Early effects of tocilizumab in the treatment of moderate to severe active rheumatoid arthritis: a one-week sub-study of a randomised controlled trial (Rapid Onset and Systemic Efficacy [ROSE] Study)

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Abstract

Objectives
Tocilizumab has demonstrated efficacy in managing rheumatoid arthritis (RA) from week 2 onward. This sub-study assessed effects of tocilizumab plus disease-modifying anti-rheumatic drugs (DMARDs) during the first week of therapy.

Methods
Rapid Onset and Systemic Efficacy was a 24-week, randomised, double-blind, placebo-controlled, parallel-group trial. Adults with moderate to severe active RA taking DMARDs received tocilizumab 8 mg/kg (or placebo) plus DMARDs every 4 weeks. Data were analysed from the first 62 patients at designated study sites who agreed to clinical evaluation and blood sampling at days 3 and 7 and had C-reactive protein levels ≥1 mg/dl. Outcomes included American College of Rheumatology core data set measures, disease activity score using 28 joints (DAS28) and routine assessment of patient index data 3 (RAPID3) scores.

Results
Baseline evaluations were similar between groups (tocilizumab, n=40; placebo, n=22). Patient global assessments of disease activity and pain improved significantly in favour of tocilizumab (mean change from baseline to day 7: -16.2 [tocilizumab], 0.8 [placebo] [p=0.005] and -12.2 [tocilizumab], 1.4 [placebo] [p=0.01], respectively). Physician global assessment of disease activity also improved more with tocilizumab (-15.4 [tocilizumab], -5.6 [placebo] [p=0.05]). Changes from baseline in tender/swollen joint counts, physical function and RAPID3 scores were not significantly different between groups. DAS28 significantly improved with tocilizumab versus placebo at day 7 (-1.16 [tocilizumab], -0.27 [placebo] [p=0.007]).

Conclusion
Tocilizumab showed significant improvement in patient-reported disease activity, pain and DAS28 score as early as day 7 after first infusion, earlier than physician-reported measures, which may take longer to manifest.

Key words
tocilizumab, rheumatoid arthritis, randomised controlled trial, outcome assessment, pain

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Introduction

In the treatment of patients with rheumatoid arthritis (RA), it is important to control the inflammatory process as quickly as possible to reduce symptoms, improve function and minimise long-term joint damage (1). This goal remains difficult to achieve for many patients, indicating a need for alternative therapies for those patients who do not fully respond to traditional disease-modifying anti-rheumatic drugs (DMARDs), anti-tumour necrosis factor (anti-TNF) therapy or both. For example, it has been reported that RA remains poorly controlled in 20% to 30% of patients initially treated with methotrexate (2). In addition, 30% of patients treated with anti-TNF therapy do not attain American College of Rheumatology 20% (ACR20) or greater improvement, and others experience loss of efficacy over time during therapy (3). In an analysis from a US claims database, approximately 50% of patients continued anti-TNF therapies after 2 years (4).

Tocilizumab is a humanised monoclonal anti-IL-6 receptor antibody (5). Several phase 3 randomised controlled trials have demonstrated the efficacy of tocilizumab in combination with traditional DMARDs (6-9) or as monotherapy (10, 11). In these studies, which report some efficacy measures starting at week 2, benefit was observed within 2 to 4 weeks of the initiation of tocilizumab treatment (6-11). There is a need for more data regarding the onset of effect of tocilizumab and the best measures with which patients and clinicians can assess early symptomatic benefits of treatment.

Here we report a sub-study of a large, 6-month, US clinical trial of tocilizumab or placebo (in combination with traditional DMARDs) in patients with moderate to severe RA (12). This substudy was specifically conducted to assess the effects of tocilizumab in combination with DMARDs during the first week of therapy. Assessments included patient- and physician-reported measures of disease activity and laboratory measures (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) at day 7 after the first treatment infusion (with CRP measured at both days 3 and 7).

Materials and methods
Study design
As described previously (12), the Rapid Onset and Systemic Efficacy (ROSE) study was a 24-week, double-blind, placebo-controlled, parallel-group, randomised trial (clinicaltrials. gov NCT00531817).

Adult patients with moderate to severe active RA who were experiencing inadequate responses to stable, non-biologic DMARD therapy (≥7 weeks before study baseline) were assigned randomly (2:1) to receive either tocilizumab 8 mg/kg plus DMARDs every 4 weeks or placebo plus DMARDs every 4 weeks. This sub-study of the trial used data from the first 62 patients (10% of the overall cohort) at designated study sites who agreed to participate in clinical evaluation and blood specimen sampling at days 3 and 7. The overall trial included adult patients with diagnoses of active RA defined according to revised 1987 ACR criteria of at least 6 months' duration. In addition, eligible patients were required to have ≥6 swollen joints and ≥6 tender joints at screening and baseline and either CRP ≥1 mg/dl or ESR ≥28 mm/h at screening. To be eligible for inclusion in the sub-study, patients were required specifically to meet the CRP entry criterion (≥1 mg/dl). All patients supplied written informed consent, and the study complied with the principles of Good Clinical Practice and the Declaration of Helsinki.

Assessments
Additional assessments performed for the sub-study included patient global assessment of disease activity and patient global assessment of pain (both using visual analogue scale [VAS] 0–100 mm), physician global assessment of disease activity (VAS 0–100 mm), patient assessment of disability measured by the Multidimensional Health Assessment Questionnaire for physical function (MDHAQ-function [FN], swollen joint count (66), tender joint count (68) and ESR at day 7; and CRP level at days 3 and 7. Also calculated at baseline and day 7 were the Disease Activity Score 28 (DAS28) and the routine assessment of patient index data 3 (RAPID3) score, which consists of three items from the

MDHAQ-FN (VAS for pain, VAS for patient assessment of global disease activity). In addition, ACR20, ACR50 and ACR70 responses were determined for day 7. Low disease activity (LDA; DAS28 ≤3.2), ACR20 and ACR50 responses were also assessed for the sub-study patients every 4 weeks for weeks 4 through 24.

Statistical analysis
Early assessments (days 3 and 7) for this sub-study were pre-defined in the protocol as secondary end points. The analysis, which occurred after the sub-study patients completed the day 7 visit, was performed by an independent data review committee. The study management team, investigational staff and monitors remained blinded to the patients' treatment assignments so that the enrolment, design or conduct of the overall study was not altered. ACR responses were analysed based on two-sided Fisher exact tests. Change from baseline for CRP, ESR, DAS28, RAPID3 and individual ACR core set measures was analysed using an analysis of covariance model with baseline value as a covariate and treatment group as a factor. The 95% confidence intervals (CIs) for the difference of change from baseline between treatment groups were also calculated. CRP data were analysed as planned. *Ad hoc* statistical testing was carried out for other parameters, in addition to the planned descriptive analyses. Percentages of patients achieving LDA, ACR20 and ACR50 responses for weeks 4 through 24 were estimated in a *post hoc* analysis.

The analysis population included randomly assigned patients from the sub-study who received at least one administration of study medication and who attended the day 3 or day 7 visit. All assessments captured for the substudy were included in the analysis. Last-observation-carried-forward values were used for missing joint counts, and non-responder imputation was used for week 24 categorical outcomes.

Results
This substudy included 62 patients (n=40 in the tocilizumab group; n=22 in the placebo group). As shown in Table

Table I. Baseline demographics of the 1-week sub-study.[a]

	Tocilizumab 8 mg/kg + DMARDs n=40	Placebo + DMARDs n=22
Women, %	75	68
Caucasian, %	78	77
Age, yrs	51.7 (14.3)	55.7 (14.2)
Duration of RA, yrs	7.2 (7.5)	6.0 (4.4)
Previous DMARDs/anti-TNF	1.4 (1.2)	1.3 (1.2)
Oral corticosteroid use, %	48	41
DAS28	6.9 (1.0)	6.5 (1.2)
CRP, mg/dl	2.9 (3.0)	3.2 (4.3)
ESR, mm/h	54.6 (32.6)	53.4 (26.0)
Tender joint count	32.1 (16.1)	28.9 (18.5)
Swollen joint count	22.9 (14.5)	19.6 (12.8)
Physician global VAS	67.9 (17.4)	67.8 (19.9)
Patient global VAS	65.4 (22.1)	67.0 (23.9)
Patient pain VAS	55.7 (24.4)	62.9 (23.5)
MDHAQ-FN	4.5 (1.5)	5.1 (2.0)

CRP: C-reactive protein; DAS28: Disease Activity Score 28; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; MDHAQ-FN: Multidimensional Health Assessment Questionnaire for physical function; RA: rheumatoid arthritis; SD: standard deviation; TNF: tumour necrosis factor; VAS: visual analogue scale (0–100 mm).
Summary statistics represent mean (SD) unless otherwise noted
[a]Inclusion criteria required CRP ≥1.0 mg/dl.

I, baseline demographics and disease characteristics were similar between groups. Most patients were women, and most were Caucasian; mean age was approximately 52 years for tocilizumab and 56 years for placebo. Mean duration of RA at baseline was 7.2 years (tocilizumab) and 6.0 years (placebo), and mean baseline DAS28 was 6.9 (tocilizumab) and 6.5 (placebo). These characteristics were similar to those of the overall study population previously reported (12).

Patient global assessments of disease activity and pain (VAS 0–100 mm) showed statistically larger reductions (improvements) from baseline to day 7 in the tocilizumab group than in the placebo group (Fig. 1A). Mean change from baseline to day 7 for patient global assessment of disease activity was -16.2 mm *versus* 0.8 mm in the tocilizumab and placebo groups, respectively (*p*=0.005; 95%CI for the difference of least square [LS] means: -30.32, -5.67). Mean change from baseline to day 7 for patient global assessment of pain was -12.2 mm *versus* 1.4 mm, respectively (*p*=0.010; 95%CI for the difference of LS means: -27.48, -3.89).
For physician global assessment of

disease activity, the mean change from baseline to day 7 was numerically greater in the tocilizumab group than in the placebo group (-15.4 mm *vs*. -5.6 mm, respectively; *p*=0.050; 95%CI for the difference of LS means: -18.54, 0.00), though statistical significance was not demonstrated for this measure (Fig. 1A). Mean changes from baseline for the individual ACR core measures tender and swollen joints as well as physical function (MDHAQ-FN) showed no statistically significant differences between tocilizumab and placebo at day 7 (Fig. 1B-1C, respectively). However, laboratory measures of inflammation (CRP and ESR) showed statistically significant early reductions for tocilizumab *versus* placebo. Mean CRP change from baseline to day 7 was -2.7 *versus* -0.3 mg/dl in the tocilizumab and placebo groups, respectively (*p*<0.001; 95%CI for the difference of LS means: -3.69, -1.70). As shown in Figure 1D, most of this reduction in the tocilizumab group occurred by day 3. Mean change from baseline to day 7 in ESR also was significantly greater in the tocilizumab than the placebo group (-25.6 *vs*. 0.3 mm/h; *p*<0.001; 95%CI for the difference of LS means: -34.97, -18.25).
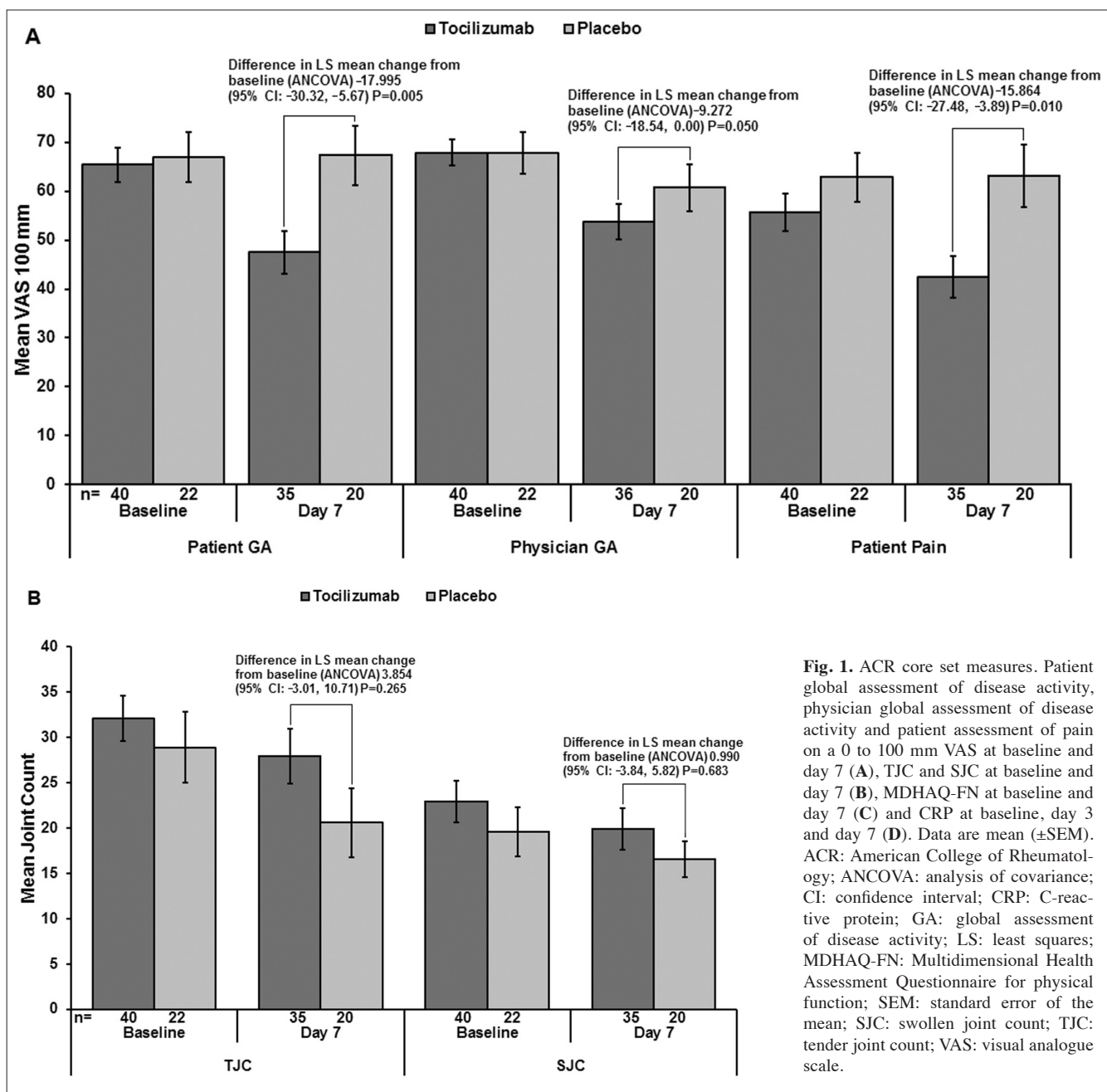
Fig. 1. ACR core set measures. Patient global assessment of disease activity, physician global assessment of disease activity and patient assessment of pain on a 0 to 100 mm VAS at baseline and day 7 (**A**), TJC and SJC at baseline and day 7 (**B**), MDHAQ-FN at baseline and day 7 (**C**) and CRP at baseline, day 3 and day 7 (**D**). Data are mean (±SEM). ACR: American College of Rheumatology; ANCOVA: analysis of covariance; CI: confidence interval; CRP: C-reactive protein; GA: global assessment of disease activity; LS: least squares; MDHAQ-FN: Multidimensional Health Assessment Questionnaire for physical function; SEM: standard error of the mean; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

At day 7, eight patients (21%) in the tocilizumab group achieved ACR20 response (*vs.* one patient in the placebo group), and two patients each achieved ACR50 and ACR70 responses (*vs.* none in the placebo group). However, differences between treatment groups were not statistically significant (ACR 20: 21% *vs.* 5%, *p*=0.138; ACR50: 5% *vs.* 0, *p*=0.534; ACR70: 5% *vs.* 0, *p*=0.534).

Figure 2 shows mean DAS28 scores calculated at baseline and at day 7 in the tocilizumab and placebo sub-study groups. This composite measure shows overall improvement in disease activity by day 7 that was statistically significantly greater with tocilizumab treatment than with placebo. Mean change from baseline to day 7 was -1.16 *versus* -0.27 in the tocilizumab and placebo groups, respectively (*p*=0.007; 95%CI for the difference of LS means for tocilizumab *vs.* placebo: -1.47, -0.25). Mean change from baseline to day 7 in RAPID3 score was numerically greater in the tocilizumab group (-0.9) than in the placebo group (-0.5), but this difference was not statistically significant (*p*=0.087; 95%CI for the difference of LS means: -1.57, 0.11).

Figure 3A-C presents the percentages of sub-study patients achieving LDA (DAS28 ≤3.2), ACR20 and ACR50 responses from weeks 4 through 24. Percentages of patients achieving these outcomes were numerically higher in the tocilizumab group than in the placebo group from week 4 through week 24. At week 24, 35.0%, 57.5% and 42.5% of patients in the tocilizumab group compared with 0.0%, 27.3% and 13.6% of patients in the placebo group achieved LDA, ACR20 and ACR50 responses, respectively. The reported differences in these comparisons were statistically significant at week 24 in
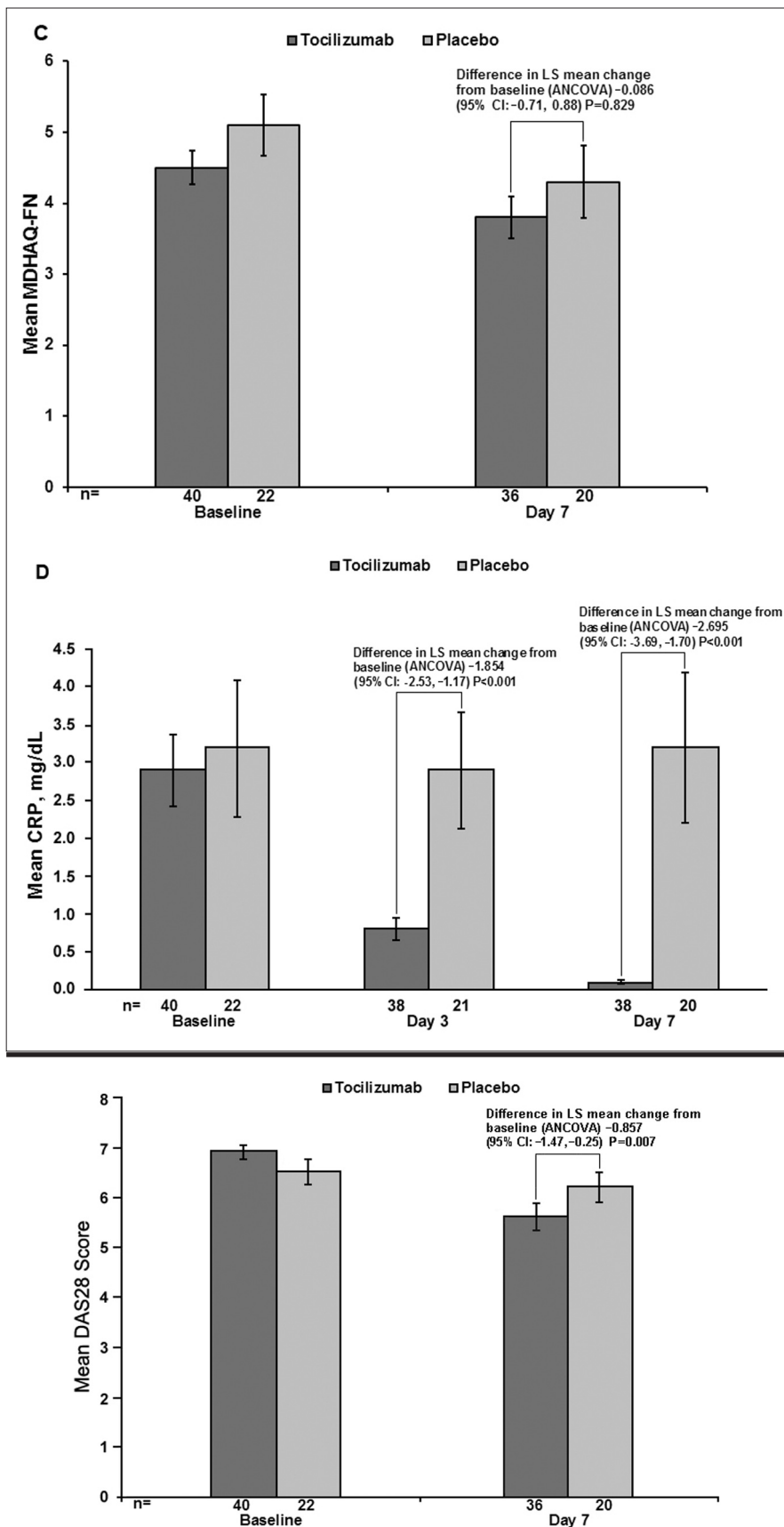
Fig. 2. DAS28 assessed at baseline and day 7. Data are mean (±SEM). ANCOVA: analysis of covariance; CI: confidence interval; DAS28: disease activity score 28; LS: least squares; SEM: standard error of the mean.
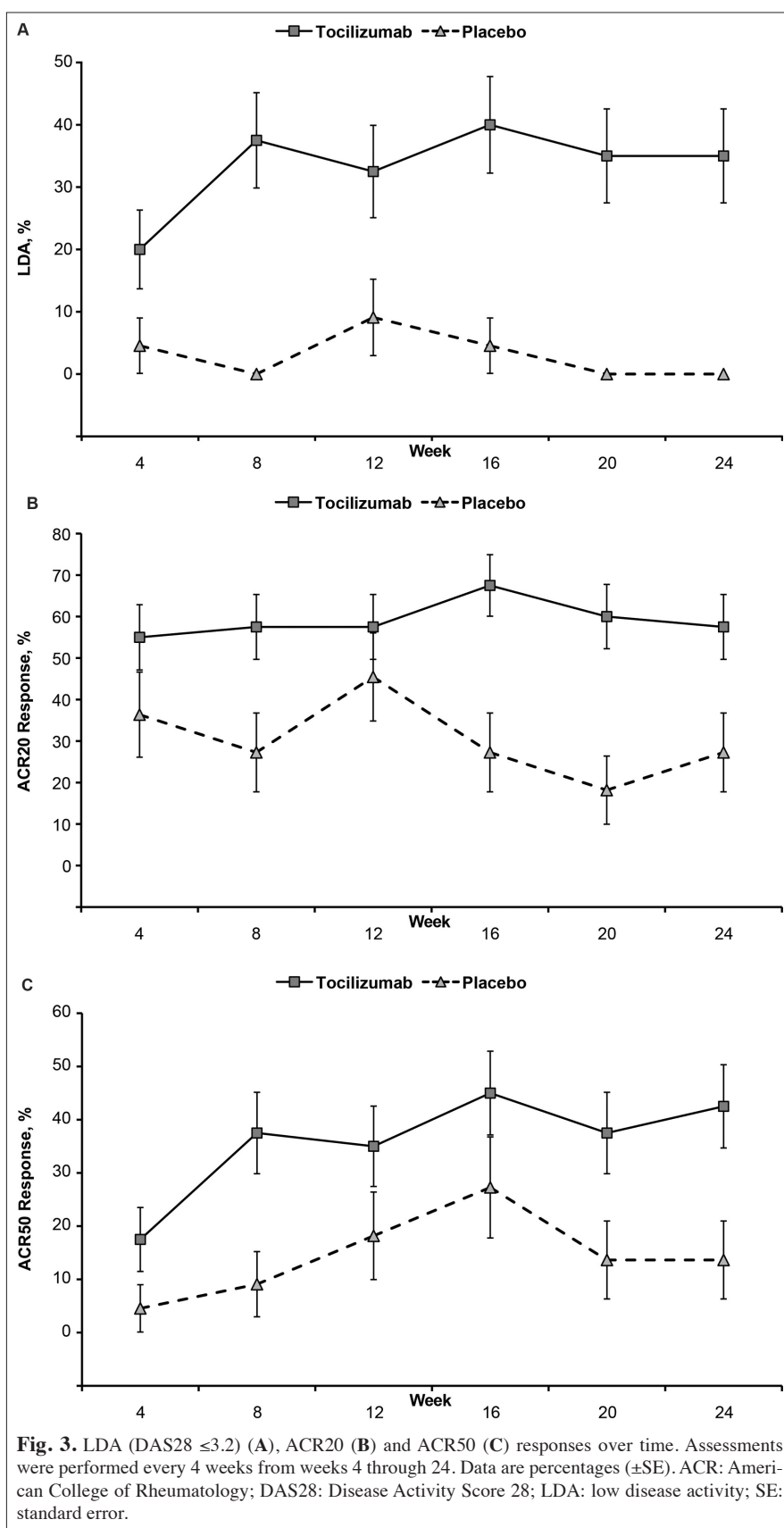
the full ROSE study ITT population (12). Adverse event reporting was not specifically analysed during the first week of treatment for this sub-study. However, as previously reported, safety information for tocilizumab is available from the full 24-week clinical trial (12).

Discussion

This sub-study of a 24-week randomised controlled trial was conducted to more thoroughly assess the early (week 1) effects of tocilizumab, in combination with DMARD therapy, on measures of disease activity in patients with moderate to severe active RA. Statistically significantly larger mean improvements in patient global assessment of disease activity and pain, laboratory measures of inflammation (CRP and ESR) and DAS28 score, including clinically meaningful change from baseline in DAS28 scores (~1.2), were reported compared with placebo (in combination with DMARDs) at day 7 after the first infusion of tocilizumab. In contrast, there were no statistically significant differences at day 7 between tocilizumab and placebo for change from baseline in MDHAQ-FN score, physician-assessed measures (physician global assessment of disease activity and tender and swollen joint counts) and RAPID3 score.

Longer term clinical responses from week 4 through 24 in the sub-study are consistent with those reported for the overall study population, in which ACR20, ACR50 and LDA responses were significantly higher for the tocilizumab group than the placebo group from week 4 through 24 (12).

These results have potentially important clinical implications, indicating that patient-reported measures of disease activity may be more sensitive than physician-reported measures in detecting the earliest symptomatic effects of treatment; previous data suggest similar findings (13, 14). Although rheumatologists may pay more attention to joint count measures than to patient-reported outcomes in assessing RA treatment effects, a comparison of different analytic measures for clinical trial data suggested that 'patient only' ACR core measures (patient global

Fig. 3. LDA (DAS28 ≤3.2) (**A**), ACR20 (**B**) and ACR50 (**C**) responses over time. Assessments were performed every 4 weeks from weeks 4 through 24. Data are percentages (±SE). ACR: American College of Rheumatology; DAS28: Disease Activity Score 28; LDA: low disease activity; SE: standard error.

assessment of disease activity, patient pain assessment and physical function) were as useful as the full core data set and other composite indices, including physician measures, for characterising response to therapy (13). Patient-reported outcome measures also have been shown to be less susceptible to placebo effects than physician-reported measures. In an analysis from two large randomised controlled trials of DMARDs, both patient-reported measures and acute-phase reactants (ESR/CRP) were better than physician-reported measures at distinguishing active treatment from placebo after 6 months (14).

Regarding comparisons of this study with those of the published literature assessing early response to RA therapy, few studies look at efficacy measures, specifically within the first week of treatment. Further, among studies that include early-response data, most lack a placebo comparator, making results difficult to interpret as treatment response. One single-arm, open-label trial reported that effects of infliximab were seen as early as week 1 for morning stiffness and number of swollen or tender joints (15). In a second single-arm, open-label trial of infliximab, significant improvements were observed in duration of morning stiffness, physician global disease assessment scores, patient global disease assessment scores and patient pain assessment scores within 48 hours (16). In a small study of adalimumab, 10 of 45 patients (22.2%) achieved ACR20 response within 24 hours of administration (17). A second study of adalimumab (n=54) reported that from day 8 onward after the first injection, improvements in ACR core criteria were significant compared with placebo (except for tender joint count, which showed significant improvement starting at day 15) (18). Finally, two placebo-controlled studies of abatacept reported that improvements in patient-reported outcomes were seen as early as day 15; one of these also noted that improvements in patient-reported outcomes preceded improvements in total ACR50 score (19, 20).

The ROSE study is the first to demonstrate the time course of very early disease activity control with the addition of tocilizumab to DMARD therapy. Some measures – particularly patient-reported global measures of disease activity and pain and DAS28 score and laboratory parameters (CRP and ESR) – showed

significant improvement as early as day 7 after the first infusion. Improvement in other measures such as physician global assessment of disease activity and swollen/tender joint counts took longer to show. Though early-response efficacy measures may be indicators of long-term benefit with biologics, they are not necessarily predictors of long-term outcomes; other criteria such as previous treatments and co-morbidities also should be considered.

Authors' contributions
HSBB, JC, AI, AK, DML, JND and YY made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. JND performed the statistical analysis. YY, JC and HSBB conceived of the study, participated in its design and coordination and drafted the manuscript. All authors read and approved the final manuscript.

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