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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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48 34 The authors declare they have no specific funding for this study.

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37 Abstract

38 Objectives

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

42 Methods

43 Thirty-one patients with RA (22 women, age 62.4 years, disease duration 13.8 years, prior TCZ
44 duration 35.7 months, 25 intravenous [8 mg/kg/4 weeks] and 6 subcutaneous [162 mg/2 weeks]
45 TCZ treatments, concomitant MTX 8.5 mg/week [35.5%], and prednisolone (PSL) 4.3 mg/day
46 [25.8%]) who showed an inadequate response to TCZ (disease activity score assessing 28 joints
47 with C-reactive protein [DAS28-CRP] 2.9, clinical disease activity index [CDAI] 15.0, 28
48 secondary inadequate responders) were treated with additional IGU (final dose 41.7 mg/day)
49 and enrolled in this 24-week, multicenter, retrospective study.

50 Results

51 Twenty-nine patients (93.5%) continued the treatment for 24 weeks (1 dropped out for
52 pneumonia and 1 for digestive symptoms). TCZ and the concomitant dose and rate of
53 conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (MTX,
54 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

73 Introduction

74 Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody
75 that has been widely used for the treatment of rheumatoid arthritis (RA) [1, 2]. The European
76 League against Rheumatism (EULAR) announced a 2016 update to the 2013 recommendations
77 for the management of RA, in which TCZ is considered as efficacious and safe as tumor
78 necrosis factor alpha (TNF- α) inhibitors, and it should be considered as a first-line biological
79 disease-modifying antirheumatic drug (bDMARD) [3]. Although the EULAR recommendations
80 support the use of all bDMARDs in combination with methotrexate (MTX), TCZ is
81 recommended as one of the first-line bDMARDs in patients with contraindications or
82 intolerance to MTX [3, 4]. This depends on the evidence that, among all bDMARDs, only TCZ
83 was shown to be superior as monotherapy over MTX or other conventional synthetic DMARDs
84 (csDMARDs) [1, 5]. In addition, TCZ also showed good efficacy and retention either with or
85 without MTX for RA patients who responded inadequately to csDMARDs and/or TNF- α
86 inhibitors [6].
87 However, some patients show an inadequate response to TCZ. In such cases, the EULAR
88 recommendations indicate changing TCZ to another bDMARD with another mode of action or
89 add-on therapy with csDMARDs [3, 4]. To date, however, there is no reliable evidence for
90 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- κ B), 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

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3 109 classification criteria of the American College of Rheumatology [16]; 2) patients who showed
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6 110 an inadequate response to TCZ followed by additional administration of IGU from February
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9 111 2014 to August 2017 in four hospitals associated with the Osaka University Graduate School of
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12 112 Medicine; 3) patients who could follow up at least 24 weeks after IGU administration, were
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15 113 retrospectively selected without any other selection bias. Finally, thirty-one patients participated
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18 114 in this retrospective study. TCZ was injected subcutaneously every 2 weeks at a dose of 162 mg
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22 115 or infused every 4 weeks at a dose of 8 mg/kg in accordance with drug labeling and the TCZ
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25 116 therapy guidelines of the Japan College of Rheumatology (JCR) [17]. An inadequate response
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28 117 to TCZ was defined as having all of the following conditions, according to the previous report
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31 118 [18]; 1) TCZ was used at the same dose for at least 8 weeks prior to IGU induction; 2) clinical
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34 119 disease activity index (CDAI) score > 2.8 (more than low disease activity) [19, 20] at IGU
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37 120 induction; 3) either tender joint count and swollen joint count more than 6, or the same or
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40 121 increased compared to those at 4 to 8 weeks prior to IGU induction. Primary non-responder was
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43 122 defined as patients who showed inadequate response to TCZ within 3 months after initiation,
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46 123 and secondary non-responder as more than 3 months after initiation. The patients were treated
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49 124 with IGU 25 mg/day at baseline, and it was then increased to 50 mg/day depending on each
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52 125 physician's decision, without changing the dosage of TCZ. Effectiveness and safety were
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55 126 evaluated at 8, 16, and 24 weeks after IGU induction.
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128 *Main outcome variable and study factors*

129 Disease activity was assessed by monitoring serum C-reactive protein (CRP), serum matrix

130 metalloproteinase-3 (MMP-3), rheumatoid factor (RF). Other parameters such as white blood

131 cell (WBC) count, lymphocyte count, estimated glomerular filtration rate (eGFR), and liver

132 function parameters (AST and ALT) were also monitored. As for composite measures, the

133 tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease

134 activity (Pt-GA, 100 mm), physician's global assessment of disease activity (Ph-GA, 100 mm),

135 disease activity score of 28 joints (DAS28) with CRP (DAS28-CRP) [21], and the clinical

136 disease activity index (CDAI) score were evaluated over time. As for physical disability, the

137 modified Health Assessment Questionnaire (mHAQ) scores [22] were also monitored. The

138 missing data was less than 2.6% for all parameters, respectively.

139 DAS28-CRP was divided into four categories: remission \leq (2.3); low disease activity (> 2.3 and

140 ≤ 2.7); moderate disease activity (> 2.7 and ≤ 4.1); and high disease activity (> 4.1). CDAI was

141 divided into four categories: remission (≤ 2.8); low disease activity (> 2.8 and ≤ 10); moderate

142 disease activity (> 10 and ≤ 22); and high disease activity (> 22) [20]. Observation points were

143 set to the following five time points: 4-8 weeks prior to the start of IGU (before IR); at the start

144 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.

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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.

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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 \pm 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 ($< 3500/\mu\text{L}$) and lymphopenia ($< 1000/\mu\text{L}$), 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

217 weeks, which increased to 64.5% at 24 weeks, although no patients reached good response
 218 during this period (Fig. 4c). Finally, the percentages of patients who achieved ACR 20 were
 219 32.3%, 45.2%, and 51.6% at 8 weeks, 16 weeks, and 24 weeks, respectively (Fig. 4d).
 220 With respect to the difference in baseline backgrounds between EULAR moderate responder
 221 (n=20) and non-responder (n=9), responder group showed higher baseline DAS28-CRP (3.2 vs.
 222 2.1; $P<0.001$) and CDAI (18.0 vs. 9.0; $P<0.001$) compared to non-responder group. This may be
 223 partially because EULAR treatment response correlates with the decreased amount of
 224 DAS28-CRP. Of note, responder group was treated with higher dose of TCZ compared to
 225 non-responder group (447.0 vs. 375.3 mg/4 weeks; $P=0.01$), suggesting add-on IGU may be
 226 more effective when combined with higher dose of TCZ.
 227 In regards to the response to IGU between with and without MTX combination,
 228 MTX-combination group (n=11) tended to show higher rate of low disease activity ($CDAI\leq 10$)
 229 (90.9 vs. 75.0%; $P=0.28$), EULAR moderate response (72.7 vs. 60.0%; $P=0.48$), and ACR20
 230 (54.5 vs. 45.0%; $P=0.61$) compared to non-MTX-combination group (n=20) at 24 weeks,
 231 although didn't reach statistical significance.
 232 Concerning the difference in the response to IGU between primary and secondary
 233 non-responders to TCZ, 100.0% (3/3) of primary non-responders and 78.6% (22/28) of
 234 secondary non-responders achieved low disease activity ($CDAI\leq 10$) at 24 weeks. Likewise,

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3 235 85.7% (12/14) of bio-naïve and 76.5% (13/17) of bio-switched patients achieved low disease
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6 236 activity (CDAI \leq 10) at 24 weeks. There was no significant difference in the rate of achieving
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14 15 16 239 **Discussion**

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19 240 To the best of our knowledge, this is the first study to investigate the efficacy and safety of
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22 241 adding IGU to RA patients who showed an inadequate response to TCZ. It has been reported
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25 242 that formation of anti-drug antibodies (ADAs) against bDMARDs is strongly linked to
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28 243 subtherapeutic serum drug levels and lack of clinical response [24]. To minimize the
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31 244 immunogenicity and likelihood of ADA formation of bDMARDs, high drug dosing, short
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35 245 interval administration, and combination with csDMARDs are advocated [24]. However,
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38 246 concerning TCZ, the proportion of ADA development following TCZ-SC or TCZ-IV treatment
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41 247 was relatively low (1.5% and 1.2%, respectively), and ADA development was not associated
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44 248 with loss of efficacy, suggesting the low immunogenicity of TCZ [25]. From these observations,
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48 249 the precise mechanisms of the inadequate response to TCZ still remain unclear, unlike for
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51 250 TNF-inhibitors. However, a recent study demonstrated that, in patients with an inadequate
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54 251 response to TCZ-SC every other week, shortening the dosing interval to every week improved
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57 252 efficacy with acceptable tolerability, suggesting that inadequate response to TCZ may be
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3 253 partially due to a lack of drug dosing [26], although adding doses and shortening intervals of
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6 254 TCZ is sometimes associated with an increased risk of infection, as well as the economic burden
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12 256 Concerning concomitant csDMARD medications with TCZ, post-marketing surveillance
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15 257 demonstrated that the combination with MTX was a positive indicator, while the combination
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18 258 with PSL was a negative indicator of EULAR good response achievement [27]. In addition, we
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21 259 have previously reported the efficacy and safety of adding low-dose TAC in patients with RA
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24 260 who showed an inadequate response to TCZ [18]. In this study, patients were treated at a
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27 261 relatively low rate (35.5%) and dose (8.5 mg/week) of MTX, and a low rate (12.9%) and dose
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30 262 (2.0 mg/day) of TAC, which did not change significantly throughout the study. This may be due
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33 263 to the patients' background characteristics and comorbidities. In such situations, adding IGU
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36 264 showed good efficacy and retention in those with an inadequate response to TCZ.
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39 265 The efficacy of adding-on IGU to TCZ might be explained by several mechanisms. First,
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42 266 previous reports demonstrated that IGU inhibited IL-1 beta and IL-6 production from a
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45 267 lipopolysaccharide (LPS)-stimulated human monocytic cell line [11], and it also inhibited
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48 268 NF- κ B activation and TNF- α production from a rat macrophage cell line [8]. Moreover, a recent
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51 269 report showed that IGU markedly decreased IL-6-induced IL-17 and MMP-3 levels in synovial
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54 270 fibroblasts from RA patients, as well as MTX [13]. These mechanisms may synergistically
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271 enhance the anti-inflammatory effects of TCZ, especially those who are not tolerant to an
 272 adequate dose of MTX. In addition, IGU inhibited immunoglobulin production by cultured B
 273 cells and decreased the high level of human IgG observed in mice engrafted with human RA
 274 tissue [14], which may have led to the significant decrease of the serum RF titer in the present
 275 study. Bloom et al. demonstrated that IGU selectively inhibits macrophage migration inhibitory
 276 factor (MIF) both *in vitro* and *in vivo*, which may synergistically enhance the effect of
 277 glucocorticoids, leading to its steroid-sparing effects, suggesting the reason for the significant
 278 decrease in the PSL dose in the present study [28].
 279 Concerning pain reduction, IGU inhibits cyclooxygenase-2, which provides a synergistic
 280 short-term action against pain and inflammation [29], and a recent report showed that IGU
 281 exerts an anti-allodynic effect in the rat model of neuropathic pain [30], which may also have
 282 contributed to the rapid decrease in tender joints in the present study.
 283 Concerning bone metabolism, we have previously demonstrated that IGU stimulates
 284 osteoblastic differentiation *in vitro* and *in vivo* [31]. Moreover, IGU decreased RANKL
 285 expression in IL-6-induced RA synoviocytes [13], and it inhibited ovariectomy-induced
 286 osteoclastogenesis and bone loss by inhibiting RANKL signaling (PPAR- γ /c-Fos pathway) [32].
 287 These positive effects on bone metabolism may contribute to the inhibition of bone erosion,
 288 although they should be confirmed in further human studies.

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3 289 There are several limitations to this study. First, this study lacked a control group, such as
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6 290 adding-on other DMARDs, and was not a randomized, comparative study. Second, side effects
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9 291 such as infection, liver dysfunction, and cutaneous symptom may be major concerns when
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12 292 combining IGU and TCZ, and these adverse effects might have been underestimated due to the
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15 293 small numbers of patients and the short duration of follow-up. Third, 4 patients (12.9%) were
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18 294 started to add-on IGU within 6 months after TCZ initiation, and the effects of IGU may be
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21 295 overestimated in such cases. Fourth, relatively high rate of comorbidities (such as interstitial
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24 296 pneumonia and renal dysfunction) and low rate of MTX combination may affect the results.
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27 297 Fifths, whether this combination therapy protects the joints from radiographic damage should be
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30 298 evaluated in prospective, randomized, large-cohort, and longer-duration studies.
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33 299 **In conclusion, the results of this retrospective study demonstrated that add-on use of IGU can be**
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36 300 **considered an effective complementary therapy for TCZ-refractory RA patients, especially those**
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39 301 **who are intolerant of an effective dose of MTX or other csDMARDs such as TAC, or TCZ**
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42 302 **loading.**
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304 **Conflict of interest**

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54 305 K.E., M.H., and H.Y. received research grants from Astellas, Daiichi Sankyo, Eisai, and
55
56
57 306 Mitsubishi Tanabe. K.E. received speaker fees from Abbvie, Astellas, Asahi-Kasei, Chugai,
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3 307 Daiichi Sankyo, Eli Lilly, Eisai, Mitsubishi Tanabe, Ono Pharmaceutical, and UCB Japan. H.T.
4
5
6 308 received speaker fees from Chugai, Mitsubishi Tanabe, Bristol-Myers Squibb and Eisai, and
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8
9 309 received research grants from Chugai and Ayumi. S.K. received speaker fees from
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11
12 310 Bristol-Myers Squibb, Chugai, Otsuka, and Takeda. M.N. received travel fees from Abbvie. H.O.
13
14
15 311 received speaker fees from Bristol Meyers, Ayumi and Chugai, and moderator fees from
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18 312 Astellas, Phyzer, Abbvie, Mitsubishi Tanabe, Bristol Meyers and Eisai. S.T. received speaker
19
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21 313 fees from Abbvie, Asahi-Kasei, Chugai, Daiichi Sankyo, Eli Lilly, Eisai, Mitsubishi Tanabe,
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24 314 Celgene and Novartis Pharma K.K. M.H. received speaker fees from Astellas, Bristol Mayers,
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27 315 Pfizer, Ono Pharmaceutical, and UCB Japan. J.H. received speaker fees from Astellas,
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30 316 Asahi-Kasei, Ayumi, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, Eisai, Hisamitsu,
31
32
33 317 Mitsubishi Tanabe, MSD, Taisho-Toyama, and Teijin Pharmaceuticals. A.M., Y.E., A.G.
34
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36 318 declare they have no conflict of interest.
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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 \leq (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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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 14 bio-naïve, 17 bio-switched	
Prior use of biologics (n)	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

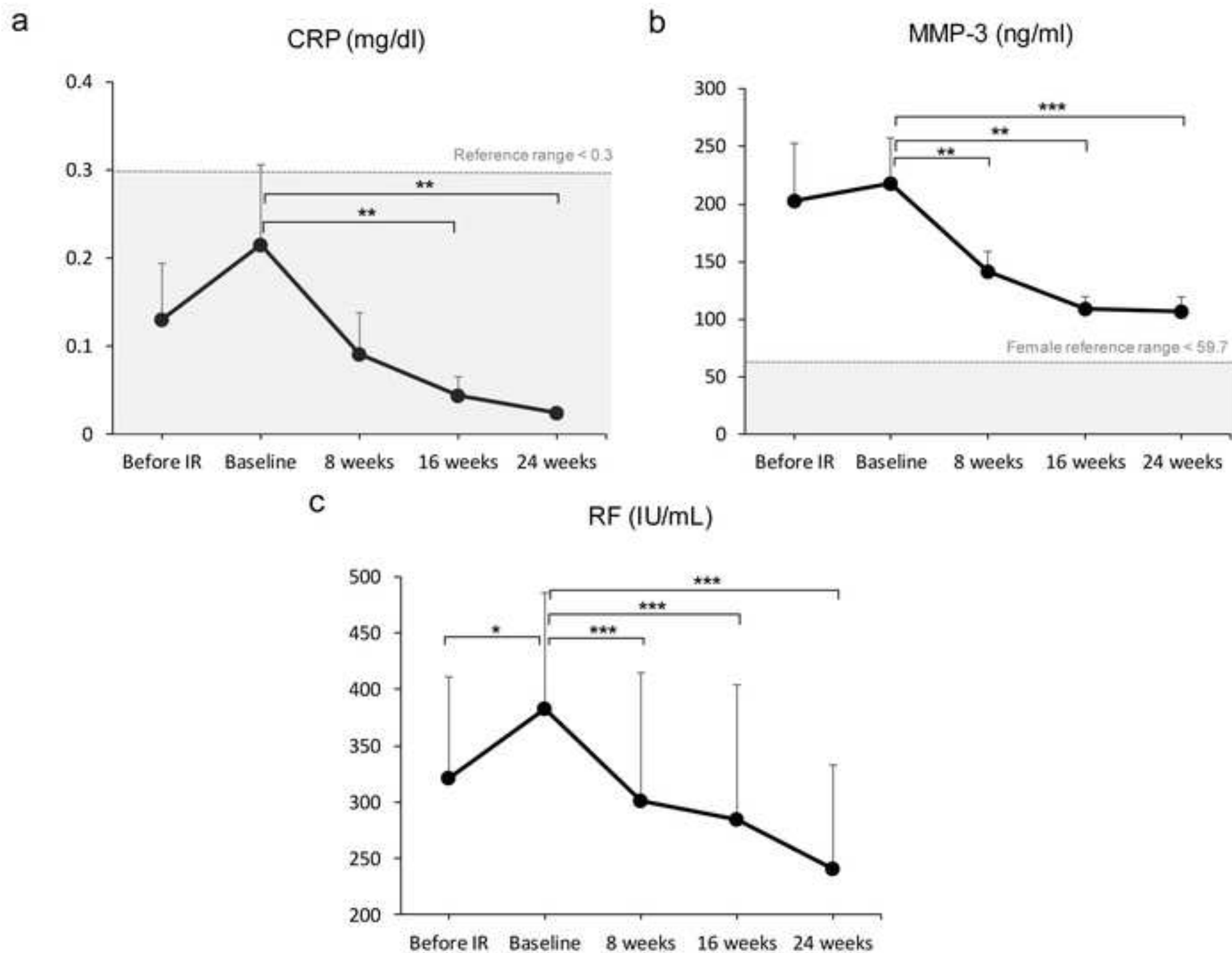


Figure 2

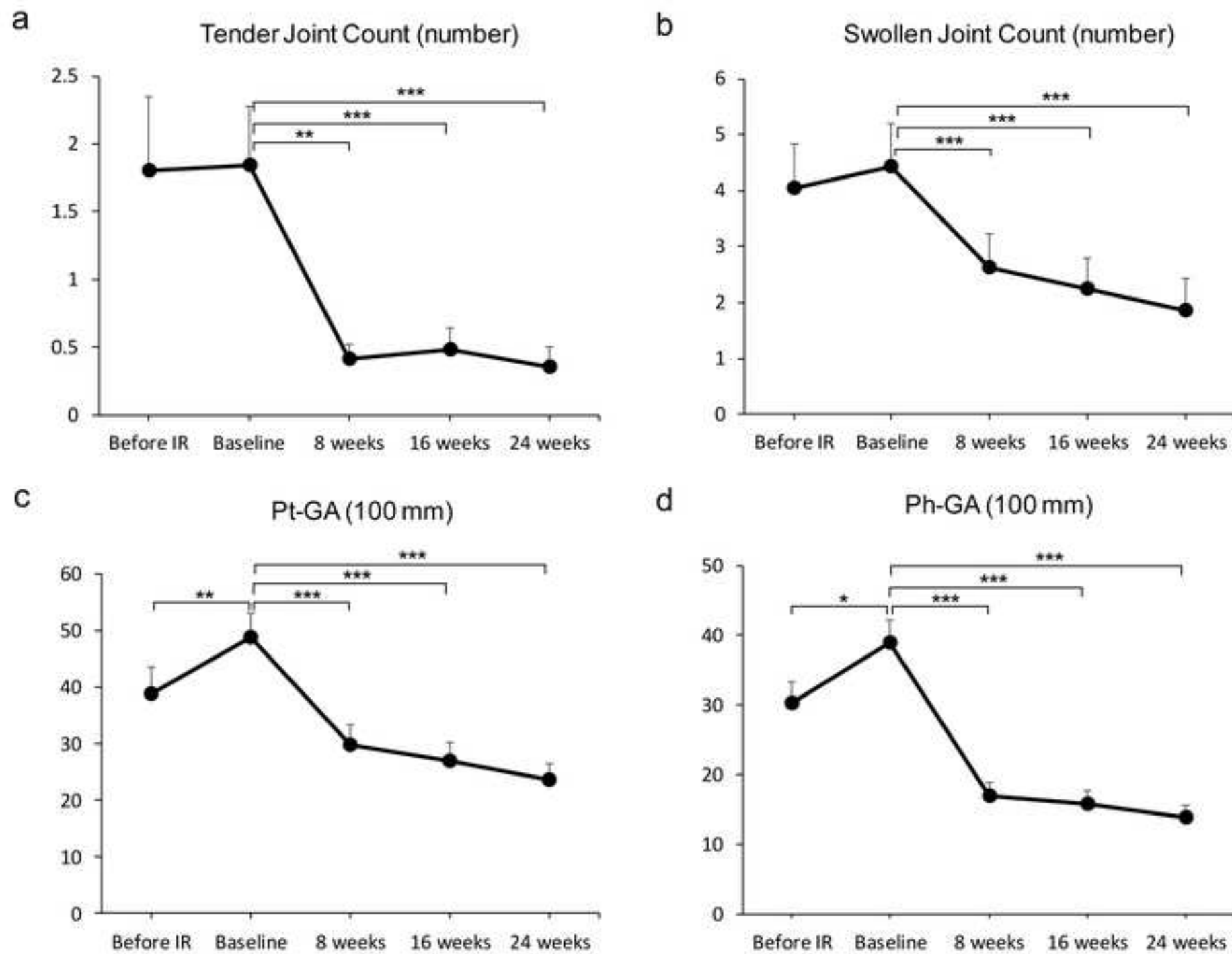


Figure 3

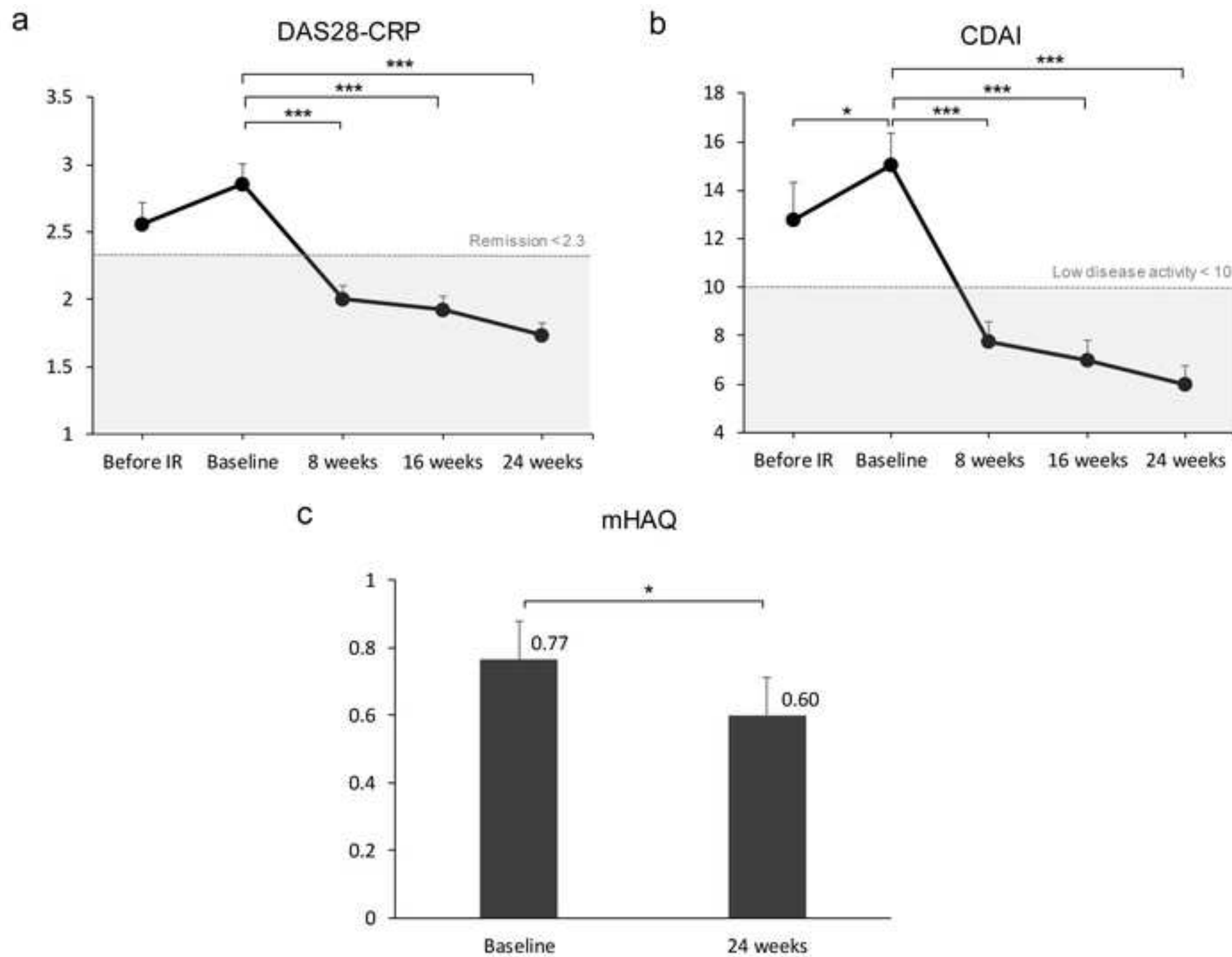


Figure 4

