

# Performance of the new 2011 ACR/EULAR remission criteria with tocilizumab using the phase IIIb study TAMARA as an example and their comparison with traditional remission criteria

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## ABSTRACT

**Background** Remission is the established goal in rheumatoid arthritis (RA) treatment. Although originally defined by a disease activity score in 28 joints (DAS28) <2.6, more stringent criteria may imply the absence of disease activity. The 2011 ACR/EULAR remission criteria provide the newest and most stringent definition of remission.

**Objectives** To evaluate post hoc the remission by ACR/EULAR criteria and compare the criteria with the conventional DAS28 in TAMARA, an open-label phase IIIb tocilizumab (TCZ) trial including patients with active RA receiving inadequate disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitor treatment.

**Results** 286 patients were enrolled, 99.7% of patients were receiving a conventional DMARD and 41.6% had TNF $\alpha$  inhibitor pretreatment. Baseline mean DAS28 of  $6.0 \pm 1.0$  fell to  $2.6 \pm 1.5$  at week 24. DAS28 <2.6 was achieved by 47.6% at week 24. Remission rates with the new ACR/EULAR Boolean-based criteria for clinical studies were 15.0% after 12 weeks and 20.3% after 24 weeks. Of note, 13.5% of patients with previous TNF $\alpha$  blocker inadequate response still achieved remission according to the new ACR/EULAR criteria after 24 weeks. Clinical Disease Activity Index and Simplified Disease Activity Index remission rates were 24.1% and 25.2%, respectively.

**Conclusions** Under the definition of the new stringent 2011 ACR/EULAR remission criteria, patients with active RA despite DMARD treatment and even after inadequate response to TNF $\alpha$  inhibitors, receiving TCZ showed significant rates of remission. Similar remission rates were achieved, when clinical practice criteria, not inclusive of acute phase reactants, were used.

## INTRODUCTION

Remission as the primary therapeutic goal of rheumatoid arthritis (RA) treatment, was commonly defined by the disease activity score in 28 joints (DAS28), with a DAS28 <2.6 indicating remission.<sup>1-5</sup> Clear limitations of the DAS28 have been recognised, as the DAS28 theoretically allows more than 10 swollen joints (SJs) for the definition of remission. Additionally, the erythrocyte sedimentation rate (ESR) at low levels is overestimated by DAS28, and an increased ESR can also be caused by inflammation processes independent of RA. Furthermore, DAS28 application in daily clinical practice may be hampered by the immediate need

for the actual ESR result. The DAS28 cut-off point for RA remission of <2.6 has therefore been considered controversial.<sup>6-11</sup>

Likewise based on 28-joint counts, both the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are more stringent for the definition of remission, because remission is limited to the appearance of a maximum of three and two SJs or tender joints (TJs), respectively. Recently, the ACR and EULAR in a joint effort presented new and even more stringent criteria for RA remission, suggesting criteria for clinical trials and for clinical practice. At any time point, a patient in a clinical trial must achieve a tender joint count (TJC)  $\leq 1$ , a swollen joint count (SJC)  $\leq 1$ , C-reactive protein (CRP)  $\leq 1$  mg/dl, a patient global assessment (PGA)  $\leq 1$ , or, as an index-based score, an SDAI  $\leq 3.3$ , to be considered in remission. For clinical practice, CRP was omitted and a CDAI  $\leq 2.8$  replaced the SDAI.<sup>12</sup>

Recently, the results of the phase IIIb study TAMARA were published.<sup>13</sup> The purpose of our analysis was to compare the high percentage of patients achieving DAS28 remission (47.6%) while receiving tocilizumab (TCZ) with the more stringent 2011 ACR/EULAR criteria. This may be particularly important when using a therapeutic agent with a significant influence on the acute phase response, such as the interleukin 6-receptor-inhibiting antibody TCZ.

## PATIENTS AND METHODS

Details of the study have been described in detail elsewhere.<sup>13</sup> Briefly, in this multicentre, open-label, non-controlled, single-arm study 286 patients with active RA (DAS28 >3.2) despite a stable dose of conventional DMARD (cDMARD) or biological DMARDs were treated with 8 mg/kg TCZ (RoActemra) at 4-weekly intervals for 24 weeks in addition to their cDMARD. One hundred and nineteen patients (41.6%) with mean disease duration of  $10.5 \pm 7.5$  years (median 8.8) had been pretreated with tumour necrosis  $\alpha$  factor (TNF $\alpha$ ) antagonists. Patients pretreated only with cDMARDs had a shorter disease duration (mean  $5.9 \pm 5.9$  years (median 4.3)). Two hundred and thirty-nine patients (83.6%) completed the full 24 weeks of the trial. The primary objective was to determine the proportion of patients reaching lowDAS <3.2 after 24 weeks, secondary end points comprised the proportion of patients showing a DAS28 remission (<2.6). For this analysis, we



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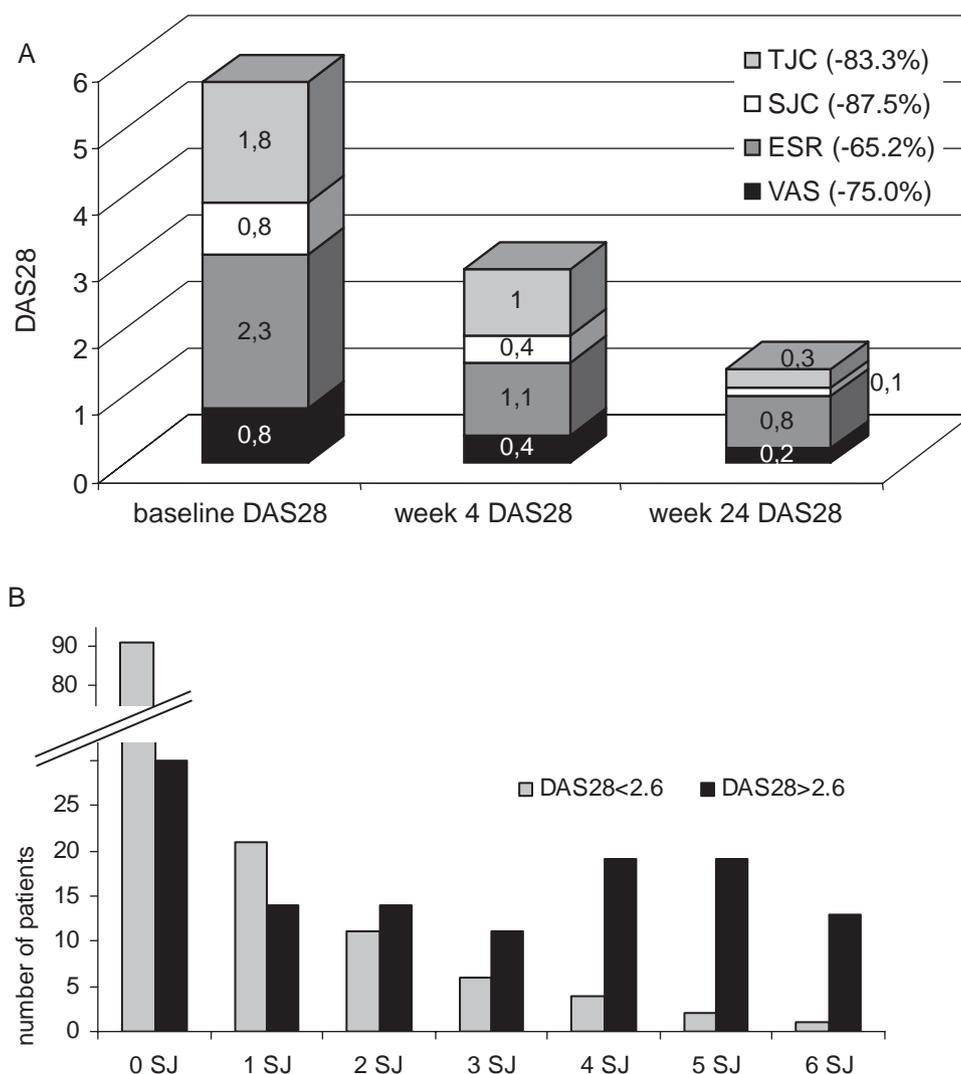
assessed remission with the novel ACR/EULAR criteria,<sup>12</sup> comparing them with DAS28 remission. The wording of the PGA Visual Analogue Scale (VAS) followed the more open DAS28 wording, in some contrast to the ACR/EULAR definition, which asks for specific arthritis complaints. Thus, the DAS PGA value had to be used as an estimate for the correct values, which might lead to underestimating Boolean rates of ACR/EULAR remission. The last observation carried forward method was used to impute missing values for continuous core variables. For categorical variables missing values were assessed as patients not reaching remission.

**RESULTS**

A total of 53.4% of patients with disease-modifying antirheumatic drug-inadequate response (DMARD-IR) RA and 41.2% of patients with TNF $\alpha$ -IR RA achieved DAS28 remission (details are published in Burmester *et al*<sup>13</sup>).

In addition to its pronounced effect on acute phase reactants (APRs), the SJC and the TJC both decreased considerably. Compared with the reduction of the APR the effect on the SJC and the TJC was even more pronounced (see figure 1A and online supplementary table 1). While most patients in DAS remission had no SJs, approximately one in five patients still had at least one, and up to six SJs (figure 1B).

Based on that observation, we assessed remission with the new ACR/EULAR Boolean based remission criteria of patients in clinical trials, defined as described above, allowing only a maximum of one TJ and one SJ. Applying these stringent criteria, 16.1% of patients were in remission after 12 weeks and 20.3% after 24 weeks (Figure 2a). Of note, when clinical practice definitions of remission (non-inclusive of APR) were employed, TCZ achieved remission in 15.0% of patients after 12 weeks and 20.3% after 24 weeks. While remission was achieved in



**Figure 1** (A) Twenty-eight joint count Disease Activity Score (DAS28) values of the patients reaching DAS remission at week 24. Each stacked bar represents the DAS28 value at the respective visit. Each segment of a single bar represents the proportion of DAS28 that is due to a specific core variable. In the figure it is, for example, shown that 2.3 points of a total DAS28 of 5.7 at baseline is due to erythrocyte sedimentation rate (ESR) or 0.1 points of a total DAS28 of 1.5 is due to swollen joints (SJs) after 24 weeks. The relative reduction between baseline and week 24 is highest for swollen joint count (SJC) and tender joint count (TJC) (87.5% and 83.5%) compared with reduction of the ESR (65.2%). It is obvious that the TJC and the ESR are weighted higher in the DAS composite than the SJC and the Visual Analogue Scale (VAS). (Please note: numbers in the figure were rounded incorrectly for ESR at week 4 and 24, thus resulting in slightly different numbers.) (B) Number of patients, who are in DAS28 remission (grey) or and with a DAS > 2.6 (black) after 24 weeks and their number of SJs. Though most patients in DAS28 remission had no SJs, some patients still had a significant number of SJs.

over a quarter of patients (27.6%) pretreated with DMARDs, 13.5% of patients with previous TNF $\alpha$  blocker IR still attained remission according to the new ACR/EULAR criteria after 24 weeks. The CDAI and SDAI were slightly higher in the overall group (24.1% and 25.2%).

To assess whether the more stringent remission criteria had an impact on patient-related outcomes, we analysed the relationship with the Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) and pain scores after 24 weeks. The proportion of patients with an HAQ-DI of <0.5 was higher in patients reaching remission according to the new stringent criteria than in patients in DAS28 remission (see figure 3A). Similarly, improvement in other patient-related outcomes was higher in patients in CDAI or SDAI remission than in patients in DAS28 remission. Nevertheless, patients with low disease activity according to CDAI, SDAI and DAS28 still benefited significantly (figure 3B).

**DISCUSSION**

The new remission criteria proposed by ACR and EULAR will probably replace the well-established DAS28-based criteria, which have always been controversial. It now remains to be established, if the novel criteria are indeed more useful in trials, which try to model routine clinical practice. The TAMARA phase IIIb study appears to be suitable for analysing this question. This trial had demonstrated very high rates of DAS28 remission of 47.6% with TCZ, while the ESR fell from 28 mm/h to 6 mm/h. Cytokine-blocking biological agents, and TCZ in particular, led to a normal APR in almost all patients. While this constitutes a positive treatment effect, such improvement in ESR might lead to an overestimation of remission rates achieved with the DAS28.<sup>14</sup> The novel ACR/EULAR remission criteria are not prone to lead to such bias. However, given that they will not allow for more than one TJ or a VAS >1, remission defined by these criteria might be very difficult to achieve.

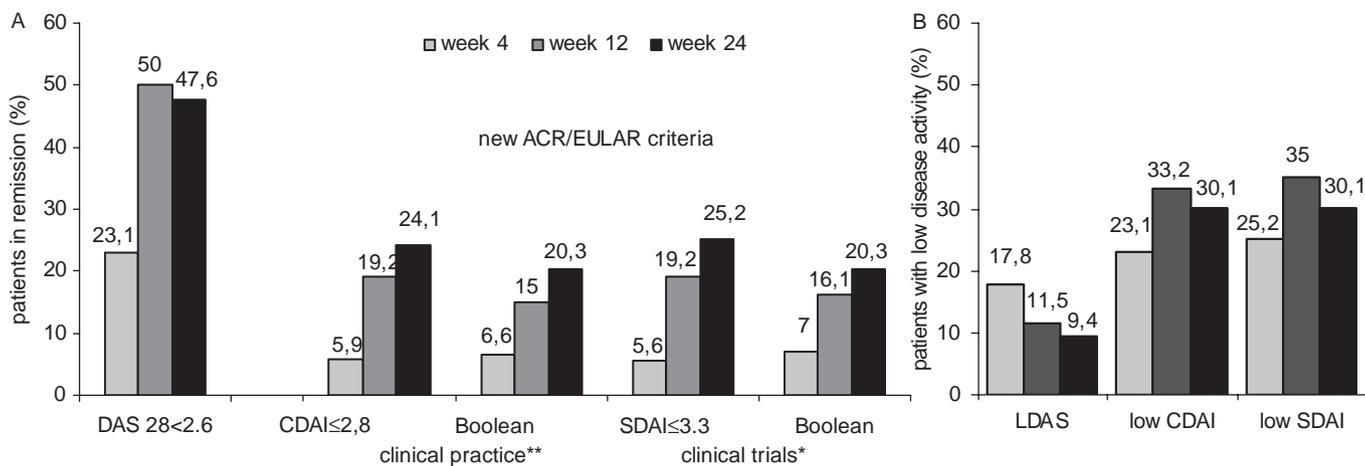
When now analysing the same patient population with these new remission criteria, it came as no surprise that the

more stringent remission criteria gave significantly lower rates. Nevertheless, TCZ still achieved ACR/EULAR remission in more than a quarter of those patients who had not had an adequate response to cDMARDs, and in 13.5% of patients with active RA despite TNF $\alpha$  inhibitor failure. Moreover, 7% were in ACR/EULAR remission as early as 4 weeks after starting TCZ.

The difference between the numbers for DAS28 and for ACR/EULAR remission was to be expected, given the narrow limits of one clinically SJ and TJ each and the  $\leq 1$  cm limit in patient self-assessment. However, these numbers indicate that ACR/EULAR remission is a meaningful concept and an attainable goal for clinical trials and clinical practice. Indeed, the new criteria showed better discrimination between RA refractory to cDMARDs and also not responding to TNF blockers. On the other hand, it was also reassuring to see that modern agents like TCZ now regularly achieve a more stringently defined remission despite inadequate response to DMARDs, and even TNF $\alpha$  blockers—that is, in a subset of patients for whom very few options would have existed 15 years ago.

CDAI and SDAI remission rates, the proposed indexed-based remission criteria,<sup>12</sup> were closely linked in our study population, despite the influence of the CRP on SDAI, in view of the absence of APRs in CDAI. This is well in line with CDAI derivation data based on other DMARDs<sup>15</sup> and with findings from the TCZ pivotal trials.<sup>14</sup> The fact that scores without ESR or CRP worked in the TAMARA trial, as well as the moderate weight of ESR changes between active disease and DAS28 remission (figure 1) suggest that the reduction of the APR is not the decisive factor in leading to remission with TCZ. Our results suggest that the CDAI (without the APR) is sufficient for the follow-up of patients receiving TCZ, because virtually all patients treated with TCZ have a normal CRP and/or ESR.

In comparison with the novel Boolean criteria, CDAI and SDAI are, however, somewhat more flexible in their attribution of points. A patient with a global self-assessment of disease activity of 2.5 cm on the 10 cm scale may still be in CDAI remission, when SJC and TJC are zero. Most probably, the somewhat



\*inclusive of CRP  
\*\*not inclusive of CRP

**Figure 2** (A) Patients achieving remission according to the different assessment tools DAS28  $((0.56 \times TJC^2) + (0.28 \times SJC^2) + (0.7 \times \ln(ESR)) + (0.014 \times PtGA)) < 2.6$  and the new ACR/EULAR criteria for clinical practice (Boolean-criteria SJC, TJC, PtGA all  $\leq 1$ ) and CDAI  $(SJC + TJC + PhGA + PtGA) \leq 2.8$  and clinical trials (Boolean-criteria SJC, TJC, PtGA, CRP all  $\leq 1$  and SDAI  $(SJC + TJC + PhGA + PtGA + CRP (mg/dl)) \leq 3.3$ ). (B) Patients achieving low disease activity (DAS  $> 2.6$  and  $\leq 3.2$ ; CDAI  $> 2.8$  and  $\leq 10$ ; SDAI  $> 3.3$  and  $\leq 11$ ). (All data shown 'as observed'). CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; DAS28, 28-joint count Disease Activity Score; ESR, erythrocyte sedimentation rate; PhGA, physician global assessment; PtGA, patient global assessment; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

higher remission rates with these scores are explained by such higher flexibility.

'True' remission may not have been achieved in many of the patients in DAS28 remission, and those who do not achieve remission according to the new ACR/EULAR criteria, in particular. Nevertheless, it is not entirely clear that these latter patients will not likewise have an excellent outcome. Although DAS28 remission may not always be sufficient to protect patients receiving methotrexate from structural damage,<sup>12</sup> the direct effects of biological response modifiers both on the APR and on joint destruction may offer additional protection. Still, the improvement in the patient-related outcomes HAQ-DI, pain and fatigue was more pronounced in patients in CDAI or SDAI remission than in those in DAS28 remission, while reaching low disease activity was already associated with obvious benefit (figure 3A,B).

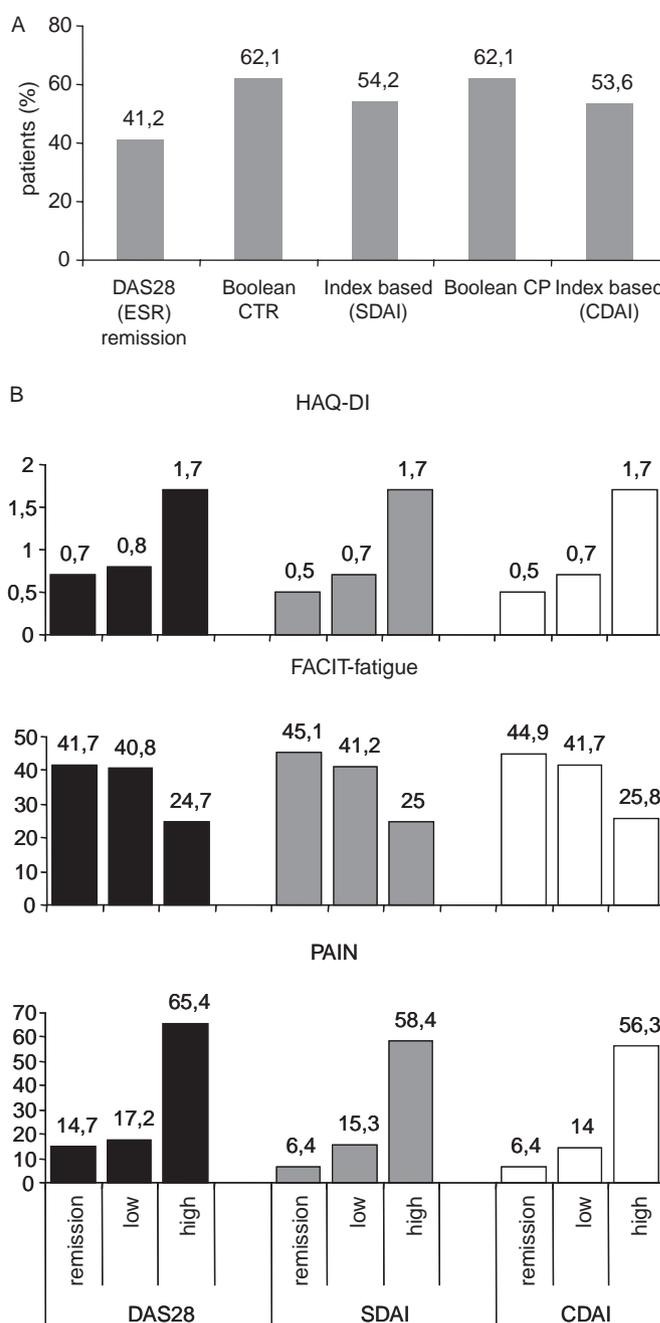
Even low disease activity may be an acceptable result for some patients (especially those with longstanding RA), and, on a conciliatory note, the overall percentages of patients achieving at least low disease activity are virtually identical between DAS28, SDAI, and CDAI (see figure 2B). This will cover approximately two out of three patients, while one-third of the patients still need a better individual treatment strategy.

Our study has some limitations: this assessment with the new remission criteria is a post hoc analysis. The predefined outcome of the study was low disease activity and remission according to DAS28. In consequence, the wording of the patient VAS was more open, while the ACR/EULAR criteria suggest concentration on arthritis complaints. This may underestimate the Boolean rate of remission. TAMARA was an open-label, one-arm trial, which could increase both investigator bias and placebo effect. This might lead to an overestimate of remission rates. Moreover, the trial had a duration of 6 months only, and radiographic change was not assessed.

Nevertheless, to the best of our knowledge, this is the first report using the new 2011 ACR/EULAR remission criteria for patients from a phase IIIb study receiving TCZ. The new criteria have been validated in clinical trials with TNF $\alpha$  blockers<sup>16-18</sup> showing remission rates in 22% of patients with early RA (data in Felson *et al*<sup>12</sup>). Such clinical trials, where patients meet stringent inclusion criteria, differ from real-life medical care.<sup>19</sup> Our data from the TAMARA study, which was designed to reflect daily clinical routine, show even higher remission rates of up to 27.6% of patients whose RA had not adequately responded to cDMARDs before. Achieving stringent and sustained remission in patients with RA remains an ambitious aim, even with the treatment options we now have available. However, the new ACR/EULAR criteria for assessing remission define a realistic, but very ambitious level of disease control, which will push us further toward reaching 'true remission'. The fact this may still be more difficult to achieve for patients with longlasting disease once again underlines the importance of early and effective treatment in daily clinical practice.

### CONCLUSIONS

Measurement of RA remission with DAS28 has been shown to be of limited usefulness for treatment with biological response modifiers. The new 2011 ACR/EULAR criteria for remission provide a new tool to stringently define remission of RA in trials and in routine clinical practice. Despite the stringency of these criteria and the highly active disease of the patients in the TAMARA study with DMARD pretreatment, TCZ induced remission rates in over a quarter of patients. Of note, significant



**Figure 3** (A) Proportion of patients with HAQ-DI remission (<math><0.5</math>) according to the five remission criteria (erythrocyte sedimentation rate (ESR); clinical trial (CTR); clinical practice (CP)). (B) Impact of clinical remission according to DAS28, CDAI or SDAI on patient-related outcome HAQ-DI (scaled from 0 to 3, 0=no disability), FACIT-fatigue (higher scores indicate better quality of life) and pain (visual analogue scale 0=no pain, 100=worst pain) after 24 weeks. The more stringent criteria CDAI and SDAI tended to have a better patient-related outcome on the HAQ-DI and pain, but not in the FACIT fatigue score. Noteworthy also patients with low disease activity benefited clearly from tocilizumab treatment. CDAI, Clinical Disease Activity Index; DAS28, 28-joint count Disease Activity Score; FACIT, Functional Assessment of Chronic Illness; HAQ-DI, Health Assessment Questionnaire-Disability Index; SDAI, Simplified Disease Activity Index.

remission rates with TCZ were even achieved after inadequate response to TNF $\alpha$  inhibitors and also with disease activity measures not inclusive of APRs such as the CDAI and the new ACR/EULAR criteria for clinical practice. Cytokine blocking

agents, such as TCZ, can rapidly achieve stringent remission after DMARD (and TNF $\alpha$  blocker) failure. Thus, the new ACR/EULAR remission criteria are feasible and produce meaningful numbers in settings close to everyday clinical routine.

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**Competing interests** GRB, EF, MA, JW and CIK are members of advisory boards, received grant support or honoraria as speakers from Roche/Chugai. ST is an employee of Roche Pharma Germany and TM is an employee of Chugai Pharma Germany.

**Ethics approval** This study was conducted with the approval of the Charite Berlin, Germany.

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**Table 1** Suppl.: Change from baseline to week 24 in number of swollen (SJC) and tender joints (TJC) and PGA of disease activity on the VAS in patients with different DAS28 baseline in correlation with DAS28 based disease activity. Compared to the acute phase response, the relative effect on the SJC and TJC in patients reaching DAS28 remission after 24 weeks was even more pronounced compared with the decrease in APR in these patients. Of note, in patients with a high DAS28 of > 5.1 at baseline, the relative effect on the swollen and tender joints was even more prominently than in patients with a DAS < 5.1. PGA and PhGA of disease activity also improved significantly after the treatment with TCZ, the ESR was within normal limits in virtually all patients in both DAS28 groups. The missing 22 patients had a DAS28 < 4.1 or a missing (DAS n = 12) at baseline (due to missing ESR).

	<b>DAS28 4.1 – 5.1 (n=47)</b>		<b>DAS28 &gt; 5.1 (n=217)</b>	
	<b>Absolute value (Mean + SD)</b>	<b>Relative difference to baseline (%) [Mean + SD]</b>	<b>Absolute value (Mean + SD)</b>	<b>Relative difference to baseline (%) [Mean + SD]</b>
<b>SJC</b>				
<b>baseline</b>	4.4 ± 2.7		11.0 ± 5.1	
<b>week 24</b>	2.0 ± 3.2	-48.6± 72.4	2.8 ± 3.7	-72.3 ± 37.6
<b>TJC</b>				
<b>baseline</b>	5.8 ± 2.9		14.5 ± 6.0	
<b>week 24</b>	2.1 ± 2.6	-55.4± 61.5	4.8 ± 6.3	-68.1± 40.4
<b>Patients assessment of disease assessment (VAS)</b>				
<b>baseline</b>	52.8 ±18.5		65.3±19.4	
<b>week 24</b>	25.4 ± 22.1	-43.9 ± 56.2	27.3 ± 25.9	-53.0 ± 55.7
<b>Physicians assessment of disease assessment (VAS)</b>				
<b>baseline</b>	54.9 ± 16.7		65.6 ± 17.3	
<b>week 24</b>	20.5 ± 21.3	-57.5 ± 54.8	17.9 ± 19.3	-62.2 ± 170.3
<b>ESR</b>				
<b>ESR baseline</b>	27,9 ± 16,9		40,3 ± 22,4	
<b>ESR week 24</b>	5,6 ± 5,6	-73,3 ± 26,6	7,6 ± 10,5	-72,4 ± 88,7