

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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1 **Original Article**

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3 ***Title:***

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

6

7 ***Authors:***

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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

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55 measures improved significantly, as follows: DAS28-CRP from 2.9 to 1.7 (P < 0.001); CDAI  
56 from 15.0 to 6.0 (P < 0.001); modified Health Assessment Questionnaire from 0.8 to 0.6 (P <  
57 0.05); and rheumatoid factor from 382.1 to 240.3 IU/mL (P < 0.001). Using the EULAR criteria,  
58 64.5% achieved a moderate response, and 51.6% achieved ACR 20 at 24 weeks.

59 **Conclusions**

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

62  
63 ***Keywords:***

64 Iguratimod, Inadequate response, Rheumatoid arthritis, Tocilizumab

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3 **73 Introduction**  
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6 74 Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody  
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9 75 that has been widely used for the treatment of rheumatoid arthritis (RA) [1, 2]. The European  
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12 76 League against Rheumatism (EULAR) announced a 2016 update to the 2013 recommendations  
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16 77 for the management of RA, in which TCZ is considered as efficacious and safe as tumor  
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19 78 necrosis factor alpha (TNF- $\alpha$ ) inhibitors, and it should be considered as a first-line biological  
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22 79 disease-modifying antirheumatic drug (bDMARD) [3]. Although the EULAR recommendations  
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25 80 support the use of all bDMARDs in combination with methotrexate (MTX), TCZ is  
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28 81 recommended as one of the first-line bDMARDs in patients with contraindications or  
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32 82 intolerance to MTX [3, 4]. This depends on the evidence that, among all bDMARDs, only TCZ  
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35 83 was shown to be superior as monotherapy over MTX or other conventional synthetic DMARDs  
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38 84 (csDMARDs) [1, 5]. In addition, TCZ also showed good efficacy and retention either with or  
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41 85 without MTX for RA patients who responded inadequately to csDMARDs and/or TNF- $\alpha$   
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44 86 inhibitors [6].  
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47 87 However, some patients show an inadequate response to TCZ. In such cases, the EULAR  
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51 88 recommendations indicate changing TCZ to another bDMARD with another mode of action or  
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54 89 add-on therapy with csDMARDs [3, 4]. To date, however, there is no reliable evidence for  
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57 90 choosing alternative bDMARDs or adding-on specific csDMARDs other than MTX for patients  
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91 who previously had an inadequate response to TCZ.

92 Iguratimod (IGU), also known as T-614, is a novel csDMARD that was introduced in clinical

93 settings in 2012 in Japan. Via inhibition of nuclear factor-kappa B (NF- $\kappa$ B), IGU inhibits the

94 production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, IL-17,

95 TNF- $\alpha$ , and interferon- $\gamma$ , in vitro (in synovial cells and monocytic cell lines) and in vivo [7-12].

96 In addition, IGU inhibits IL-6-induced IL-17 and matrix-metalloprotease 3 (MMP-3)

97 expressions in human synovial fibroblasts from patients with RA [13], and also reduces

98 immunoglobulin (Ig) production by human B lymphocytes [14]. Concerning combination

99 therapy with bDMARDs, only one study demonstrated the effects of add-on IGU in patients

100 who showed inadequate responses to bDMARDs, mainly TNF-inhibitors [15].

101 Thus, we hypothesized that adding IGU may be a promising complementary therapy for patients

102 with an inadequate response to TCZ, especially in patients who are intolerant to an adequate

103 dose of MTX, and the effectiveness and safety of this combination therapy were examined in

104 this 24-week, multicenter, retrospective study.

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106 **Methods**

107 *Patients*

108 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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19 114 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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35 119 disease activity index (CDAI) score > 2.8 (more than low disease activity) [19, 20] at IGU  
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38 120 induction; 3) either tender joint count and swollen joint count more than 6, or the same or  
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41 121 increased compared to those at 4 to 8 weeks prior to IGU induction. Primary non-responder was  
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44 122 defined as patients who showed inadequate response to TCZ within 3 months after initiation,  
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47 123 and secondary non-responder as more than 3 months after initiation. The patients were treated  
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51 124 with IGU 25 mg/day at baseline, and it was then increased to 50 mg/day depending on each  
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54 125 physician's decision, without changing the dosage of TCZ. Effectiveness and safety were  
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57 126 evaluated at 8, 16, and 24 weeks after IGU induction.  
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6 128 *Main outcome variable and study factors*  
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9 129 Disease activity was assessed by monitoring serum C-reactive protein (CRP), serum matrix  
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12 130 metalloproteinase-3 (MMP-3), rheumatoid factor (RF). Other parameters such as white blood  
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16 131 cell (WBC) count, lymphocyte count, estimated glomerular filtration rate (eGFR), and liver  
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19 132 function parameters (AST and ALT) were also monitored. As for composite measures, the  
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22 133 tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease  
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25 134 activity (Pt-GA, 100 mm), physician's global assessment of disease activity (Ph-GA, 100 mm),  
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28 135 disease activity score of 28 joints (DAS28) with CRP (DAS28-CRP) [21], and the clinical  
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32 136 disease activity index (CDAI) score were evaluated over time. As for physical disability, the  
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35 137 modified Health Assessment Questionnaire (mHAQ) scores [22] were also monitored. **The**  
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38 138 **missing data was less than 2.6% for all parameters, respectively.**  
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41 139 DAS28-CRP was divided into four categories: remission  $\leq$  (2.3); low disease activity ( $>$  2.3 and  
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44 140  $\leq$  2.7); moderate disease activity ( $>$  2.7 and  $\leq$  4.1); and high disease activity ( $>$  4.1). CDAI was  
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47 141 divided into four categories: remission ( $\leq$  2.8); low disease activity ( $>$  2.8 and  $\leq$  10); moderate  
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51 142 disease activity ( $>$  10 and  $\leq$  22); and high disease activity ( $>$  22) [20]. Observation points were  
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54 143 set to the following five time points: 4-8 weeks prior to the start of IGU (before IR); at the start  
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57 144 of IGU (baseline); 8, 16, and 24 weeks after the start of IGU. Clinical responses were defined by  
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145 the American College of Rheumatology (ACR) 20% improvement criteria [23] and EULAR  
146 response criteria [21]. All adverse events occurring during the follow-up period were also  
147 examined.

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149 ***Procedures***

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

155

156 ***Statistical analysis***

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

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164 **Results**

165 *Demographic data and concomitant medications*

166 Patients' clinical characteristics at baseline and 24 weeks are shown in Table 1. Thirty-one  
167 patients (22 women) had inadequate responses to TCZ, and they were then treated with add-on  
168 IGU [mean dose 25 mg/day at baseline and 41.7 mg/day (20 patients were treated by 50  
169 mg/day) at 24 weeks. Their mean age was 62.4 years, and disease duration was 13.8 years. IGU  
170 was started at 35.7 months after the initiation of TCZ. Twenty-five patients were treated with  
171 intravenous TCZ infusion (8 mg/kg/month), and 6 were treated with subcutaneous TCZ  
172 injection (162 mg/2 weeks). TCZ was introduced as the first biologic in 14 patients, and 17  
173 were bio-switched. With respect to concomitant csDMARDs, mean dose and usage rates of  
174 combined MTX were 8.5 mg/week (0-12) and 35.5% at baseline, and 8.0 mg/week (0-12) and  
175 35.5% at 24 weeks, respectively. There were 20 patients without MTX combination, and the  
176 reasons assessed by each attending physician were history of interstitial pneumonia (n=7), renal  
177 dysfunction (n=3), digestive symptom by MTX (n=3), history of malignancy (n=3), liver  
178 dysfunction (n=2), history of MTX-associated lymphoproliferative disorders (n=1), and allergic  
179 to MTX (n=1), respectively. Likewise, 4 patients (12.9%) received tacrolimus (TAC), and 3  
180 patients (9.7%) received salazosulfapyridine (SASP). No significant changes in the mean doses

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

185

186 *Adverse events*

187 Of all of the patients, 29 (87.1%) continued the combination treatment until 24 weeks. One  
188 patient discontinued due to pneumonia, and 1 discontinued for digestive symptoms. During the  
189 follow-up period, 2 patients (6.5%) developed leukopenia (< 3500/ $\mu$ L) and lymphopenia (<  
190 1000/ $\mu$ L), and 3 patients (9.7%) showed levels of AST (maximum 71 U/L) and ALT (maximum  
191 149 U/L) exceeding the reference values, although these patients could continue the  
192 combination treatment by decreasing IGU or other concomitant csDMARDs or PSL. No  
193 significant changes were observed in the mean WBC, lymphocyte count, eGFR, and liver  
194 function parameters (AST and ALT) throughout the study.

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196 *Effectiveness*

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

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3 199 mean serum CRP level (mg/dL) (Fig. 1a), MMP-3 level (ng/mL) (Fig. 1b), and RF level (IU/mL)  
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6 200 (Fig. 1c) significantly improved from 8-16 weeks after IGU treatment.  
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9 201 Fig. 2 shows longitudinal changes in clinical variables associated with disease activity. The  
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12 202 mean TJC (Fig. 2a), SJC (Fig. 2b), Pt-GA (Fig. 2c), and Ph-GA (Fig. 2d) significantly improved  
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16 203 from 8 weeks after IGU treatment.  
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19 204 Fig. 3 a-b shows longitudinal changes in composite measures of disease activity. The mean  
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22 205 DAS28-CRP (Fig. 3a) and CDAI (Fig. 3b) significantly improved from 8 weeks after IGU  
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25 206 treatment. As for physical function, the mean mHAQ score significantly improved after 24  
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28 207 weeks of IGU therapy (Fig. 3c).  
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31 208 Fig. 4 shows longitudinal changes in disease activity distribution and treatment response. Based  
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35 209 on DAS28-CRP, 58.1% of patients had moderate or high disease activity at baseline, which  
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38 210 decreased to 6.5% at 24 weeks (Fig. 4a). With the CDAI, 67.7% of patients had moderate or  
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41 211 high disease activity at baseline, which decreased to 12.9% at 24 weeks (Fig. 4b). The patients  
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44 212 with high disease activity (CDAI>22) at baseline tended to achieve lower rate of low disease  
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47 213 activity (CDAI≤10) at 24 weeks compared to the patients with lower than moderate disease  
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50 214 activity (CDAI≤22) at baseline (60.0 vs. 84.6%; P=0.20), although didn't reach statistical  
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53 215 significance.

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57 216 Concerning the EULAR treatment response, 51.6% of patients showed a moderate response at 8  
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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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235 85.7% (12/14) of bio-naïve and 76.5% (13/17) of bio-switched patients achieved low disease  
236 activity (CDAI $\leq$ 10) at 24 weeks. There was no significant difference in the rate of achieving  
237 low disease activity between the groups.

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239 **Discussion**

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

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253 partially due to a lack of drug dosing [26], although adding doses and shortening intervals of  
254 TCZ is sometimes associated with an increased risk of infection, as well as the economic burden  
255 [26].  
256 Concerning concomitant csDMARD medications with TCZ, post-marketing surveillance  
257 demonstrated that the combination with MTX was a positive indicator, while the combination  
258 with PSL was a negative indicator of EULAR good response achievement [27]. In addition, we  
259 have previously reported the efficacy and safety of adding low-dose TAC in patients with RA  
260 who showed an inadequate response to TCZ [18]. In this study, patients were treated at a  
261 relatively low rate (35.5%) and dose (8.5 mg/week) of MTX, and a low rate (12.9%) and dose  
262 (2.0 mg/day) of TAC, which did not change significantly throughout the study. This may be due  
263 to the patients' background characteristics and comorbidities. In such situations, adding IGU  
264 showed good efficacy and retention in those with an inadequate response to TCZ.  
265 The efficacy of adding-on IGU to TCZ might be explained by several mechanisms. First,  
266 previous reports demonstrated that IGU inhibited IL-1 beta and IL-6 production from a  
267 lipopolysaccharide (LPS)-stimulated human monocytic cell line [11], and it also inhibited  
268 NF- $\kappa$ B activation and TNF- $\alpha$  production from a rat macrophage cell line [8]. Moreover, a recent  
269 report showed that IGU markedly decreased IL-6-induced IL-17 and MMP-3 levels in synovial  
270 fibroblasts from RA patients, as well as MTX [13]. These mechanisms may synergistically



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3 271 enhance the anti-inflammatory effects of TCZ, especially those who are not tolerant to an  
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6 272 adequate dose of MTX. In addition, IGU inhibited immunoglobulin production by cultured B  
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9 273 cells and decreased the high level of human IgG observed in mice engrafted with human RA  
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12 274 tissue [14], which may had led to the significant decrease of the serum RF titer in the present  
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15 275 study. Bloom et al. demonstrated that IGU selectively inhibits macrophage migration inhibitory  
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18 276 factor (MIF) both *in vitro* and *in vivo*, which may synergistically enhance the effect of  
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21 277 glucocorticoids, leading to its steroid-sparing effects, suggesting the reason for the significant  
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24 278 decrease in the PSL dose in the present study [28].  
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28 279 Concerning pain reduction, IGU inhibits cyclooxygenase-2, which provides a synergistic  
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31 280 short-term action against pain and inflammation [29], and a recent report showed that IGU  
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34 281 exerts an anti-allodynic effect in the rat model of neuropathic pain [30], which may also have  
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37 282 contributed to the rapid decrease in tender joints in the present study.  
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41 283 Concerning bone metabolism, we have previously demonstrated that IGU stimulates  
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44 284 osteoblastic differentiation *in vitro* and *in vivo* [31]. Moreover, IGU decreased RANKL  
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47 285 expression in IL-6-induced RA synoviocytes [13], and it inhibited ovariectomy-induced  
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50 286 osteoclastogenesis and bone loss by inhibiting RANKL signaling (PPAR- $\gamma$ /c-Fos pathway) [32].  
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53 287 These positive effects on bone metabolism may contribute to the inhibition of bone erosion,  
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56 288 although they should be confirmed in further human studies.  
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289 There are several limitations to this study. First, this study lacked a control group, such as  
290 adding-on other DMARDs, and was not a randomized, comparative study. Second, side effects  
291 such as infection, liver dysfunction, and cutaneous symptom may be major concerns when  
292 combining IGU and TCZ, and these adverse effects might have been underestimated due to the  
293 small numbers of patients and the short duration of follow-up. Third, 4 patients (12.9%) were  
294 started to add-on IGU within 6 months after TCZ initiation, and the effects of IGU may be  
295 overestimated in such cases. Fourth, relatively high rate of comorbidities (such as interstitial  
296 pneumonia and renal dysfunction) and low rate of MTX combination may affect the results.  
297 Fifths, whether this combination therapy protects the joints from radiographic damage should be  
298 evaluated in prospective, randomized, large-cohort, and longer-duration studies.

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

303  
304 **Conflict of interest**

305 K.E., M.H., and H.Y. received research grants from Astellas, Daiichi Sankyo, Eisai, and  
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.  
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6 308 received speaker fees from Chugai, Mitsubishi Tanabe, Bristol-Myers Squibb and Eisai, and  
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9 309 received research grants from Chugai and Ayumi. S.K. received speaker fees from  
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12 310 Bristol-Myers Squibb, Chugai, Otsuka, and Takeda. M.N. received travel fees from Abbvie. H.O.  
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16 311 received speaker fees from Bristol Meyers, Ayumi and Chugai, and moderator fees from  
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19 312 Astellas, Phyzer, Abbvie, Mitsubishi Tanabe, Bristol Meyers and Eisai. S.T. received speaker  
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22 313 fees from Abbvie, Asahi-Kasei, Chugai, Daiichi Sankyo, Eli Lilly, Eisai, Mitsubishi Tanabe,  
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25 314 Celgene and Novartis Pharma K.K. M.H. received speaker fees from Astellas, Bristol Meyers,  
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28 315 Pfizer, Ono Pharmaceutical, and UCB Japan. J.H. received speaker fees from Astellas,  
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31 316 Asahi-Kasei, Ayumi, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, Eisai, Hisamitsu,  
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35 317 Mitsubishi Tanabe, MSD, Taisho-Toyama, and Teijin Pharmaceuticals. A.M., Y.E., A.G.  
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38 318 declare they have no conflict of interest.  
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325 **Figure Legends**

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

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

331

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

333 Mean values of (a) TJC, (b) SJC, (c) Pt-GA, and (d) Ph-GA. \* P < 0.05, \*\* P < 0.01, \*\*\* P <  
334 0.001. Bars indicate standard error. IR, inadequate response; TJC, tender joint count; SJC,  
335 swollen joint count; Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's  
336 global assessment of disease activity.

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

340 Mean values of (a) DAS28-CRP, (b) CDAI, and (c) mHAQ. \* P < 0.05, \*\* P < 0.01, \*\*\* P <  
341 0.001. Bars indicate standard error. IR, inadequate response; DAS28-CRP, disease activity  
342 score assessing 28 joints with C-reactive protein; CDAI, clinical disease activity index; mHAQ,

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343 modified Health Assessment Questionnaire.

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

347 (a) Distribution of DAS28-CRP. Disease activity was defined as follows: remission  $\leq$  (2.3); low  
348 disease activity ( $> 2.3$  and  $\leq 2.7$ ); moderate disease activity ( $> 2.7$  and  $\leq 4.1$ ); and high disease  
349 activity ( $> 4.1$ ).

350 (b) Distribution of CDAI. Disease activity was defined as follows: remission ( $\leq 2.8$ ); low  
351 disease activity ( $> 2.8$  and  $\leq 10$ ); moderate disease activity ( $> 10$  and  $\leq 22$ ); and high disease  
352 activity ( $> 22$ ).

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

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

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

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361 **References**

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1. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis.* 2007;66(9):1162-7.
2. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet.* 2008;371(9617):987-97.
3. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis.* 2017;76(6):960-77.
4. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73(3):492-509.
5. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis.* 2010;69(1):88-96.
6. Izumi K, Kaneko Y, Yasuoka H, Seta N, Kameda H, Kuwana M, et al. Tocilizumab is clinically, functionally, and radiographically effective and safe either with or without low-dose methotrexate in active rheumatoid arthritis patients with inadequate responses to DMARDs and/or TNF inhibitors: a single-center retrospective cohort study (KEIO-TCZ study) at week 52. *Mod Rheumatol.* 2015;25(1):31-7.
7. Aikawa Y, Tanuma N, Shin T, Makino S, Tanaka K, Matsumoto Y. A new anti-rheumatic drug, T-614, effectively suppresses the development of autoimmune encephalomyelitis. *J Neuroimmunol.* 1998;89(1-2):35-42.
8. Aikawa Y, Yamamoto M, Yamamoto T, Morimoto K, Tanaka K. An anti-rheumatic agent T-614 inhibits NF-kappaB activation in LPS- and TNF-alpha-stimulated THP-1 cells without interfering with IkappaBalpha degradation. *Inflamm Res.* 2002;51(4):188-94.
9. Du F, Lu LJ, Fu Q, Dai M, Teng JL, Fan W, et al. T-614, a novel immunomodulator, attenuates joint inflammation and articular damage in collagen-induced arthritis. *Arthritis Res Ther.* 2008;10(6):R136.
10. Kawakami A, Tsuboi M, Urayama S, Matsuoka N, Yamasaki S, Hida A, et al. Inhibitory effect of a new anti-rheumatic drug T-614 on costimulatory molecule expression, cytokine production, and antigen presentation by synovial cells. *J Lab Clin Med.* 1999;133(6):566-74.

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396 11. Tanaka K, Aikawa Y, Kawasaki H, Asaoka K, Inaba T, Yoshida C. Pharmacological studies on  
397 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one (T-614), a novel  
398 antiinflammatory agent. 4th communication: inhibitory effect on the production of interleukin-1 and  
399 interleukin-6. *J Pharmacobiodyn.* 1992;15(11):649-55.

400 12. Tanaka K, Urata N, Mikami M, Ogasawara M, Matsunaga T, Terashima N, et al. Effect of  
401 iguratimod and other anti-rheumatic drugs on adenocarcinoma colon 26-induced cachexia in mice.  
402 *Inflamm Res.* 2007;56(1):17-23.

403 13. Wei Y, Sun X, Hua M, Tan W, Wang F, Zhang M. Inhibitory Effect of a Novel Antirheumatic  
404 Drug T-614 on the IL-6-Induced RANKL/OPG, IL-17, and MMP-3 Expression in Synovial Fibroblasts  
405 from Rheumatoid Arthritis Patients. *Biomed Res Int.* 2015;2015:214683.

406 14. Tanaka K, Yamamoto T, Aikawa Y, Kizawa K, Muramoto K, Matsuno H, et al. Inhibitory  
407 effects of an anti-rheumatic agent T-614 on immunoglobulin production by cultured B cells and  
408 rheumatoid synovial tissues engrafted into SCID mice. *Rheumatology (Oxford).* 2003;42(11):1365-71.

409 15. Yoshikawa A, Yoshida S, Kimura Y, Tokai N, Fujiki Y, Kotani T, et al. Add-on iguratimod as a  
410 therapeutic strategy to achieve remission in patients with rheumatoid arthritis inadequately responding to  
411 biological DMARDs: A retrospective study. *Mod Rheumatol.* 2017;1-8.

412 16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American  
413 Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis*  
414 *Rheum.* 1988;31(3):315-24.

415 17. Koike R, Harigai M, Atsumi T, Amano K, Kawai S, Saito K, et al. Japan College of  
416 Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor  
417 monoclonal antibody, in rheumatoid arthritis. *Mod Rheumatol.* 2009;19(4):351-7.

418 18. Kaneshiro S, Ebina K, Hirao M, Tsuboi H, Nishikawa M, Nampei A, et al. The efficacy and  
419 safety of additional administration of tacrolimus in patients with rheumatoid arthritis who showed an  
420 inadequate response to tocilizumab. *Mod Rheumatol.* 2017;27(1):42-9.

421 19. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase  
422 reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical  
423 activity score. *Arthritis Res Ther.* 2005;7(4):R796-806.

424 20. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease  
425 Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp*  
426 *Rheumatol.* 2005;23(5 Suppl 39):S100-8.

427 21. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL.  
428 Development and validation of the European League Against Rheumatism response criteria for  
429 rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World  
430 Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum.*  
431 1996;39(1):34-40.

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58  
59  
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432 22. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient  
433 satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire.  
434 *Arthritis Rheum.* 1983;26(11):1346-53.

435 23. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American  
436 College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.*  
437 1995;38(6):727-35.

438 24. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic  
439 therapies for rheumatoid arthritis. *Nat Rev Rheumatol.* 2013;9(3):164-72.

440 25. Burmester GR, Choy E, Kivitz A, Ogata A, Bao M, Nomura A, et al. Low immunogenicity of  
441 tocilizumab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2017;76(6):1078-85.

442 26. Ogata A, Tanaka Y, Ishii T, Kaneko M, Miwa H, Ohsawa S. A randomized, double-blind,  
443 parallel-group, phase III study of shortening the dosing interval of subcutaneous tocilizumab  
444 monotherapy in patients with rheumatoid arthritis and an inadequate response to subcutaneous  
445 tocilizumab every other week: Results of the 12-week double-blind period. *Mod Rheumatol.*  
446 2018;28(1):76-84.

447 27. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety  
448 of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J*  
449 *Rheumatol.* 2014;41(1):15-23.

450 28. Bloom J, Metz C, Nalawade S, Casabar J, Cheng KF, He M, et al. Identification of Igaratimod  
451 as an Inhibitor of Macrophage Migration Inhibitory Factor (MIF) with Steroid-sparing Potential. *J Biol*  
452 *Chem.* 2016;291(51):26502-14.

453 29. Mucke HA. Igaratimod: a new disease-modifying antirheumatic drug. *Drugs Today (Barc).*  
454 2012;48(9):577-86.

455 30. Morimoto K, Miura A, Tanaka K. Anti-allodynic action of the disease-modifying  
456 anti-rheumatic drug iguratimod in a rat model of neuropathic pain. *Inflamm Res.* 2017;66(10):855-62.

457 31. Kuriyama K, Higuchi C, Tanaka K, Yoshikawa H, Itoh K. A novel anti-rheumatic drug, T-614,  
458 stimulates osteoblastic differentiation in vitro and bone morphogenetic protein-2-induced bone formation  
459 in vivo. *Biochem Biophys Res Commun.* 2002;299(5):903-9.

460 32. Wu YX, Sun Y, Ye YP, Zhang P, Guo JC, Huang JM, et al. Igaratimod prevents  
461 ovariectomy-induced bone loss and suppresses osteoclastogenesis via inhibition of peroxisome  
462 proliferator-activated receptor- $\gamma$ . *Mol Med Rep.* 2017;16(6):8200-8.



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 <sup>2</sup> )	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) <sup>***</sup>
DAS28-CRP	2.9 ± 0.2 (1.6-4.7)	1.7 ± 0.1 (0.6-2.8) <sup>***</sup>
CDAI	15.0 ± 1.4 (2.0-34.5)	6.0 ± 0.8 (2.0-22.9) <sup>***</sup>

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- 2 Data are expressed as mean ± standard error (range).
- 3 n/N (%) = number of patients with measurements/total number of patients (%)
- 4 RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide (anti-CCP) antibody;
- 5 TCZ, tocilizumab; i.v., intravenous; s.c., subcutaneous; IFX, infliximab; ETN, etanercept; ABT,
- 6 abatacept; ADA, adalimumab; GLM, golimumab; MTX, methotrexate; PSL, prednisolone; SASP,
- 7 salazosulfapyridine; TAC, tacrolimus; CRP, C-reactive protein; MMP-3, matrix metalloproteinase-3;
- 8 WBC, white blood cell; eGFR, estimated glomerular filtration rate; SJC, swollen joint count; TJC, tender
- 9 joint count; Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's global assessment
- 10 of disease activity; DAS28-CRP, disease activity score assessing 28 joints with CRP; CDAI, clinical
- 11 disease activity index.
- 12 \* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001

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Figure 1

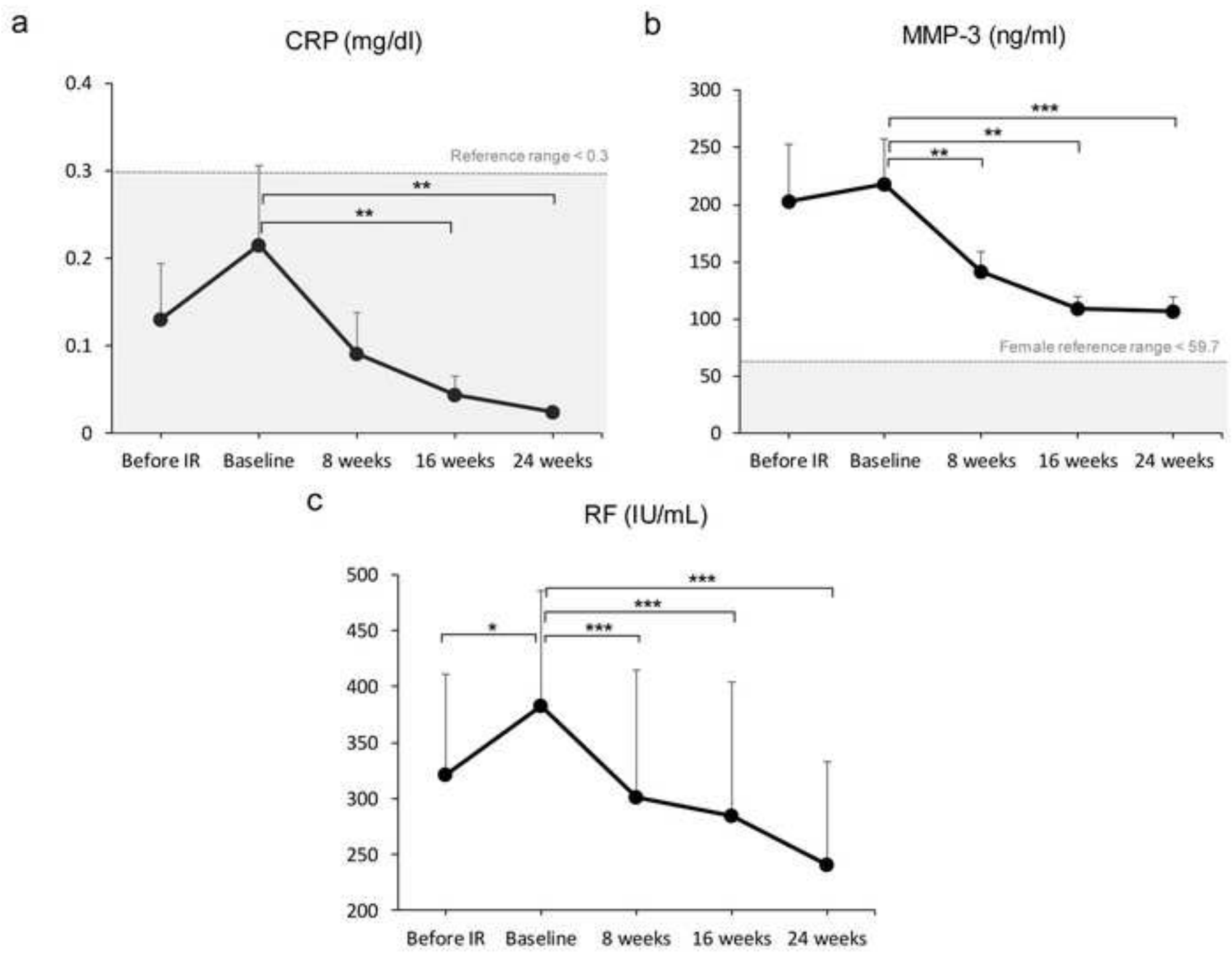


Figure 2

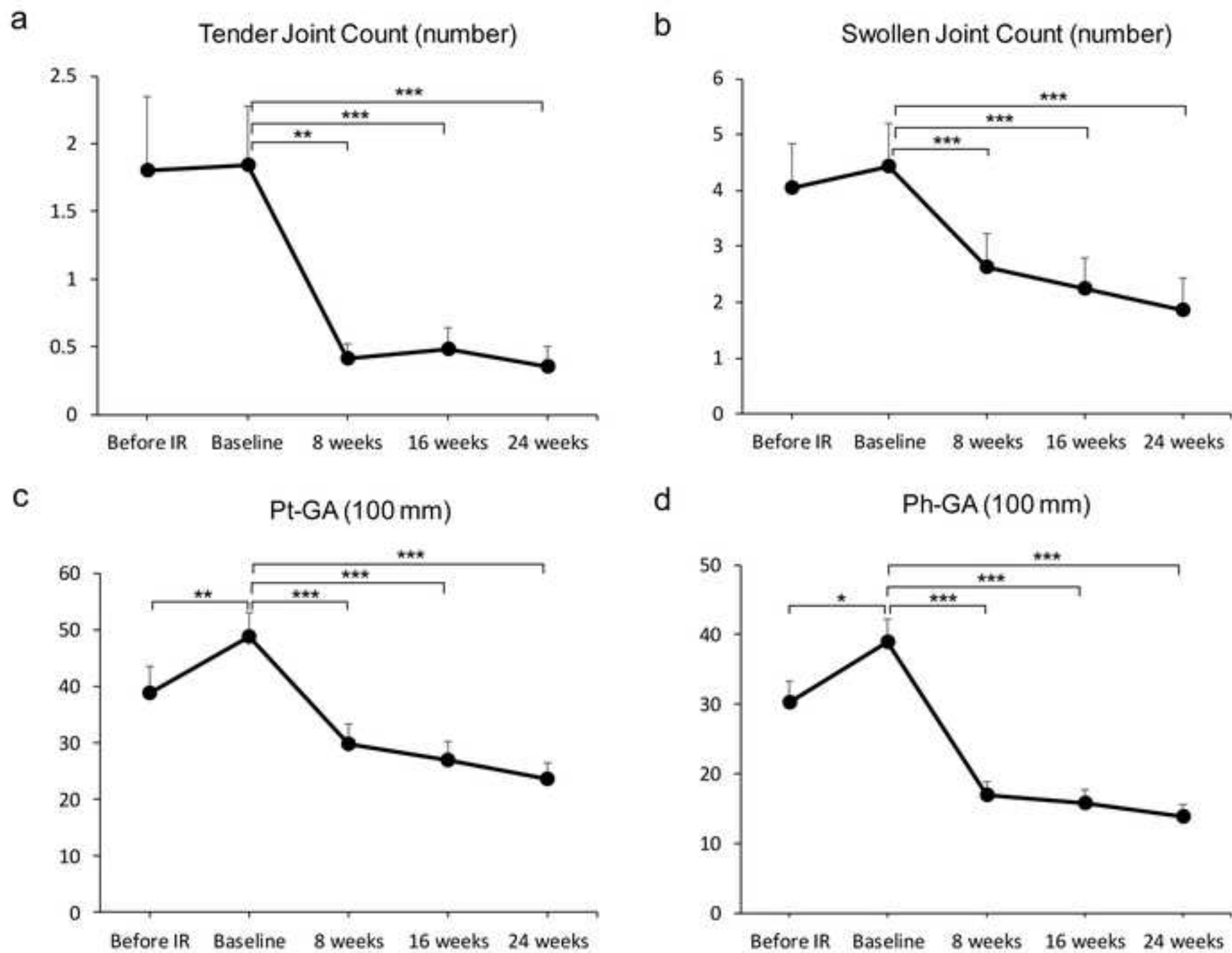


Figure 3

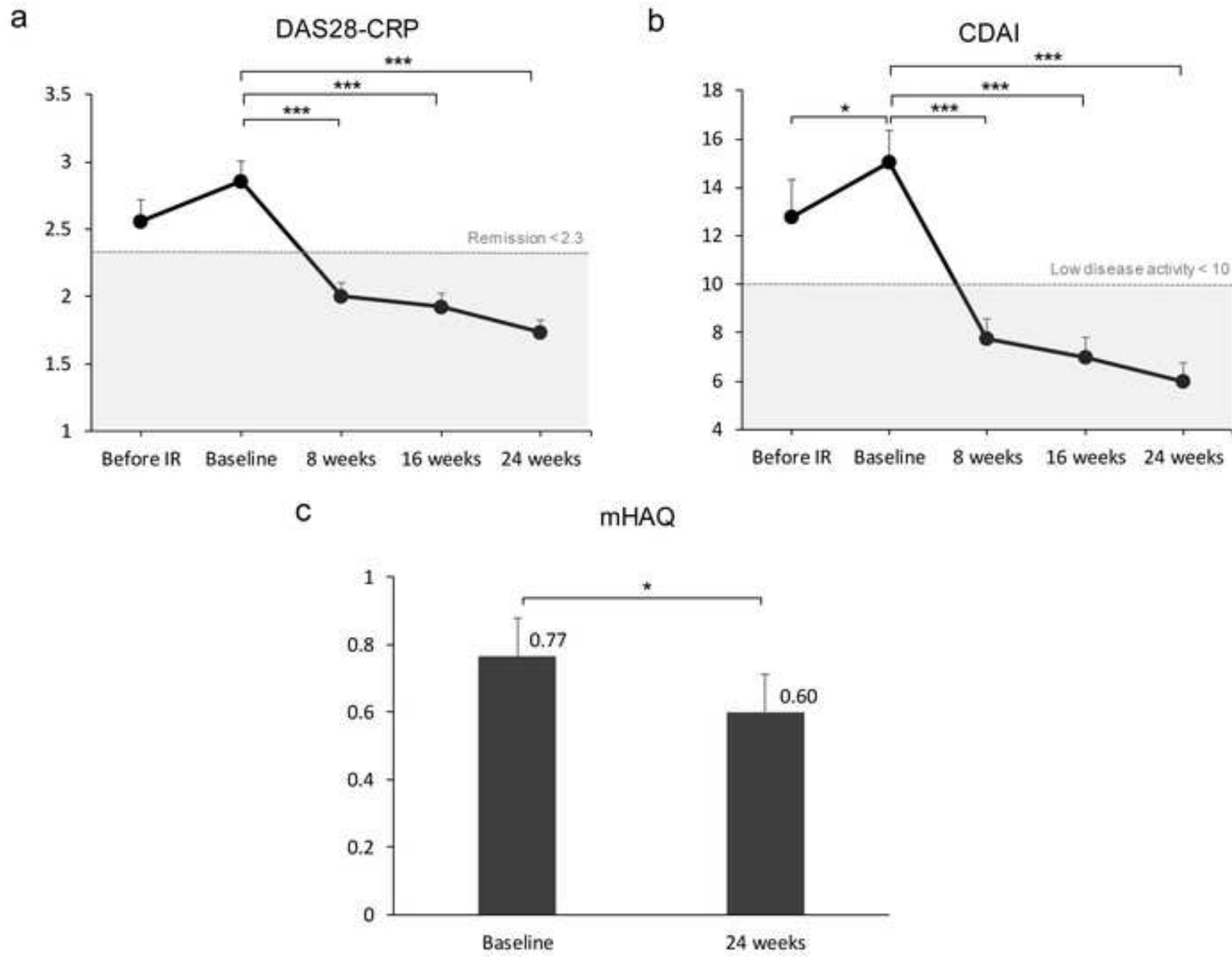


Figure 4

