose TAC in patients with RA who showed an inadequate response to TCZ [18]. In this study, patients were treated at a relatively low rate (35.5%) and dose (8.5 mg/week) of MTX, and a low rate (12.9%) and dose (2.0 mg/day) of TAC, which did not change significantly throughout the study. This may be due to the patients' background characteristics and comorbidities. In such situations, adding IGU showed good efficacy and retention in those with an inadequate response to TCZ.

The efficacy of adding-on IGU to TCZ might be explained by several mechanisms. First, previous reports demonstrated that IGU inhibited IL-1 beta and IL-6 production from a lipopolysaccharide (LPS)-stimulated human monocytic cell line [11], and it also inhibited NF-κB activation and TNF-α production from a rat macrophage cell line [8]. Moreover, a recent report showed that IGU markedly decreased IL-6-induced IL-17 and MMP-3 levels in synovial fibroblasts from RA patients, as well as MTX [13]. These mechanisms may synergistically

enhance the anti-inflammatory effects of TCZ, especially those who are not tolerant to an adequate dose of MTX. In addition, IGU inhibited immunoglobulin production by cultured B cells and decreased the high level of human IgG observed in mice engrafted with human RA tissue [14], which may had led to the significant decrease of the serum RF titer in the present study. Bloom et al. demonstrated that IGU selectively inhibits macrophage migration inhibitory factor (MIF) both *in vitro* and *in vivo*, which may synergistically enhance the effect of glucocorticoids, leading to its steroid-sparing effects, suggesting the reason for the significant decrease in the PSL dose in the present study [28].

Concerning pain reduction, IGU inhibits cyclooxygenase-2, which provides a synergistic short-term action against pain and inflammation [29], and a recent report showed that IGU exerts an anti-allodynic effect in the rat model of neuropathic pain [30], which may also have contributed to the rapid decrease in tender joints in the present study.

Concerning bone metabolism, we have previously demonstrated that IGU stimulates osteoblastic differentiation in vitro and in vivo [31]. Moreover, IGU decreased RANKL expression in IL-6-induced RA synoviocytes [13], and it inhibited ovariectomy-induced osteoclastogenesis and bone loss by inhibiting RANKL signaling (PPAR-γ/c-Fos pathway) [32]. These positive effects on bone metabolism may contribute to the inhibition of bone erosion, although they should be confirmed in further human studies.

There are several limitations to this study. First, this study lacked a control group, such as adding-on other DMARDs, and was not a randomized, comparative study. Second, side effects such as infection, liver dysfunction, and cutaneous symptom may be major concerns when combining IGU and TCZ, and these adverse effects might have been underestimated due to the small numbers of patients and the short duration of follow-up. Third, 4 patients (12.9%) were started to add-on IGU within 6 months after TCZ initiation, and the effects of IGU may be overestimated in such cases. Fourth, relatively high rate of comorbidities (such as interstitial pneumonia and renal dysfunction) and low rate of MTX combination may affect the results. Fifths, whether this combination therapy protects the joints from radiographic damage should be evaluated in prospective, randomized, large-cohort, and longer-duration studies.

In conclusion, the results of this retrospective study demonstrated that add-on use of IGU can be considered an effective complementary therapy for TCZ-refractory RA patients, especially those who are intolerant of an effective dose of MTX or other csDMARDs such as TAC, or TCZ loading.

Conflict of interest

K.E., M.H., and H.Y. received research grants from Astellas, Daiichi Sankyo, Eisai, and Mitsubishi Tanabe. K.E. received speaker fees from Abbvie, Astellas, Asahi-Kasei, Chugai,

Daiichi Sankyo, Eli Lily, Eisai, Mitsubishi Tanabe, Ono Pharmaceutical, and UCB Japan. H.T. received speaker fees from Chugai, Mitsubishi Tanabe, Bristol-Myers Squibb and Eisai, and received research grants from Chugai and Ayumi. S.K. received speaker fees from Bristol-Myers Squibb, Chugai, Otsuka, and Takeda. M.N. received travel fees from Abbie. H.O. received speaker fees from Bristol Meyers, Ayumi and Chugai, and moderator fees from Astellas, Phyzer, Abbvie, Mitsubishi Tanabe, Bristol Meyers and Eisai. S.T. received speaker fees from Abbvie, Asahi-Kasei, Chugai, Daiichi Sankyo, Eli Lily, Eisai, Mitsubishi Tanabe, Celgene and Novartis Pharma K.K. M.H. received speaker fees from Astellas, Bristol Mayers, Pfizer, Ono Pharmaceutical, and UCB Japan. J.H. received speaker fees from Astellas, Asahi-Kasei, Ayumi, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eli Lily, Eisai, Hisamitsu, Mitsubishi Tanabe, MSD, Taisho-Toyama, and Teijin Pharmaceuticals. A.M., Y.E., A.G. declare they have no conflict of interest.

Figure Legends

Figure 1. Changes in clinical laboratory variables at each time point following iguratimod initiation.

Mean values of (a) CRP, (b) MMP-3, and (c) RF. * P < 0.05, ** P < 0.01, *** P < 0.001. Bars indicate standard error. IR, inadequate response; CRP, C-reactive protein; MMP-3, matrix metalloproteinase-3; RF, rheumatoid factor.

Figure 2. Changes in clinical variables at each time point following iguratimod initiation.

Mean values of (a) TJC, (b) SJC, (c) Pt-GA, and (d) Ph-GA. * P < 0.05, ** P < 0.01, *** P < 0.001. Bars indicate standard error. IR, inadequate response; TJC, tender joint count; SJC, swollen joint count; Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's global assessment of disease activity.

Figure 3. Changes in composite measures of disease activity and physical disability at each time point following iguratimod initiation.

Mean values of (a) DAS28-CRP, (b) CDAI, and (c) mHAQ. * P < 0.05, ** P < 0.01, *** P < 0.001. Bars indicate standard error. IR, inadequate response; DAS28-CRP, disease activity score assessing 28 joints with C-reactive protein; CDAI, clinical disease activity index; mHAQ,

modified Health Assessment Questionnaire.

Figure 4. Changes in distribution of disease activity and clinical responses at each time point following iguratimod initiation.

(a) Distribution of DAS28-CRP. Disease activity was defined as follows: 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).

(b) Distribution of CDAI. Disease activity was defined as follows: remission (≤ 2.8); low disease activity (> 2.8 and ≤ 10); moderate disease activity (> 10 and ≤ 22); and high disease activity (> 22).

(c) Response to treatment according to the EULAR criteria.

(d) Response to treatment according to the ACR 20% criteria.

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

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Table

1 **Table 1. Patients' clinical characteristics at baseline and at 24 weeks**

Variable	Baseline	24 weeks
Gender	22 females, 9 males	
Age (years)	62.4 ± 2.0 (40-82)	
Body weight (kg)	55.4 ±1.9 (41.0-85.0)	
Duration of disease (years)	13.8± 1.9 (1-46)	
Steinbrocker' s stage (n)	Stage Ⅰ(3) Ⅱ(7) Ⅲ(6) Ⅳ(15)	
Steinbrocker' s functional class (n)	Class Ⅰ(19) Ⅱ(9) Ⅲ(3) Ⅳ(0)	
RF positivity, n/N (%)	26/31 (83.8%)	
ACPA positivity, n/N (%)	29/31 (93.5%)	
Duration of TCZ treatment (months)	35.7 ± 5.6 (2-101)	
Formulation of TCZ	i.v. (25), s.c. (6)	
Type of TCZ failure (n)	3 primary, 28 secondary	
Prior use of biologics (n)	14 bio-naïve, 17 bio-switched IFX(6) ETN (6) ABT(3) ADA (1) GLM (1)	
IGU dose (mg/day)	25.0 ± 0.0	41.7 ± 2.2***
MTX dose (mg/week), usage (% patients)	8.5 ± 0.8 (0-12), 35.5%	8.0 ± 0.7 (0-12), 35.5%
PSL dose (mg/day), usage (% patients)	4.3 ± 0.4 (0-5), 25.8%	2.3 ± 0.2 (0-5)*, 25.8%
SASP dose (mg/day), usage (% patients)	1000 ± 0.0 (0-1000), 9.7%	1000 ± 0.0 (0-1000), 6.5%
TAC dose (mg/day), usage (% patients)	2.0 ± 0.1 (0-3), 12.9%	2.0 ± 0.1 (0-3), 12.9%
CRP (mg/dL)	0.21 ± 0.09 (0.02-2.05)	0.03± 0.00 (0.02-0.06) **
MMP-3 (ng/mL)	217.7 ± 39.8 (30.5-1128)	106.5 ± 12.9 (26.6-281)***
RF (IU/mL)	382.1 ± 103.0 (3.6-1805.1)	240.3 ± 92.6 (0-1126.4)***
WBC count (cells/μl)	6278 ± 421 (2280-11300)	5237 ± 247 (2970-7600)
Lymphocyte count (cells/μl)	1577 ± 144 (446-3794)	1525 ± 102 (451-2660)
eGFR (ml/min/1.73 m^2)	69.8± 4.5(23.4-136.0)	63.7± 4.1(21.1-118.8)
AST (IU/L)	23.7± 0.9(14-32)	24.7±1.4 (11-49)
ALT (IU/L)	20.5± 1.4(10-30)	23.0±2.0 (9-55)
SJC (swollen joint count), 0-28	4.4± 0.8 (0-18)	1.9 ± 0.6 (0-16)***
TJC (tender joint count), 0-28	1.8 ± 0.4 (0-12)	0.4 ± 0.1 (0-4)***
Pt-GA (0-100 mm)	48.8 ± 4.2 (5-85)	23.7 ± 2.8 (3-50)***

Ph-GA (0-100 mm)	38.9 ± 3.4 (5-75)	13.8 ± 1.7 (3-40)***
DAS28-CRP	2.9 ± 0.2 (1.6-4.7)	1.7 ± 0.1 (0.6-2.8)***
CDAI	15.0 ± 1.4 (2.0-34.5)	6.0 ± 0.8 (2.0-22.9)***

Data are expressed as mean ± standard error (range).

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

RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide (anti-CCP) antibody; TCZ, tocilizumab; i.v., intravenous; s.c., subcutaneous; IFX, infliximab; ETN, etanercept; ABT, abatacept; ADA, adalimumab; GLM, golimumab; MTX, methotrexate; PSL, prednisolone; SASP, salazosulfapyridine; TAC, tacrolimus; CRP, C-reactive protein; MMP-3, matrix metalloproteinase-3; WBC, white blood cell; eGFR, estimated glomerular filtration rate; 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; DAS28-CRP, disease activity score assessing 28 joints with CRP; CDAI, clinical disease activity index.

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

Figure 1

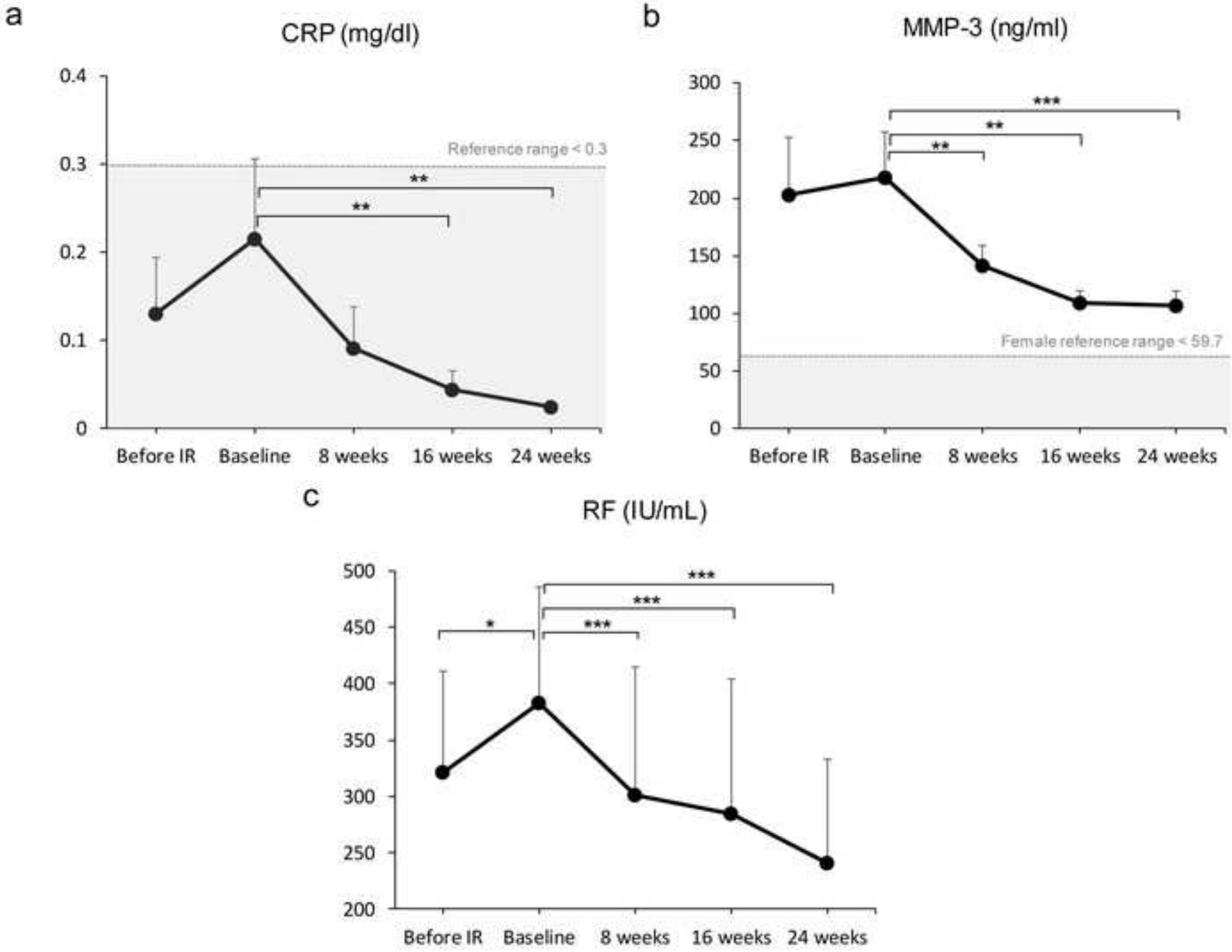

a
CRP (mg/dl)
0.4
0.3
0.2
0.1
0
Reference range < 0.3
**
**
Before IR
Baseline
8 weeks
16 weeks
24 weeks
b
MMP-3 (ng/ml)
300
250
200
150
100
50
0
***
**
**
Female reference range < 59.7
Before IR
Baseline
8 weeks
16 weeks
24 weeks
c
RF (IU/mL)
500
450
400
350
300
250
200
*
***
***
***
Before IR
Baseline
8 weeks
16 weeks
24 weeks

Figure 2

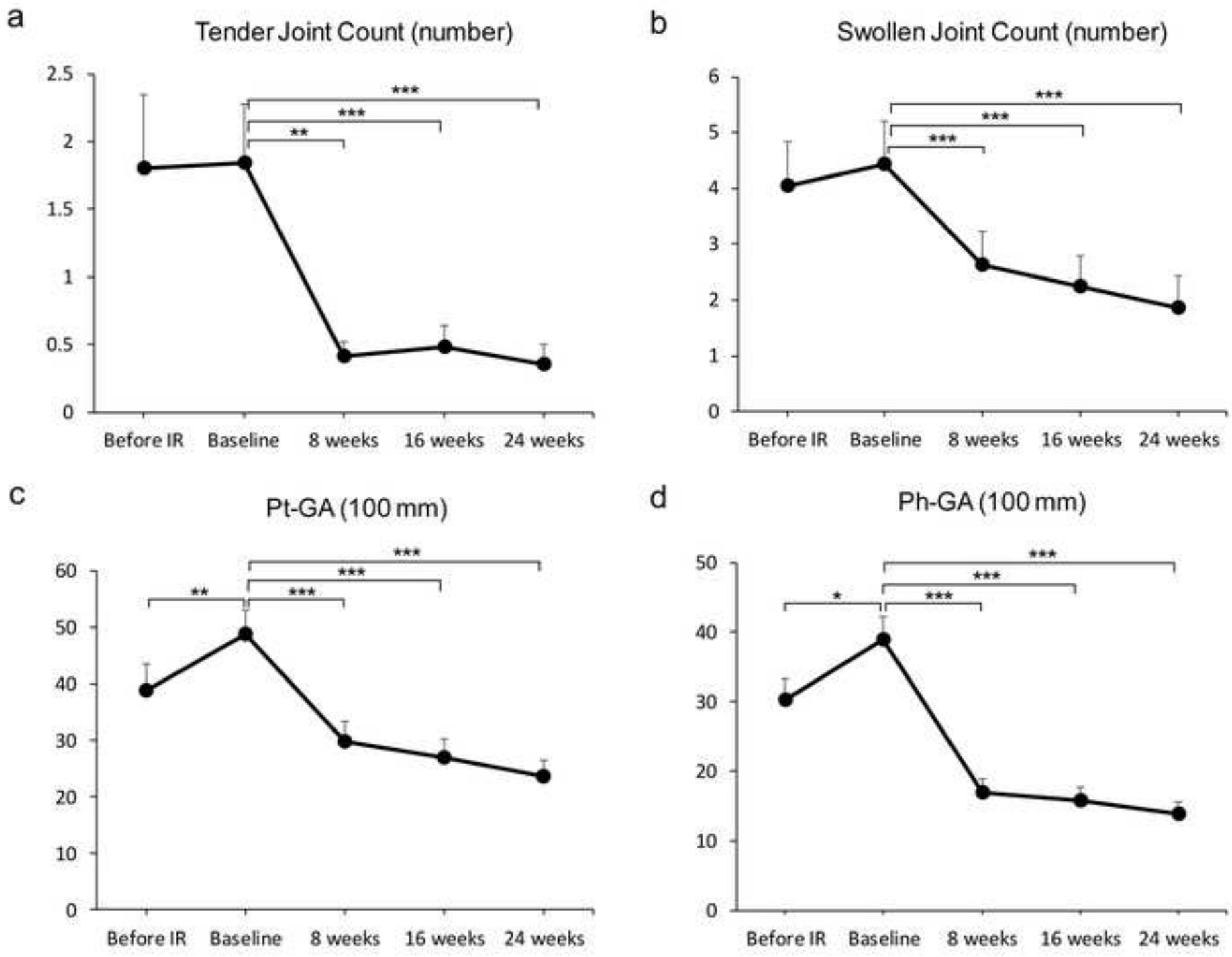

a
Tender Joint Count (number)
2.5
2
1.5
1
0.5
0
**
***
***
Before IR
Baseline
8 weeks
16 weeks
24 weeks
b
Swollen Joint Count (number)
6
5
4
3
2
1
0
***
***
***
Before IR
Baseline
8 weeks
16 weeks
24 weeks
c
Pt-GA (100 mm)
60
50
40
30
20
10
0
**
***
***
***
Before IR
Baseline
8 weeks
16 weeks
24 weeks
d
Ph-GA (100 mm)
50
40
30
20
10
0
*
***
***
***
Before IR
Baseline
8 weeks
16 weeks
24 weeks

Figure 3

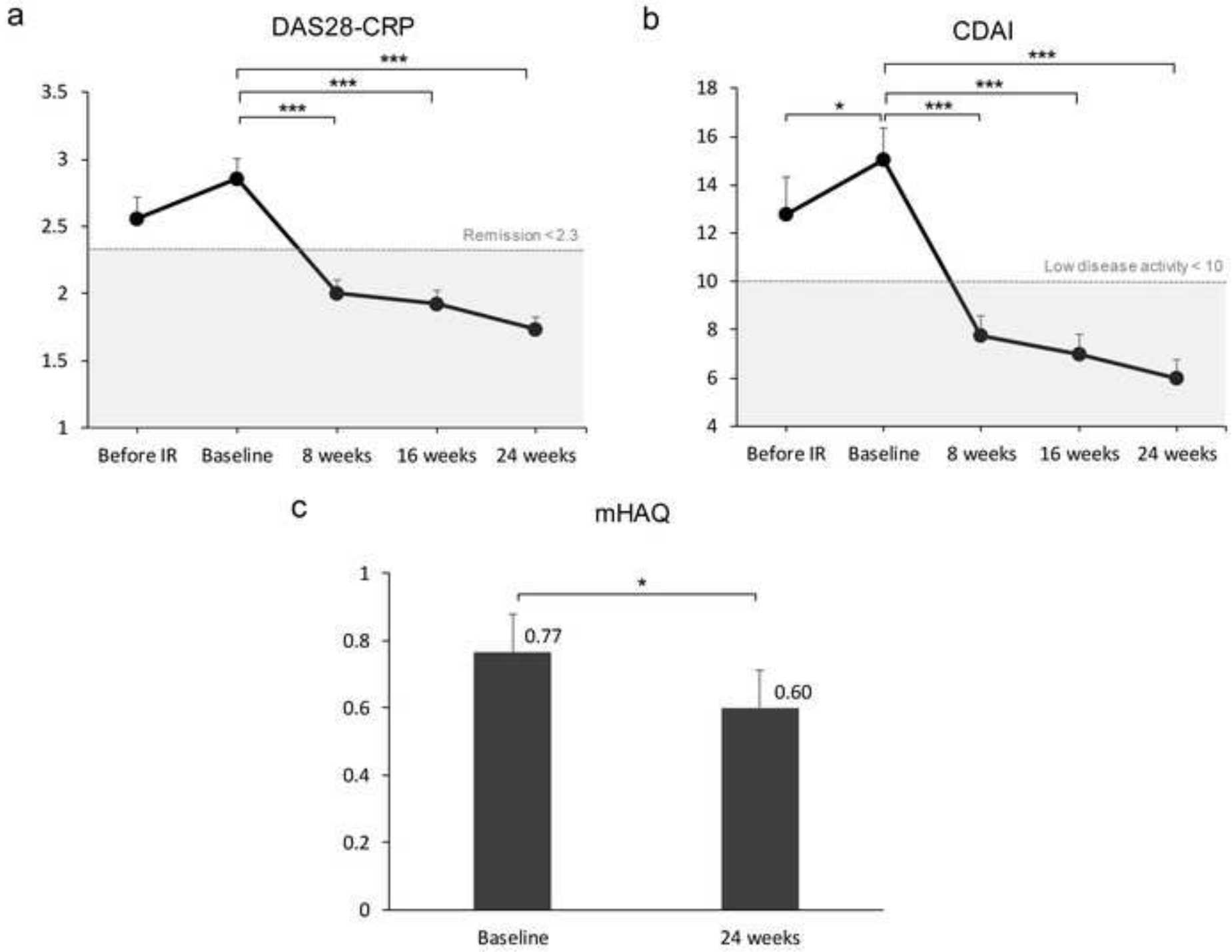
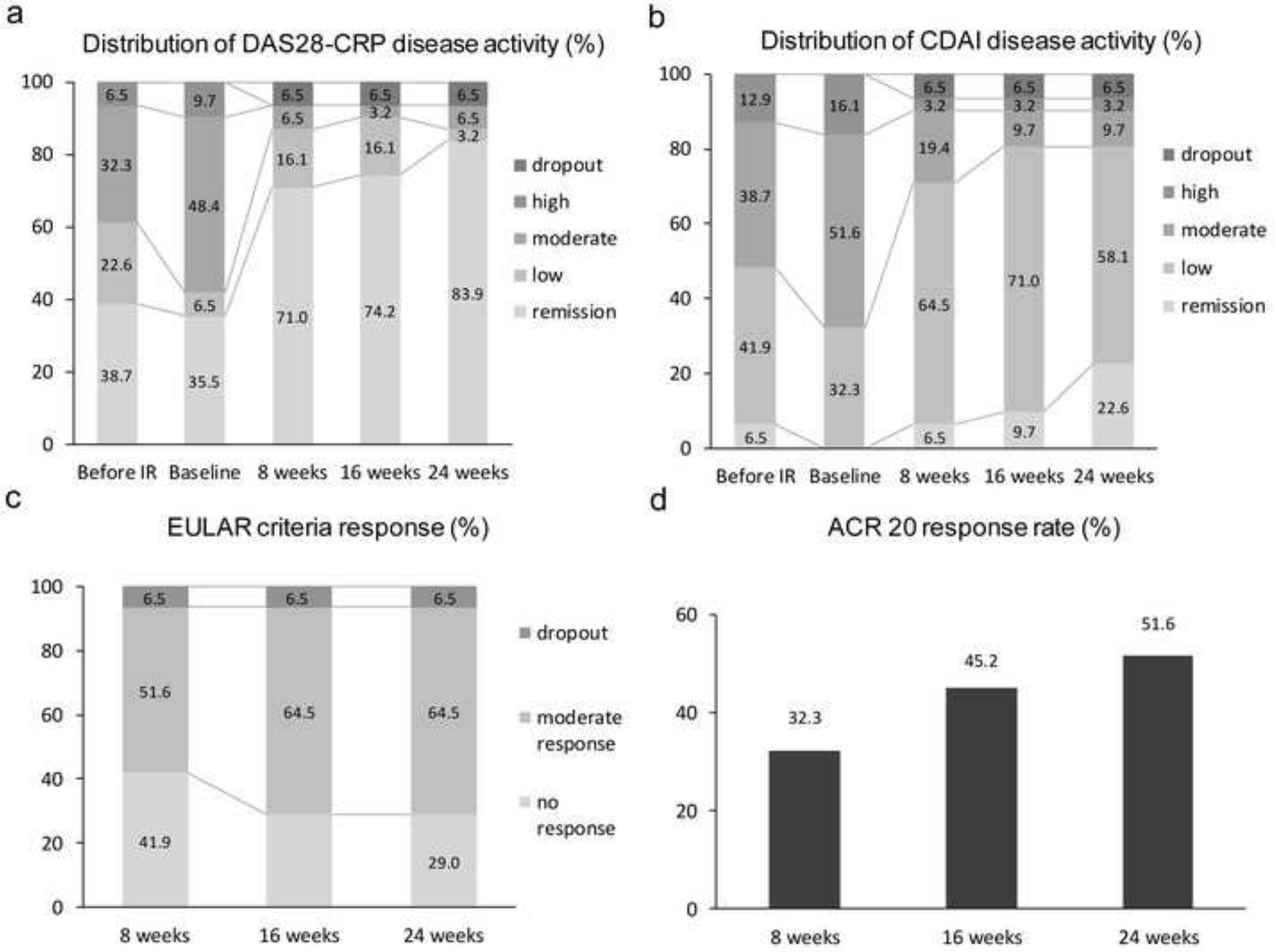

a
DAS28-CRP
***
***
***
3.5
3
2.5
2
1.5
1
Remission < 2.3
Before IR
Baseline
8 weeks
16 weeks
24 weeks
b
CDAI
***
***
*
***
18
16
14
12
10
8
6
4
Low disease activity < 10
Before IR
Baseline
8 weeks
16 weeks
24 weeks
c
mHAQ
*
1
0.8
0.6
0.4
0.2
0
0.77
0.60
Baseline
24 weeks

Figure 4


a
Distribution of DAS28-CRP disease activity (%)
100
80
60
40
20
0
6.5
32.3
22.6
38.7
9.7
48.4
6.5
35.5
6.5
6.5
16.1
71.0
6.5
3.2
16.1
74.2
6.5
3.2
83.9
Before IR
Baseline
8 weeks
16 weeks
24 weeks
dropout
high
moderate
low
remission
b
Distribution of CDAI disease activity (%)
100
80
60
40
20
0
12.9
38.7
41.9
6.5
16.1
51.6
32.3
6.5
6.5
3.2
19.4
64.5
6.5
6.5
3.2
9.7
71.0
9.7
6.5
3.2
9.7
58.1
22.6
Before IR
Baseline
8 weeks
16 weeks
24 weeks
dropout
high
moderate
low
remission
c
EULAR criteria response (%)
100
80
60
40
20
0
6.5
51.6
41.9
6.5
64.5
6.5
64.5
29.0
8 weeks
16 weeks
24 weeks
dropout
moderate response
no response
d
ACR 20 response rate (%)
60
40
20
0
32.3
45.2
51.6
8 weeks
16 weeks
24 weeks