

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

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3 ***Title:***

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

6

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25
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36 ***This article contains 4 figures and 1 table.***

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

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3 **40 Abstract**

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6 **41 Objectives**

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9 **42** Tocilizumab (TCZ) shows good retention in patients with rheumatoid arthritis (RA), but no
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12 **43** previous reports demonstrated hopeful treatment options against inadequate response to TCZ.
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16 **44** Tacrolimus (TAC) has proved to show efficacy against inadequate response to tumor necrosis
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19 **45** factor alpha inhibitors, yet its add-on effects on TCZ remain unknown.
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22 **46 Methods**

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25 **47** Twenty patients with RA (17 women, age 58.6 y, disease duration 12.1 y, prior TCZ duration 2.6
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28 **48** y, 18 intravenous [8 mg/kg/month] and 2 subcutaneous [324 mg/month] TCZ treatment,
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32 **49** methotrexate 6.1mg/week [70.0%]) who showed an inadequate response to TCZ (clinical
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35 **50** disease activity index [CDAI] \geq 5.8, 18 secondary nonresponders) were additionally treated
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38 **51** with TAC (1.1 mg/day), and enrolled in this 24-week, prospective study.
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41 **52 Results**

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44 **53** Seventeen patients (85.0%) continued the treatment for 24 weeks. Statistically significant
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48 **54** decreases in outcome measures were as follows: disease activity score based on 28 joints with
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51 **55** C-reactive protein (DAS28-CRP) from 3.3 at baseline to 2.1 at week 24 ($P < 0.001$), CDAI from
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54 **56** 17.7 to 7.6 ($P < 0.001$), and serum matrix metalloproteinase-3 levels from 232.8 to 66.2 ng/mL
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57 **57** ($P < 0.001$). 15 patients (75%) achieved low disease activity or remission (DAS28-CRP \leq 2.7 or
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58 CDAI \leq 10) at week 24.

59 Conclusions

60 Adding low-dose TAC to inadequate responders to TCZ may be a promising complementary

61 treatment option.

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3 **63 Introduction**
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6 64 Tocilizumab (TCZ) is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody
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9 65 of the IgG1 subclass directed at the IL-6R α chain. It was originally developed in Japan and has
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12 66 been widely used for the treatment of rheumatoid arthritis (RA) [1, 2] in clinical settings since
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16 67 2008 in Japan, 2009 in Europe, and 2010 in the USA. Recently, the European League against
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19 68 Rheumatism (EULAR) announced a 2013 update to the 2010 recommendations for the
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22 69 management of RA with synthetic and biological DMARDs, in which TCZ is essentially
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26 70 considered to be as efficacious and safe as tumor necrosis factor alpha (TNF- α) inhibitors and
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29 71 should be considered as a first-line biologic agent [3]. In addition, we have previously
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32 72 demonstrated that TCZ therapy is associated with reduced serum oxidative stress levels [4] and
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35 73 may also promote osteoblast differentiation in patients with RA [5].
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38 74 The EULAR recommendations support the use of all biological agents in combination with
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41 75 methotrexate (MTX) [3]. In patients with MTX contraindications or intolerance, TCZ may be
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44 76 considered as part of the first-line treatment strategy with biological agents [3]. Among all
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48 77 biological agents, only TCZ has been demonstrated to be superior as a monotherapy over MTX
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51 78 or other conventional DMARDs [1, 6]. In addition, TCZ is also effective and safe either with or
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54 79 without low-dose MTX for patients with active RA who inadequately respond to DMARDs
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57 80 and/or TNF- α inhibitors [7]. Therefore, TCZ tends to be chosen for patients who cannot tolerate
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81 MTX in real-world setting.

82 However, there are some patients who experience lack of efficacy or loss of efficacy with TCZ.

83 In such cases, the EULAR recommendations suggest changing TCZ to another biologic with

84 another mode of action or add-on therapy with conventional DMARDs [3]. To date, however,

85 we lack reliable evidence for choosing alternative treatments for individual patients with RA

86 who previously had an inadequate response to TCZ, and frequent changes of biologics may lead

87 to multiple biologic failures.

88 Tacrolimus (TAC) is an antibiotic that was isolated from the fungus *Streptomyces tsukubaensis*

89 in Japan in 1984. In 1993, TAC was approved as a rejection inhibitor, and it is the most widely

90 used immunosuppressive drug in the transplantation field globally. In 2005, it was also

91 approved for use in RA, and the clinical efficacy of TAC as a single agent in RA has been

92 reported [8, 9]. Moreover, the concomitant use of small doses of TAC has been shown to be

93 effective when DMARDs [10] and TNF- α inhibitors have resulted in insufficient effects or in

94 cases of secondary failure [11, 12]. Therefore, we hypothesized that adding TAC may be a

95 hopeful complementary therapy for patients with an inadequate response to TCZ and examined

96 the efficacy and safety in this 24-week, prospective study.

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3 98 **Patients and methods**
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6 99 All of the patients with RA included in this study fulfilled the 1987 classification criteria of the
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9 100 American College of Rheumatology [13]. TCZ was infused every 4 weeks at a dose of 8 mg/kg
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12 101 or subcutaneously injected every 2 weeks at a dose of 162 mg in accordance with drug labeling
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15 102 and the TCZ therapy guidelines of the Japan College of Rheumatology (JCR) [14]. Twenty
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18 103 patients who had an inadequate response to TCZ in four hospitals associated with the Osaka
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22 104 University Graduate School of Medicine participated in this prospective study from January
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25 105 2012 to April 2015. An inadequate response to TCZ was defined as having all of the following
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28 106 conditions met: clinical disease activity index (CDAI) score > 2.8 [15, 16] when TAC was
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32 107 started; both tender joint count and swollen joint count were the same or increased compared to
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35 108 those at 4 to 8 weeks prior to TAC; and TCZ was used at same dose for at least 8 weeks prior to
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38 109 TAC. The patients were treated with TAC combination without changing the dosage of TCZ.
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41 110 Efficacy and safety were evaluated 8 weeks later, 16 weeks later, and 24 weeks later. This
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44 111 observational study was conducted in accordance with the ethical standards of the Declaration
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48 112 of Helsinki and approved by the ethical review boards of the Osaka University Graduate School
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51 113 of Medicine (approval number, 11258) and informed consent was obtained from patients
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54 114 included in the study.
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116 **Evaluation of the activity of RA**

117 Efficacy and safety were assessed by comparing changes in tender joint count (TJC) 28, swollen
118 joint count (SJC) 28, patient’s global assessment of disease activity (Pt-GA, 100 mm),
119 physician’s global assessment of disease activity (Ph-GA, 100 mm), serum C-reactive protein
120 (CRP), serum matrix metalloproteinase-3 (MMP-3), white blood cell (WBC) count, lymphocyte
121 count, and functional assessments according to the modified Health Assessment Questionnaire
122 (mHAQ) scores [17] over time. Disease activity was assessed by measures including: disease
123 activity score on 28 joints (DAS28) alone and with CRP (DAS28-CRP) [19], and CDAI score.
124 DAS28-CRP was divided into four categories: remission \leq (2.3), low disease activity ($>$ 2.3 and
125 \leq 2.7), moderate disease activity ($>$ 2.7 and \leq 4.1), and high disease activity ($>$ 4.1). CDAI was
126 divided into four categories: remission (\leq 2.8), low disease activity ($>$ 2.8 and \leq 10), moderate
127 disease activity ($>$ 10 and \leq 22), and high disease activity ($>$ 22) [16]. Observation points were
128 set to the following five time points: 4-8 weeks prior to the start of TAC, at the start of TAC, 8
129 weeks after the start of TAC (week 8), 16 weeks after the start of TAC (week 16), and 24 weeks
130 after the start of TAC (week 24). Clinical responses were defined by EULAR response criteria
131 [19] and also with the American College of Rheumatology (ACR) 20% improvement criteria
132 [20]. Trough whole-blood TAC concentrations were monitored, and any adverse events during
133 the follow-up period were also examined.

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135 **Statistical analysis**

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

143

144 **Results**

145 **Demographic data and drug therapy**

146 Twenty patients (17 women) had inadequate responses to **TCZ** (2 primary non-responders and
147 18 secondary non-responders), and were then treated with add-on low-dose TAC (0.5–2
148 mg/day). Eighteen patients were treated with intravenous TCZ infusion, and two were treated
149 with subcutaneous TCZ injection (Table 1).
150 Their mean age was 58.6 y (range, 40–73 y), and mean disease duration was 12.1 y (range,
151 1–25 y). Of all the patients, 80.0% were in Steinbrocker’s stage III or IV, and 25.0% were in

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

164

165 **Retention rate and combined TAC dose**

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

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171 **Adverse effects**

172 **During the follow-up period, 1 patient developed leukopenia (< 3500/ μ L) and 3 patients**
173 **developed lymphopenia (< 1000/ μ L), although no apparent signs of infection were observed.**

174 Serious adverse events that required medical intervention were not observed during the
175 follow-up period.

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178 **Efficacy**

179 Figs. 1, 2, and 3 show changes in clinical variables. The graphs include the data at 4-8 weeks
180 prior to TAC initiation as representative data before an inadequate response to TCZ. The mean
181 scores of DAS28-CRP were 2.6 ± 0.8 at 4–8 weeks prior to the start of TAC, 3.3 ± 0.8 at start of
182 TAC, 2.4 ± 0.7 at week 8, 2.4 ± 0.9 at week 16, and 2.1 ± 0.6 at week 24 (Fig. 1a); the mean
183 scores of CDAI were 11.5 ± 7.8 , 17.7 ± 7.6 , 9.6 ± 4.6 , 8.9 ± 7.3 , and 7.6 ± 4.4 , for the same
184 periods, respectively (Fig. 1b). The mean serum MMP-3 level was 175.1 ± 203.4 ng/mL, 232.8
185 ± 241.2 ng/mL, 85.6 ± 70.3 ng/mL, 82.0 ± 98.2 ng/mL, and 66.2 ± 39.7 ng/mL, for the same
186 periods, respectively (Fig. 1c). The mean serum CRP level was 0.16 ± 0.46 mg/dL, 0.27 ± 0.73
187 mg/dL, 0.05 ± 0.06 mg/dL and 0.05 ± 0.08 mg/dL, 0.05 ± 0.06 mg/dL, for the same periods,
188 respectively (Fig. 1d). All scores were significantly improved from 8 weeks after TAC treatment.

189 **The mean serum RF level was 154.5 ± 192.5 at baseline and 173.4 ± 252.0 at week 24, which**

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190 didn't show significant change throughout the study.

191 The mean SJC was 3.3 ± 3.8 at 4–8 weeks prior to the start of TAC, 5.4 ± 4.0 at the start of TAC,
192 2.5 ± 2.7 at week 8, 1.6 ± 2.7 at week 16, and 1.4 ± 1.3 at week 24, respectively (Fig. 2a). The
193 mean TJC was 2.2 ± 3.1 , 2.7 ± 3.4 , 1.4 ± 2.3 , 2.2 ± 3.5 , 1.2 ± 2.3 , for the same periods,
194 respectively (Fig. 2b). The mean Pt-GA was 42.1 ± 19.7 , 54.8 ± 19.6 , 36.4 ± 20.4 , 35.0 ± 22.7 ,
195 29.5 ± 16.7 , for the same periods, respectively (Fig. 2c). The mean Ph-GA was 31.5 ± 13.5 , 45.4
196 ± 16.4 , 24.2 ± 9.7 , 19.6 ± 13.6 , 18.9 ± 11.2 , for the same periods, respectively (Fig. 2d). All of
197 which declined over time after the start of TAC.

198 No significant differences in changes in the WBC and lymphocyte counts were observed from
199 the initiation of TAC to after the initiation of TAC (Fig. 3a and b). The mean serum trough TAC
200 concentration (ng/ml) was 3.2 ± 3.0 at week 8, 3.7 ± 3.7 at week 16, and 3.2 ± 3.1 at week 24,
201 respectively (Fig. 3c). Only 10.0% (2/20) of patients obtained recommended reference value of
202 serum trough TAC concentration (5.0 - 20.0 ng/ml) at week 24. However, 83.3% (10/12) of
203 patients who showed lower serum trough TAC concentration than 5.0 ng/ml achieved low
204 disease activity ($CDAI \leq 10$) at week 24. Improvements were also seen in physical function.

205 The mean mHAQ score was 0.9 ± 0.4 at the start of TAC, which significantly improved to $0.5 \pm$
206 0.4 after 24 weeks of TAC therapy (Fig. 3d).

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

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6 209 upon DAS28-CRP disease activity (Fig. 4a). In the same fashion, 14 (70.0%) had low disease
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9 210 activity, and three (15.0%) had moderate disease activity, except three patients (15.0%) who
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12 211 discontinued TAC based upon CDAI disease activity (Fig. 4b). At week 24, 12 of 19 (63.2%)
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15 212 patients achieved more than a moderate response according to the improvement criteria for
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18 213 response to treatment proposed by the EULAR (Fig. 4c). Percentages of patients who attained
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22 214 ACR 20 were 64.7%, 58.8%, and 70.6% at 8 weeks, 16 weeks, and 24 weeks, respectively (Fig.
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25 215 4d).

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28 216 Concerning the difference in the response to TAC between primary and secondary
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31 217 non-responders to TCZ, 100% (2/2) primary non-responders and 66.7% (12/18) secondary
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34 218 non-responders achieved low disease activity ($CDAI \leq 10$) at week 24. Likewise, difference in
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37 219 the response to TAC between bio-naïve and bio-switched patients, 57.1 % (4/7) bio-naïve and
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40 220 76.9% (10/13) bio-switched patients achieved low disease activity ($CDAI \leq 10$) at week 24.
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43 221 There was no significant difference in the achievement ratio of low disease activity between the
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46 222 groups, respectively.
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54 224 **Discussion**

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57 225 Previously, Mori reported the efficacy of additional use of TAC after switching to TCZ in
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3 226 patients who showed inadequate response to IFX, although the number of patients was only
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6 227 three, and also prior treatment was limited to IFX [21]. Recently, Ishida et al. reported the
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9 228 add-on effect of TAC in RA who showed inadequate response to biologics, although the ratio of
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12 229 TCZ was only 16.3%, and the clinical results were not distinguished between each biologics
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15 230 [22]. Taken together, this may be the first prospective report that focused on the safety and
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18 231 efficacy of additional treatment with TAC in a constant number of patients with RA, who
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21 232 showed an inadequate response to TCZ.
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25 233 The efficacy might be explained by several mechanisms. Firstly, TAC forms a complex with
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28 234 FK506 binding protein 12 (FKBP-12), which in turn binds to calcineurin, blocking its activity.
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31 235 This process suppresses T-cell and B-cell activation, the production of antibodies by B cells
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34 236 [23], and also the production of pro-inflammatory cytokines such as TNF- α and IL-6 by
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37 237 activated T cells [24, 25]. This process may synergistically suppress the production of
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40 238 pro-inflammatory cytokines with TCZ and may also inhibit the production of autologous
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43 239 antibodies against biologics, which may lead to loss of efficacy [26]. Secondly, TAC also
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46 240 suppresses IL-6-induced inflammatory processes such as up-regulation of the receptor activator
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49 241 of NF- κ B ligand (RANKL) in fibroblast-like synoviocytes, by up-regulation of a suppressor of
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52 242 cytokine (SOCS3) signaling and consequent down-regulation of IL-6/Janus activated kinase
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55 243 (JAK2)/signal transducer and an activator of transcription-3 (STAT3) [27]. Moreover, TAC has
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3 244 been proved to inhibit nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1
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6 245 (NFATc1) signaling and consequent osteoclasts differentiation [28]. TAC add-on therapy may
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9 246 enhance or restore the anti-inflammatory and anti-bone resorption effects of TCZ through these
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12 247 mechanisms. Thirdly, the long-term use of conventional DMARDs can result in a gradual
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15 248 decrease in their primary effects, such as “escape phenomenon” [29]. It has been reported that
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18 249 P-glycoprotein, which exports steroids and immunosuppressants from inside the target cells and
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22 250 mitigates their therapeutic effects, are induced when the transcription of multidrug resistance-1
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25 251 is induced [30]. By contrast, calcineurin inhibitors, such as TAC, bind to P-glycoprotein
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28 252 antagonistically, preventing drug export from target cells [30-32]. From these mechanisms,
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32 253 TAC may also restore the effects of other combined conventional DMARDs or glucocorticoids.
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35 254 Concerning the effective dose and serum concentration of TAC, the prescription dose of TAC
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38 255 was relatively small (1.1mg/day; range 0.5-2mg/day), and only 10.0% (2/20) of patients
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41 256 obtained the reference value of serum trough TAC concentration (5.0 - 20.0 ng/ml) at week 24.
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44 257 However, 83.3% (10/12) of patients who showed lower serum trough TAC concentration than
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47 258 5.0 ng/ml achieved low disease activity (CDAI \leq 10) at week 24. Taken together, lower serum
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51 259 TAC concentration than reference value may suffice for rescuing inadequate response to TCZ.
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54 260 Naniwa et al. [12] demonstrated the efficacy of additional TAC (1.5–2 mg/day) in patients with
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57 261 RA who were resistant to TNF- α inhibitors in combination with MTX. Recently, the efficacy
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262 and safety of the combination of abatacept and TAC have been reported [33, 34]. Taken together,
263 TAC seems to be a realistic therapeutic option in the treatment of active RA, especially for
264 patients who cannot tolerate MTX and have an inadequate response to biologics.
265 There are several limitations to this study. **First, this study lacks control group such as**
266 **adding-on other DMARDs and is not a randomized comparative study. Second, leukopenia,**
267 **lymphopenia, and consequent infection is major concerns when combining immunosuppressive**
268 **agents,** and the rates of these adverse effects might have been underestimated due to the small
269 numbers of patients and short durations of follow-up. **Third,** precise mechanisms explaining
270 how add-on TAC restores the efficacy of TCZ, even in low serum concentration, could not be
271 specifically elucidated and should be evaluated in further studies. **Fourth,** whether this
272 combination therapy consequently protects the joints from radiographic damage should be
273 evaluated in large-cohort, longer-duration, randomized studies.
274 In conclusion, the results of this prospective study demonstrate that additional use of TAC can
275 be considered as an effective complementary therapy for TCZ-refractory RA patients, especially
276 those with intolerance to MTX.

278 ***Conflict of interest***

279 No authors have any conflicts of interest.

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280 **Figure Legends**

281

282 **Figure 1.** Changes in clinical variables for all patients

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

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

285 IR, inadequate response; TCZ, tocilizumab; DAS28-CRP, disease activity score assessing 28

286 joints with CRP; CDAI, clinical disease activity index; MMP-3, matrix metalloproteinase-3;

287 CRP, C-reactive protein

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289 **Figure 2.** Changes in clinical variables for all patients

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

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

292 IR, inadequate response; TCZ, tocilizumab; SJC, swollen joint count; TJC, tender joint count;

293 Pt-GA, patient's global assessment of disease activity; Ph-GA, physician's global assessment of

294 disease activity

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296 **Figure 3.** Changes in clinical variables for all patients

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

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

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

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

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

304 (a) Distribution of disease activity at the time of TAC initiation, 8 weeks, 16 weeks, and 24

305 weeks after TAC initiation; disease activity was defined using DAS28-CRP scores as follows:

306 remission, $DAS28-CRP \leq 2.3$; low disease activity, $2.3 < DAS28-CRP \leq 2.7$; moderate disease

307 activity, $2.7 < DAS28-CRP \leq 4.1$; high disease activity, $4.1 < DAS28-CRP$.

308 (b) Distribution of disease activity at the time of TAC initiation, 8 weeks, 16 weeks, and 24

309 weeks after TAC initiation; disease activity was defined using CDAI scores as follows:

310 remission, $CDAI \leq 2.8$; low disease activity, $2.8 < CDAI \leq 10$; moderate disease activity, $10 <$

311 $CDAI \leq 22$; high disease activity, $22 < CDAI$.

312 (c) Response to treatment according to the EULAR criteria at the time of TAC initiation, 8

313 weeks, 16 weeks, and 24 weeks after TAC initiation.

314 (d) Response to treatment according to the ACR 20% criteria at the time of TAC initiation, 8

315 weeks, 16 weeks, and 24 weeks after TAC initiation.

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3 316 TAC, tacrolimus; DAS28-CRP, disease activity score assessing 28 joints with CRP; CDAI,
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6 317 clinical disease activity index; ACR20, American College of Rheumatology 20% improvement
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1 Table 1. Baseline characteristics of 20 patients

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

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3 Data are expressed as mean ± SD.

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

5 golimumab; ADA, adalimumab; MTX, methotrexate; PSL, prednisolone; BUC, bucillamine;

6 SASP, salazosulfapyridine; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide

7 (anti-CCP) antibody; CRP, C-reactive protein; DAS28-CRP, disease activity score assessing 28

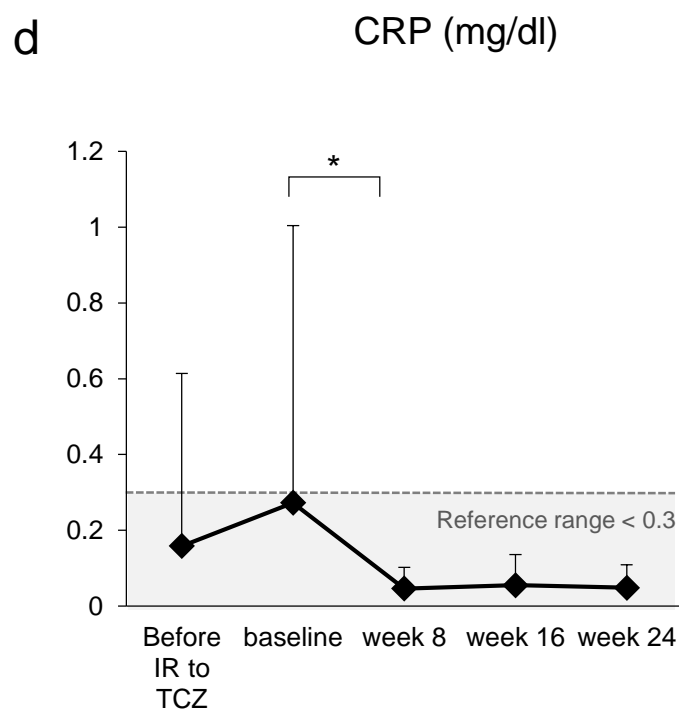
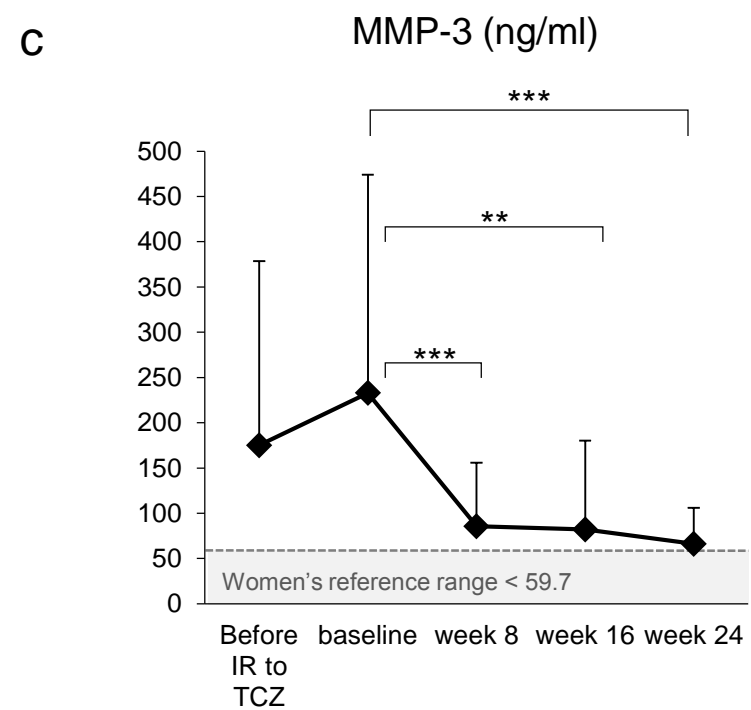
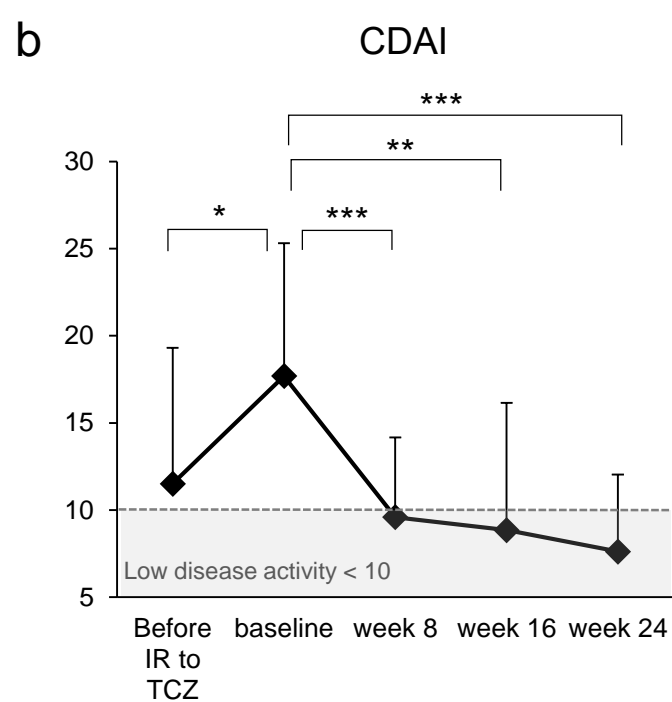
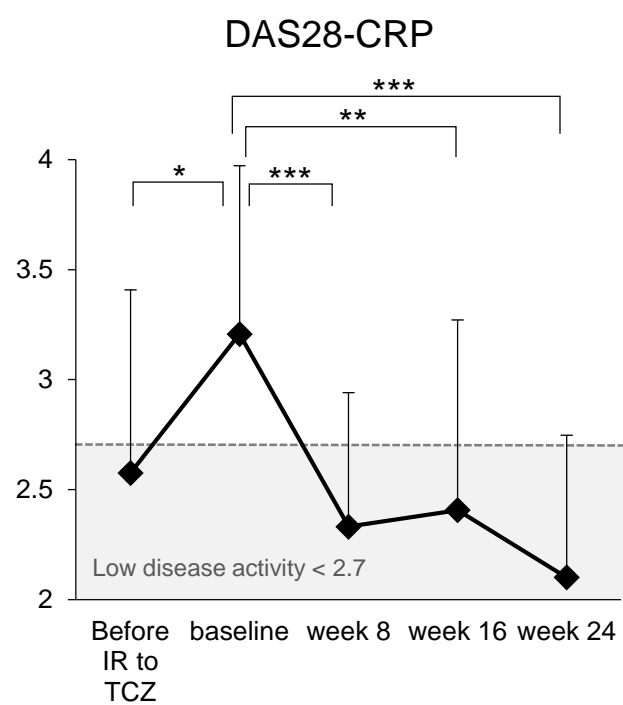
8 joints with CRP, SJC, swollen joint count; TJC, tender joint count; Pt-GA, patient's global

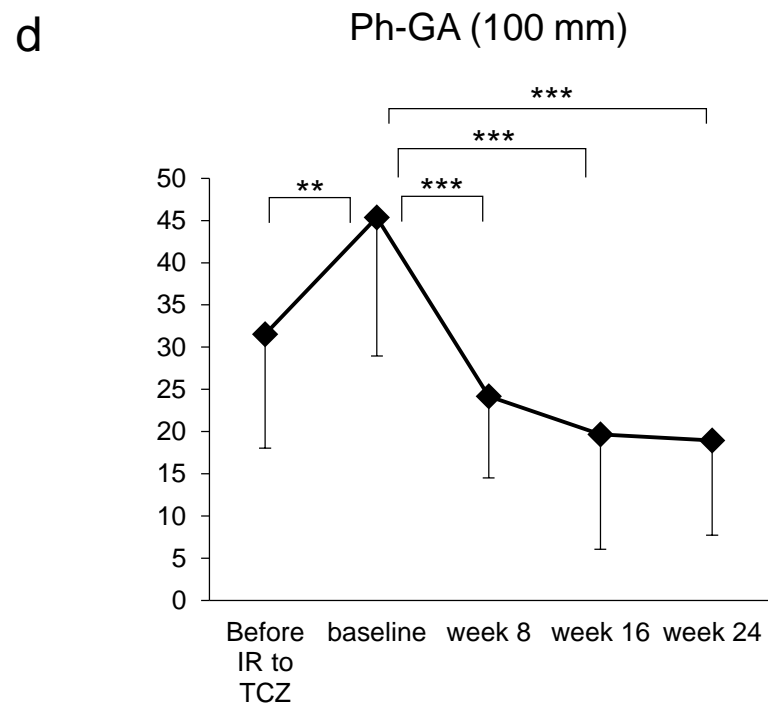
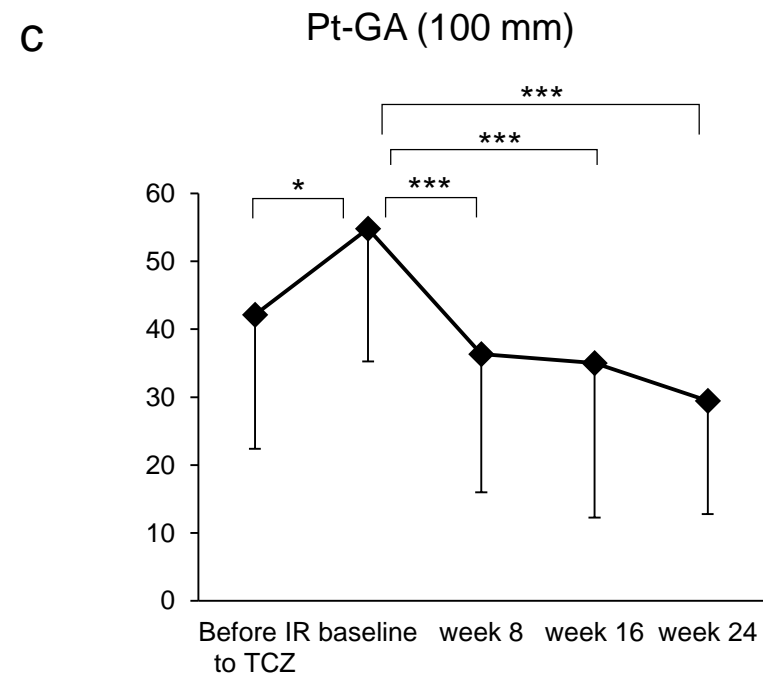
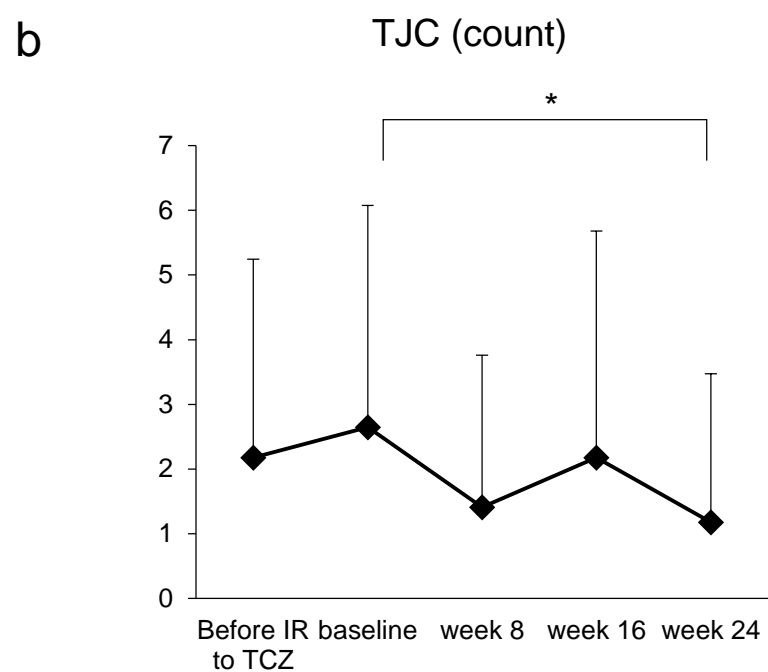
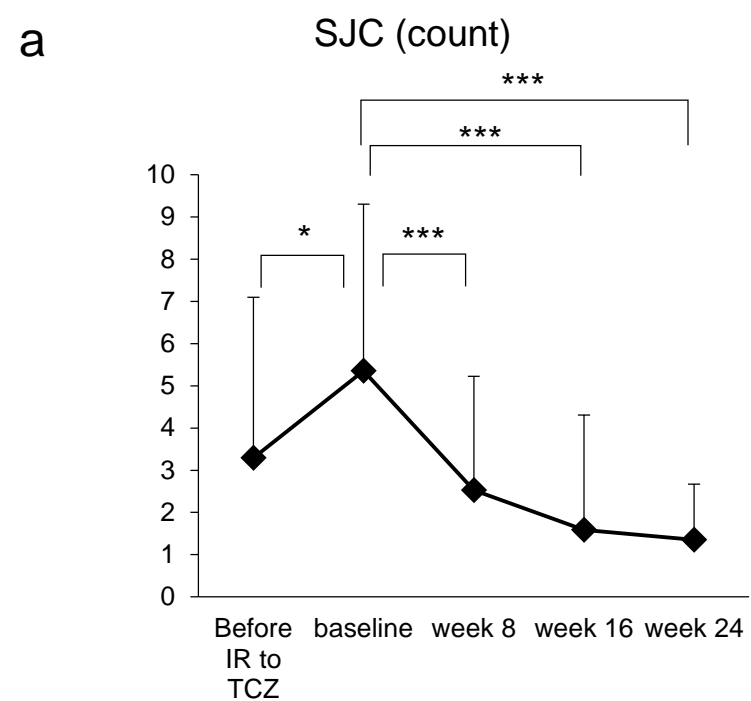
9 assessment of disease activity; Ph-GA, physician's global assessment of disease activity; CDAI,

10 clinical disease activity index; MMP-3, matrix metalloproteinase-3; WBC, white blood cell

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

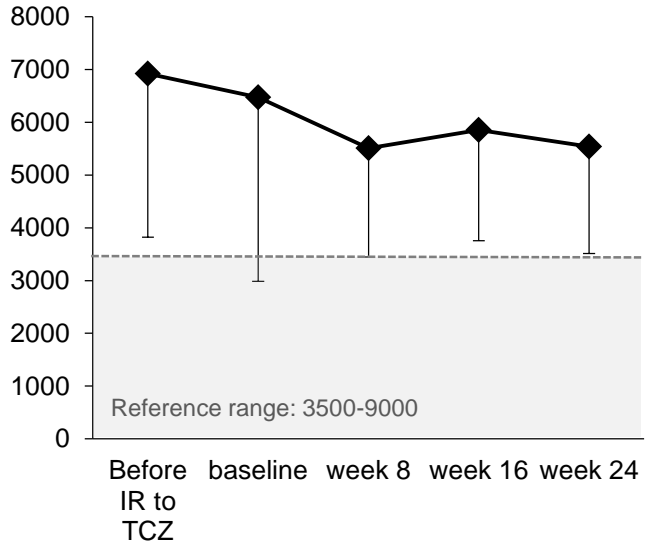
12





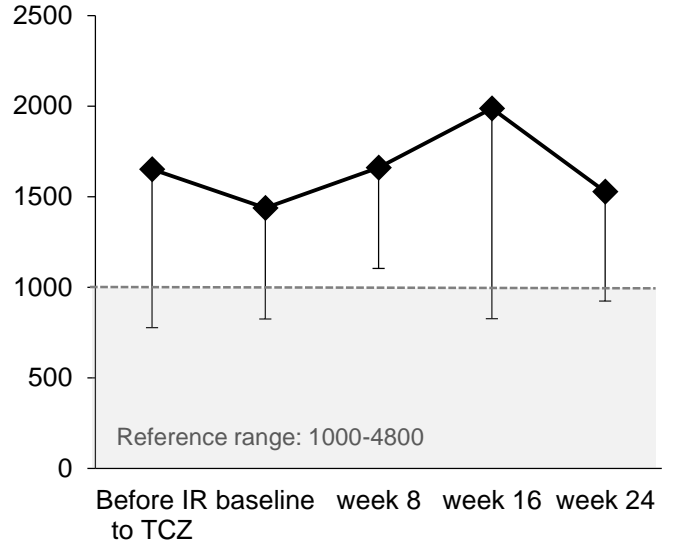
a

WBC (cells/ μ l)



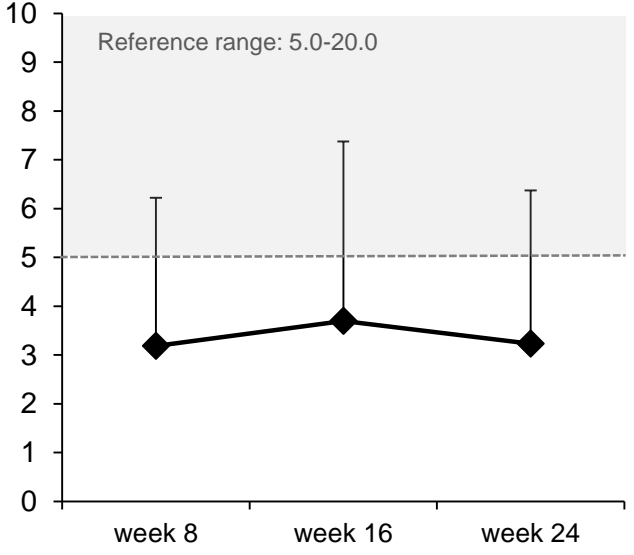
b

Lymphocyte (cells/ μ l)



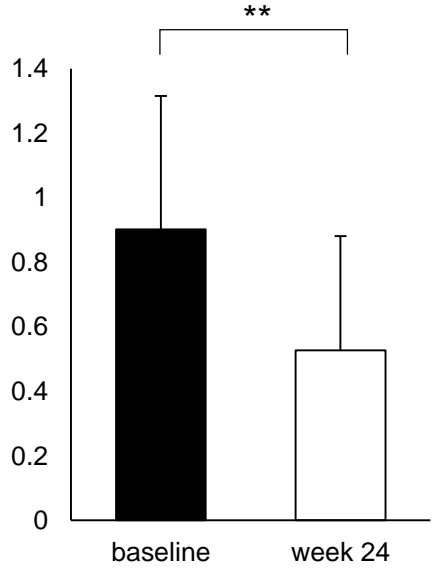
c

Trough TAC concentration (ng/ml)

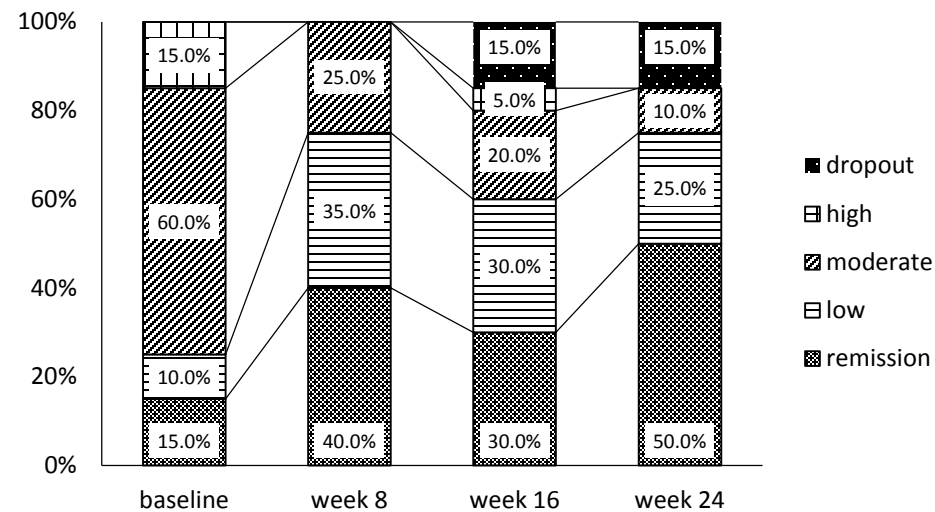


d

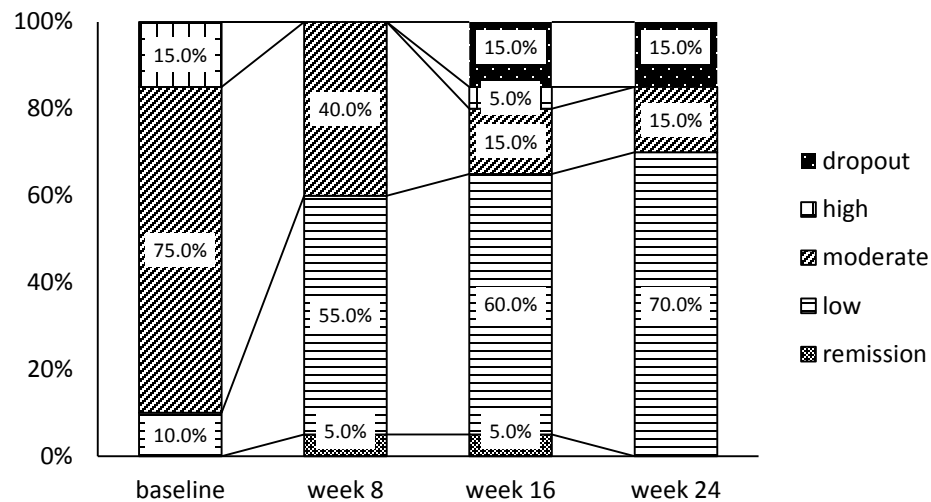
mHAQ



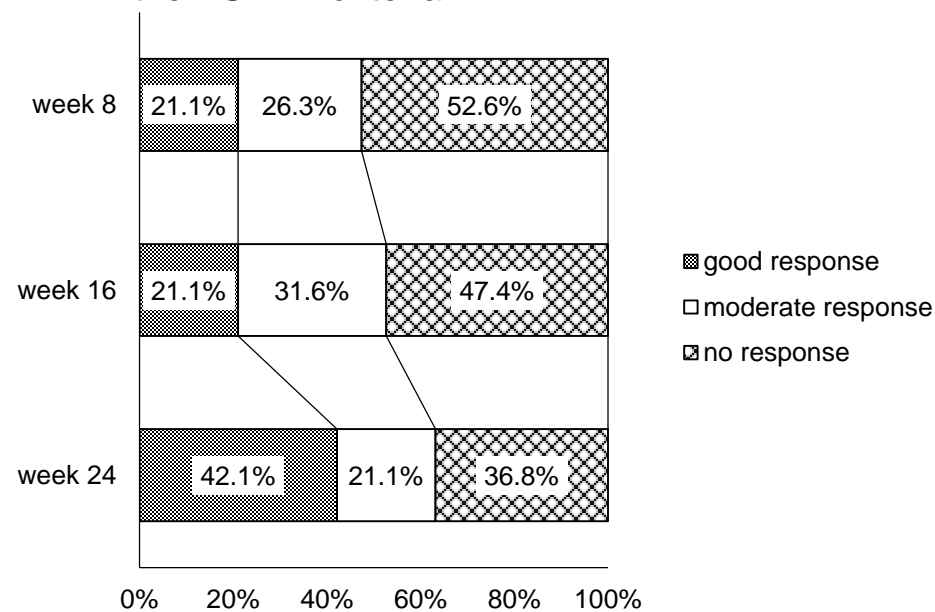
a Distribution of DAS28-CRP disease activity



b Distribution of CDAI disease activity



c Response to treatment according to the EULAR criteria



d ACR 20 response rate

