Early and late responses in patients with rheumatoid arthritis who were conventional synthetic disease-modifying anti-rheumatic drug inadequate responders and were treated with tocilizumab or switched to rituximab: an open-label phase 3 trial (MIRAI)

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Abstract

Objective

To evaluate early and late responses in biological-naïve patients with rheumatoid arthritis (RA) initiating tocilizumab and early tocilizumab non-responders who switched to rituximab.

Methods

In this open-label, non-randomised phase 3 study, RA patients with inadequate response to conventional synthetic DMARDs received tocilizumab 8 mg/kg intravenously at study begin and weeks 4, 8 and 12. After evaluation at week 16, early responders (Disease Activity Score based on 28 joints-erythrocyte sedimentation rate [DAS28-ESR] <2.6) completed the study; partial responders (DAS28-ESR decrease >1.2 or DAS28-ESR ≥2.6–≤3.2) were to continue tocilizumab through week 28; non-responders (DAS28-ESR decrease ≤1.2) switched to rituximab (1000 mg, weeks 16 and 18) with safety follow-up through week 66.

Results

Of 519 patients, 222 (42.8%) achieved early DAS28-ESR remission at week 16; 240 patients continued treatment, 213 (41.0%) received tocilizumab, and 27 (5.2%) switched to rituximab. At week 32 DAS28-ESR remission was achieved by 117/213 patients (54.9%) who continued tocilizumab and 4/27 patients (14.8%) who switched to rituximab; good EULAR response was achieved by 66.7% and 25.9% and CDAI remission by 19.2% and 14.8% of patients, respectively. Serious adverse events occurred through week 32 in 45/490 patients (9.2%) who received tocilizumab (serious infections, 2.7%) and through week 66 in 8/27 patients (29.6%) who switched to rituximab.

Conclusion

Early response to tocilizumab was observed in 42.8% of patients. Half of early partial responders benefitted from continuing tocilizumab. Switching non-responders to rituximab seems feasible. No new safety signals were observed in patients treated with tocilizumab or switched to rituximab.

Key words

biologic agents, inflammation, rheumatoid arthritis

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Competing interests: see page 944.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a complex pathogenesis (1, 2). RA 'treat-to-target' (T2T) recommendations developed by an international task force determined clinical remission the main treatment target and low disease activity state (LDAS) acceptable for patients with long-standing disease (3, 4). T2T recommendations indicate that treatment should be adjusted at least every 3 months until the desired target is reached (3, 4). Although US and European guidelines recommend switching biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients with inadequate response (5, 6), evidence supporting the efficacy and safety of this recommendation is limited to clinical studies that enrol biological-experienced patients at baseline (7-9); studies prospectively evaluating switching from one biological to another are scarce.

To address T2T recommendations for patients whose biological must be switched because of inadequate response, the induction of clinical remission was investigated during initial anti-interleukin-6 receptor-alpha (IL-6Rα) therapy with tocilizumab in biological-naïve patients with active RA and during continued tocilizumab therapy in partial responders or in non-responders who switched to anti-CD20 therapy with rituximab. This study represents one of the largest prospective studies addressing clinical remission and the management of switching biologicals (bio-switching) in rheumatology practice.

Patients and methods

Study design and patients

This open-label, multicentre, two-arm, non-randomised phase 3 study (MIRAI) was conducted at 77 centres across Germany between March 2011 and February 2014. The study was approved by institutional review boards and independent ethics committees at all institutions and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and local regulations. All patients provided written informed consent.

The study enrolled adults (≥18 years of age) with active RA, defined by 1987 American College of Rheumatology (ACR) classification criteria (10), for ≥6 months, Disease Activity Score based on 28 joint counts and erythrocyte sedimentation rate (DAS28-ESR) >3.2, and ESR ≥28 mm/h or C-reactive protein (CRP) ≥7 mg/L. Patients had to be receiving ≥1 conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) with current csDMARD therapy at a stable dose for at least 4 weeks prior to baseline. Oral corticosteroids (≤10 mg/day prednisone or equivalent at stable doses for ≥4 weeks before baseline) were permitted and could be continued throughout the study. Patients who previously received treatment with a bDMARD (*e.g.* tocilizumab, rituximab, tumour necrosis factor [TNF] inhibitors) and those receiving methotrexate and leflunomide combination therapy ≤4 weeks before enrolment were excluded (see Supplementary Appendix 1 for complete inclusion criteria).

A pre-defined treatment algorithm based on DAS28-ESR responses to initial tocilizumab treatment was used (Suppl. Figure S1). During the first treatment period, each eligible patient received four intravenous infusions of tocilizumab 8 mg/kg at 4-week intervals, ending at week 16 with evaluation of the primary endpoint (remission, defined as DAS28-ESR <2.6). Patients who achieved DAS28-ESR remission were considered responders (in accordance with T2T recommendations), and they completed the study and transferred to routine clinical practice. The remaining patients entered a second treatment period and were divided into two treatment arms based on their week 16 response. In arm 1, patients with partial response to tocilizumab (defined as DAS28-ESR decrease >1.2 from baseline or a DAS28-ESR value of ≥2.6 to ≤3.2 at week 16) were to continue treatment with four additional infusions of tocilizumab 8 mg/kg every 4 weeks from weeks 16 to 28, with final assessment at week 32. In arm 2, patients with non-response to tocilizumab (defined as DAS28-ESR decrease ≤1.2 from baseline and DAS28-ESR >3.2) subsequently received two infusions of rituximab at weeks 16 and 18 (1000 mg),

with assessment visits at weeks 24 and 32. All rituximab-treated patients who completed the week 32 visit entered an observational, non-treatment safety follow-up (SFU) period through week 66, during which they received treatment according to best medical judgement.

Assessments

The primary efficacy endpoint was the proportion of patients in early DAS28 remission, defined as DAS28-ESR <2.6 at week 16. Secondary efficacy endpoints included proportions of patients achieving DAS28-ESR <2.6 at week 32; proportions of patients achieving LDAS (DAS28-ESR ≤3.2), European League Against Rheumatism (EULAR) response rates, ACR20/50/70 response rates and remission according to ACR/EULAR 2011 Boolean (tender joint count [TJC] (68) ≤1, swollen joint count [SJC] (66) ≤1, Patient Global Assessment of Disease Activity visual analogue scale [VAS, cm] ≤1, CRP ≤1 mg/dl) or index (Simplified Disease Activity Index [SDAI] ≤3.3) criteria (11) at weeks 16 and 32; longitudinal analysis of DAS28; and changes in Clinical/Simplified Disease Activity Index (CDAI/SDAI). Exploratory analyses included evaluation of CDAI remission (≤2.8) and low CDAI (≤10.0).

Safety was assessed via standard reporting of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs), categorised by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* v. 17.0.

Statistical analysis

The intent-to-treat (ITT)-main population constituted all patients who received ≥1 dose of tocilizumab. For additional efficacy analyses, three ITT subpopulations were defined based on response to tocilizumab in the first 16-week treatment period and treatment thereafter. Safety was assessed in the tocilizumab safety population (all patients who received ≥1 dose of tocilizumab and no dose of rituximab) and the rituximab safety population (all patients who received ≥1 dose of rituximab with ≥1 safety evaluation under rituximab treatment).

Using the null hypothesis that the proportion of patients in early DAS28 remission at week 16 would be ≤45%, the analysis of the primary efficacy endpoint was performed using an exact one-sided binomial test on single proportions with a significance level of α=0.025. Secondary efficacy endpoints were evaluated descriptively. Post-hoc logistic regression analyses were performed to determine the effect of various baseline parameters on the likelihood of response to tocilizumab at week 16 or week 32. Additional information on statistical methods is summarised in Suppl. Appendix 2.

Results

Patients and treatment

ITT main and safety populations included 519 of 715 screened patients who entered the first treatment period and received ≥1 dose of tocilizumab (Fig. 1). Of 463 patients evaluated at week 16, 223 (43.0%) completed the study after the first treatment period, including 217 (41.8%) who achieved early DAS28 remission (ITT1). Among the remaining 240 patients (46.2%) entering the second treatment period, 213 (41.0%) continued tocilizumab (ITT2) and 27 (5.2%) were switched to rituximab (ITT3). At week 32, 200 patients on continued tocilizumab completed the study and 26 patients switched to rituximab entered the observational rituximab SFU period.

Baseline demographics and disease characteristics are shown in Table I for all patients and Suppl. Table SI for the subpopulations. Concomitant csDMARD and corticosteroid treatments and dose changes are described in Table I and Suppl. Appendix 3, respectively.

Efficacy of tocilizumab during the first 16 weeks of treatment

In the ITT-main population, 222/519 patients (42.8%; 95% confidence interval [CI]: 38.5% to 47.2%) achieved remission defined as DAS28 <2.6 (p=0.16) at week 16 after the first tocilizumab treatment period. This did not meet the predefined threshold of 45%. Among these early responders, 2 patients had already withdrawn from treatment due to adverse events, and 3 patients erroneously received an additional tocilizumab infusion at week 16 and were counted among the subpopulation with continued tocilizumab treatment (ITT2). Thus, 217 patients completed the study at week 16 as planned (subpopulation ITT1). Additional efficacy results for the overall study population and sensitivity analysis of the primary endpoint are summarised in Table II.

Early and late efficacy responses to tocilizumab

DAS28 early response to tocilizumab was achieved by 217 ITT1 patients. In addition, 117/213 patients (54.9%) in the ITT2 subpopulation achieved late response (DAS28 <2.6 at week 32) during continued tocilizumab treatment (Suppl. Table SII). A majority (62.4%) of ITT2 patients achieved DAS28 ≤3.2 at week 16 that was maintained at week 32. The only notable difference between seropositive and seronegative patients in proportions achieving DAS28 remission was in the ITT2 subpopulation, of whom 58.8% of anti-cyclic citrullinated peptide (aCCP) antibody-positive patients and 37.1% of aCCP antibody-negative patients achieved DAS28 <2.6 (Suppl. Table SII).

Median [interquartile range] change from baseline to week 16 in DAS28-ESR was -3.8 [-4.8, -2.9] in the ITT1 subpopulation and -2.7 [-3.3, -2.0] in the ITT2 subpopulation. Further improvement in median DAS28-ESR was observed at week 32 in the ITT2 subpopulation (-3.6 [-4.5, -2.7]). Similar trends were observed for CDAI and SDAI (Suppl. Table SII).

ACR/EULAR 2011 Boolean remission was achieved by 33.2% of ITT1 patients and 0.9% of ITT2 patients at week 16. Continued treatment with tocilizumab in the ITT2 subpopulation resulted in 18.8% of patients achieving ACR/EULAR 2011 Boolean remission at week 32. Similar trends were observed for CDAI remission with 39.2% of ITT1 patients achieving CDAI remission at week 16 and 19.2% of ITT2 patients achieving it at week 32 (Suppl. Table SII).

Onset of response to tocilizumab was rapid with moderate and good EULAR

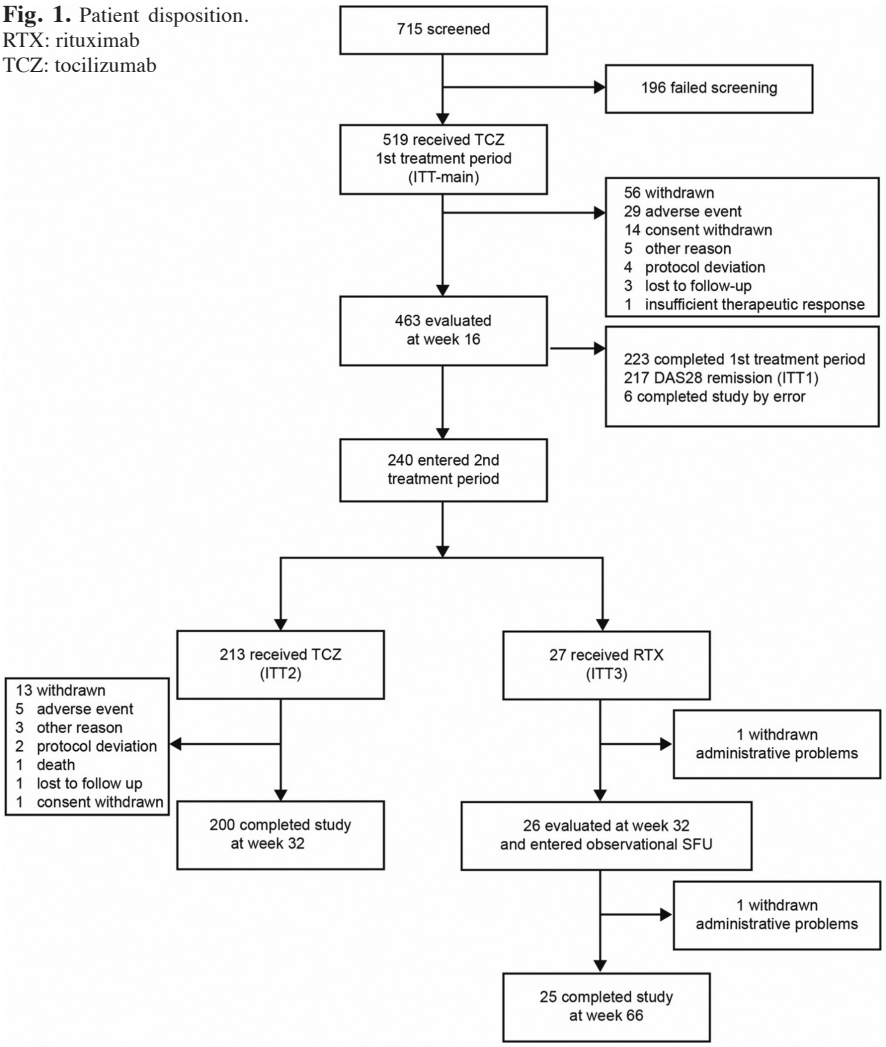

Fig. 1. Patient disposition.
RTX: rituximab
TCZ: tocilizumab

Table I. Baseline demographics and disease characteristics in the overall population.

Variable	ITT main n=519
Female, n (%)	352 (67.8)
Age, years	56.0 (48.0; 65.0)
BMI, kg/m^2	27.3 (23.7; 30.3)
RA disease duration, years	4.1 (1.5; 9.8)
No. of previous csDMARDs*	2.0 (1.0; 3.0)
No. of concomitant csDMARDs†	
Any, n (%)	504 (97.1)
1	469 (90.4)
2	30 (5.8)
3	5 (1.0)
Concomitant csDMARDs†	
Methotrexate, n (%)	365 (70.3)
Leflunomide, n (%)	92 (17.7)
Sulphasalazine, n (%)	39 (7.5)
(Hydroxy-)chloroquine, n (%)	38 (7.3)
Receiving corticosteroids, n (%)	402 (77.5)
Methotrexate, mg/week	15.0 (15.0; 20.0)
RF, U/mL	48.8 (20.0; 183.3)
Anti-CCP, U/mL	58.0 (4.0; 208.3)
RF positive, n/N (%)‡	332/478 (69.5)
Anti-CCP positive, n/N (%)‡	257/344 (74.7)
DAS28-ESR	5.7 (5.0; 6.4)
SJC28	7.0 (5.0; 11.0)
TJC28	9.0 (6.0; 14.0)
ESR, mm/hour	32.0 (22.0; 42.0)
CRP, mg/L	10.4 (5.3; 19.7)
Patient DA VAS, mm	65.0 (50.0; 80.0)
SJC66	9.0 (6.0; 13.0)
TJC68	12.0 (8.0; 20.0)
Physician DA VAS, mm	61.0 (50.0; 75.0)
Patient pain VAS, mm	67.0 (51.0; 80.0)
HAQ-DI	1.25 (0.75; 1.75)

Data are presented as median (interquartile range) unless otherwise stated.
*All patients were biological DMARD naive as defined by the study protocol.
†Medication being received or begun after the start of study treatment and before the last regular visit.
‡Relative frequencies based on the number of patients with an available RF or anti-CCP value.
BMI: body mass index; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DA: disease activity; DAS28: Disease Activity Score using 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; ITT: intent to treat; RA: rheumatoid arthritis; RF: rheumatoid factor; RTX: rituximab; SJC: swollen joint count; TCZ: tocilizumab; TJC: tender joint count; VAS: visual analogue scale.

responses evident as early as weeks 4 and 8 (Fig. 2A-B). At week 16, good EULAR response was achieved by all ITT1 patients and the majority (61.0%) of ITT2 patients. In the ITT2 subpopulation, the proportion of good EULAR responders steadily increased from 61.0% (week 16) to a maximum of 72.8% (week 28) with continued tocilizumab therapy (Fig. 2B). ACR20/50/70 response rates followed a similar pattern; for example, ACR20 response was achieved by 87.1% of ITT1 patients and 68.1% of ITT2 patients at week 16 and by 75.6% of ITT2 patients at week 32 (Suppl. Fig. S1)

Profile of early responder patients and logistic regression analysis for predictive markers of early versus late response to tocilizumab

ITT1 patients tended to be younger and have lower DAS28, TJC, SJC, patient and physician reported disease activity and pain at baseline than ITT2 and ITT3 patients (Suppl. Table SI). In contrast, ITT3 patients experienced the longest duration of disease (median, 6.8 years) and the lowest median ESR (22.0 mm/h) at baseline. Methotrexate dose was higher in ITT3 patients (median, 20.0 mg/week) than in the other groups (median, 15.0 mg/week).

Post hoc logistic regression analysis comparing early and late responders demonstrated that younger age, male gender, longer duration of RA, lower SJC28, lower patient reported disease activity and higher Health Assessment Questionnaire-Disability Index (HAQ-DI) scores were associated with early response (DAS28 <2.6) to tocilizumab at week 16 (Table III). Given that DAS28 is a continuous variable, EULAR response was evaluated in a separate logistic regression analysis comparing EULAR good responders and non-responders (as shown in Figure 2A-B). Results of this analysis indicated that younger age and lower TJC28 were associated with good EULAR response (Table III).

Response to rituximab in primary tocilizumab non-responders

Only 27 patients were classified as pri-

Table II. Summary of efficacy outcomes at week 16 in the overall population during the initial 16 weeks of tocilizumab treatment.

Variable	ITT-main n=519
DAS28 <2.6, n (%) [95% CI]	222 (42.8) [38.5 to 47.2][†]
DAS28 ≤3.2, n (%)	357 (68.8)
EULAR response (good/moderate), n (%)	354 (68.2)/105 (20.2)
ACR20	348 (67.1)
ACR50	237 (45.7)
ACR70	127 (24.5)
ACR/EULAR 2011 remission Boolean, n (%)	74 (14.3)
DAS28, median (IQR)	
Baseline	5.7 (5.0; 6.4)
Change to week 16*	-3.0 (-3.9; -2.2)
CDAI, median (IQR)	
Baseline	29.2 (22.9; 37.7)
Change to week 16*	-18.5 (-26.8; -11.9)
SDAI, median (IQR)	
Baseline	31.1 (24.3; 39.9)
Change to week 16*	-19.3 (-28.4; -12.7)
ESR, mm/h, median (IQR)	
Baseline	32.0 (22.0; 42.0)
Change to week 16*	-25.0 (-36.0; 15.0)
CRP, mg/dl, median (IQR)	
Baseline	1.0 (0.5; 2.0)
Change to week 16*	–0.8 (-.7; -0.3)
Sensitivity analysis of the primary endpoint	Per-protocol set n=485[‡]
DAS28 <2.6, n (%) [95% CI]	211 (43.5) [39.0 to 48.0][§]

Overall study population: patients who received at least one dose of TCZ.
*Compared with baseline. [†]p=0.1648. [‡]All patients of the ITT-main population who did not have a major protocol violation. [§]p=0.2693.
ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index (28 joints); CI: confidence interval; CRP: C-reactive protein; DAS28: Disease Activity Score using 28 joints; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; IQR: interquartile range; ITT: intent to treat; NA: not applicable; SDAI: Simplified Disease Activity Index; TCZ: tocilizumab.

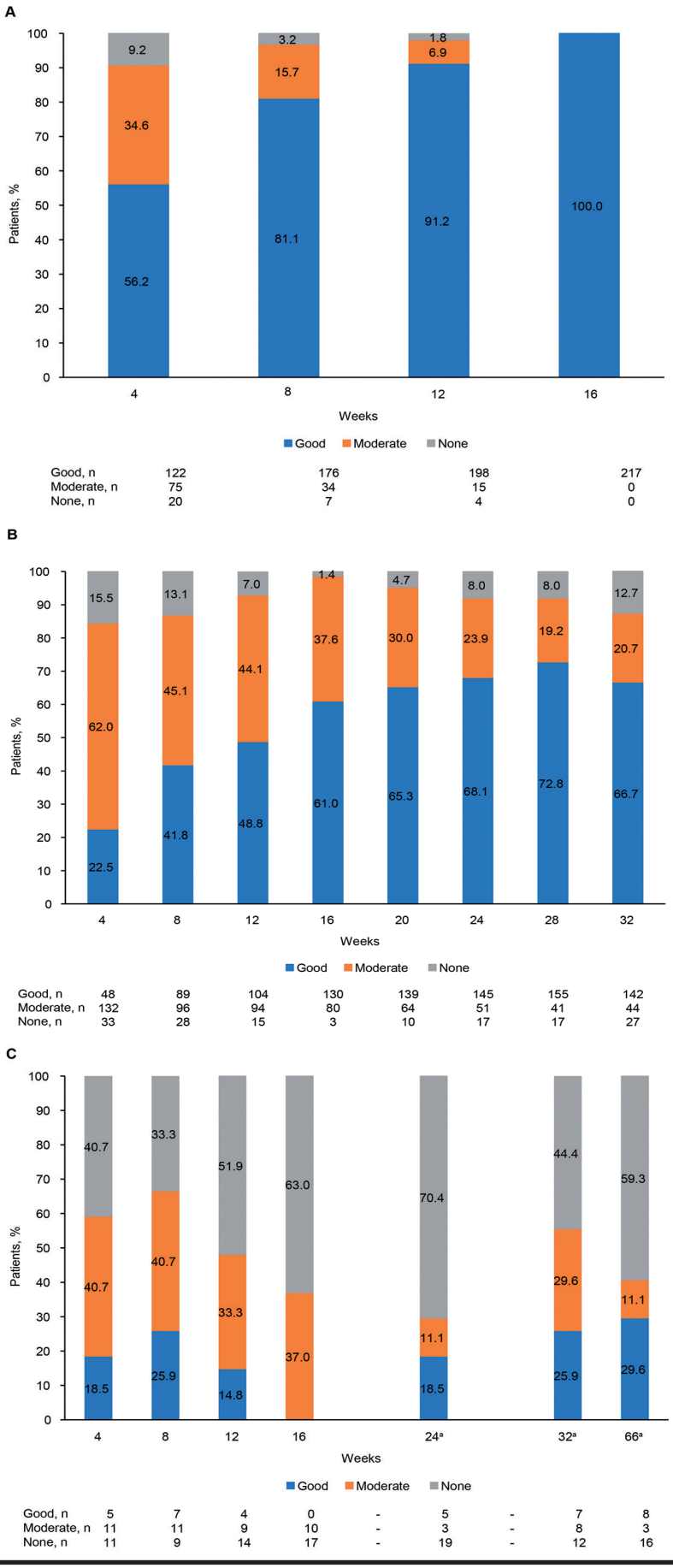

Fig. 2. Proportions of patients achieving good, moderate or no EULAR response during the course of the study.
A: Early responders (ITT1, n=217);
B: Patients continuing on tocilizumab (ITT2, n=213);
C: Patients switching to rituximab (ITT3, n=27).
[a]Compared with week 16.

mary non-responders to tocilizumab at week 16 and were switched to rituximab (ITT3 subpopulation). Although some patients achieved remission according to various criteria (Suppl. Table SII), EULAR good response (Fig. 2C) or ACR20 response (Suppl. Fig. S2) after switching to rituximab, the rates may be overestimated or underestimated because they are based on only 27 patients. The small sample size also precluded robust comparisons of DAS28 remission by RF and aCCP status for the ITT3 subpopulation.

Safety

Incidences of TEAEs and SAEs in the 490 patients who received tocilizumab only and the 27 patients who switched from tocilizumab to rituximab were 64.9% and 9.2% based on 16 to 32 weeks of follow-up and 74.1% and 29.6% based on 66 weeks of follow-up, respectively (Table IV). AEs in the infections and infestations system order class were the most frequently reported AEs and SAEs in tocilizumab-treated patients, occurring at rates of 34.5% and 2.7%, respectively, in the tocilizumab safety population. The most common infections reported in ≥1% of patients were nasopharyngitis, bronchitis, oral herpes, urinary tract infection, herpes zoster and respiratory tract infection. One patient died of a craniocerebral injury after a fall within 24 hours of tocilizumab infusion. This was assessed by the investigator as possibly drug related because of the temporal relationship. Of the 27 patients who subsequently received rituximab, 59.3% reported an AE up to the week 66 SFU visit after rituximab administration (most were infections, none opportunistic); 22.2% of patients reported SAEs, none of which were considered related to rituximab. Further safety details are included in Suppl. Appendix 4.

Of 519 patients enrolled in the study, 333 and 78 were still receiving concomitant methotrexate or leflunomide, respectively, at their last study visit. Early discontinuation from the study was reported in 10.2% of patients receiving concomitant methotrexate and 23.1% receiving concomitant leflunomide; 50.8% of patients receiving concomitant methotrexate and 80.8% receiving concomitant leflunomide previously received ≥2 csDMARDs. Adverse events were reported in 60.7% of patients receiving concomitant methotrexate and 65.4% receiving concomitant leflunomide, and serious infections were reported in 1.8% and 5.1%, respectively. Incidences of hepatic events were similar in patients receiving concomitant methotrexate and concomitant leflunomide.

Table III. Logistic regression analysis for early response to tocilizumab and response based on EULAR criteria.

Effect/category	Estimate	SE	*p*-value	Odds ratio [95% CI]
Early response to tocilizumab*				
Age, years	-0.028	0.011	0.0080	0.972 [0.952 to 0.993]
SJC28	-0.134	0.029	<0.0001	0.875 [0.826 to 0.926]
Patient DA VAS, mm	-0.026	0.007	0.0003	0.975 [0.961 to 0.988]
HAQ-DI	0.684	0.229	0.0028	1.983 [1.266 to 3.105]
Duration of RA, years	0.046	0.020	0.0230	1.047 [1.006 to 1.090]
Gender, category=female	-0.385	0.143	0.0069	0.463 [0.265 to 0.810]
Response based on EULAR criteria†				
Age, years	-0.043	0.021	0.0416	0.958 [0.919 to 0.998]
TJC28	-0.118	0.033	0.0003	0.889 [0.834 to 0.948]
Patient DA VAS, mm	0.014	0.011	0.1848	1.014 [0.993 to 1.035]
Duration of RA, years	0.060	0.041	0.1467	1.062 [0.979 to 1.151]

Probability modelled is early response = yes.
*Early response: DAS28 <2.6 at week 16 (ITT1); late response: DAS28 <2.6 at week 32 for ITT2 patients who did not discontinue before week 32.
†Good EULAR response at week 16 (all ITT1 patients) or good EULAR response at week 16 and/or week 32 for ITT2 patients.
Non-response: ITT3: patients without EULAR response at Week 16; ITT2: patients without EULAR response at Week 32. Only ITT2 patients who did not continue before Week 32 have been taken into consideration. ITT2 patients who fulfilled response and non-response criteria have not been taken into consideration.
CI: confidence interval; DA: disease activity; HAQ-DI: Health Assessment Questionnaire-Disability Index; SE: standard error.

Discussion

In this open-label phase 3 study, ACR/EULAR T2T recommendations (3) were investigated in csDMARD-IR patients with RA initiating tocilizumab with the target of achieving early remission (DAS28-ESR <2.6 within 16 weeks). In order to determine whether late response was achievable, patients with only partial response at week 16 could receive another 16 weeks of tocilizumab therapy, and non-responders were switched to rituximab according to the T2T recommendations for switching biologicals. Although 43% of patients in the study achieved early response to tocilizumab as demonstrated by DAS28-ESR remission after 16 weeks of treatment, this did not meet the predefined threshold of 45%. While 66.8% of patients who achieved DAS28 remission by week 16 and completed the first treatment period (ITT1 subpopulation) responded already by week 8, only 23.0% of patients continuing tocilizumab after week 16 (ITT2 subpopulation) had achieved DAS28 remission by week 8, possibly reflecting their slightly higher baseline DAS28. Furthermore, a sizeable proportion of DMARD-IR patients required prolonged tocilizumab treatment to achieve the remission target; 54.9% of the ITT that continued tocilizumab therapy achieved DAS28-ESR remission at week 32, suggesting they benefitted from continued tocilizumab treatment without dose adjustment or additional therapy.

Early response to tocilizumab has been reported in randomised controlled trials and observational studies in patients with RA (12-17) with clinical improvements as early as 4 weeks following the first tocilizumab infusion. In this study, high proportions of early responders who achieved DAS28 remission at week 16 also achieved low CDAI (90.3%) or CDAI remission (39.2%). Furthermore, one-third of early responders achieved ACR/EULAR 2011 Boolean remission, the most stringent response criterion. These results are consistent with those of the U-Act Early trial, which examined T2T in csDMARD-naïve patients

Table IV. Summary of safety data (safety populations).

Number of subjects, n (%)	TCZ safety n=490	RTX safety n=27
Total TEAEs	318 (64.9)	20 (74.1)
Severe	26 (5.3)	4 (14.8)
Life threatening	2 (0.4)	0 (0.0)
TCZ related	187 (38.2)	10 (37.0)
RTX related	NA	4 (14.8)
Total treatment-emergent SAEs	45 (9.2)	8 (29.6)
TCZ related, treatment emergent	23 (4.7)	0 (0.0)
RTX related, treatment emergent	NA	0 (0.0)
Total treatment-emergent serious infections	10 (2.0)	1 (3.7)
TCZ related, treatment emergent	10 (2.0)	0 (0.0)
RTX related, treatment emergent	NA	0 (0.0)
Total AEs leading to discontinuation	33 (6.7)	0 (0.0)
Deaths (treatment emergent)	1 (0.2)	0 (0.0)
Summary of AE by primary SOC ≥5% of all patients		
Infections and infestations	169 (34.5)	8 (29.6)
Investigations	77 (15.7)	6 (22.2)
Gastrointestinal disorders	72 (14.7)	8 (29.6)
Musculoskeletal and connective tissue disorders	62 (12.7)	8 (29.6)
Skin and subcutaneous tissue disorders	54 (11.0)	3 (11.1)
Nervous system disorders	37 (7.6)	6 (22.2)
Vascular disorders	36 (7.3)	5 (18.5)
Injury, poisoning and procedural complications	36 (7.3)	3 (11.1)
Metabolism and nutrition disorders	33 (6.7)	6 (22.2)
General disorders and administration site conditions	30 (6.1)	5 (18.5)
Blood and lymphatic system disorders	30 (6.1)	3 (11.1)
Respiratory, thoracic and mediastinal disorders	26 (5.3)	6 (22.2)
Summary of serious AE by primary SOC ≥1% of all patients		
Infections and infestations	13 (2.7)	1 (3.7)
Musculoskeletal and connective tissue disorders	8 (1.6)	2 (7.4)
Injury, poisoning and procedural complications	7 (1.4)	1 (3.7)
Cardiac disorders	3 (0.6)	2 (7.4)
Gastrointestinal disorders	4 (0.8)	1 (3.7)
Summary of rates/100 PY of SAEs by primary SOC ≥2/100 PY in any group		
Total patient years	236.8	35.5
Musculoskeletal and connective tissue disorders	3.4	8.4
Infections and infestations	6.8	2.8
Cardiac disorders	1.3	5.6
Injury, poisoning and procedural complications	4.2	2.8
Gastrointestinal disorders	2.5	2.8
General disorders and administration site conditions	0.4	2.8

Infections including all opportunistic infections and non-serious infections as defined by those treated with intravenous anti-infectives.
AE: adverse event; NA: not applicable; PY: patient-years; RTX: rituximab; SAE: serious adverse event; SOC: system organ class; TCZ: tocilizumab; TEAE: treatment-emergent adverse event.

with early RA initiating treatment with tocilizumab monotherapy or with tocilizumab and methotrexate combination therapy (18).

The beneficial effect of continued tocilizumab in partial responders was more apparent for higher-hurdle response parameters at week 32. Although DAS28-ESR remission was not achieved at week 16, a substantial proportion of patients in the ITT2 subpopulation (62%) had LDAS (DAS28-ESR ≤3.2). Although the proportion of patients with LDAS did not increase to week 32, improvements in higher-hurdle measures – including DAS28 remission (54.9%) and CDAI remission (19.2%) – were observed. Increased good EULAR responder rates from 61% at week 16 to a maximum of 73% at week 28 were also demonstrated in the ITT2 subpopulation. Post hoc regression analyses suggested that older patients with higher disease activity may require more prolonged treatment with tocilizumab to reach their target or any kind of remission. Notably, patterns of csDMARD and corticosteroid use were similar between ITT1 and ITT2 patients, suggesting they did not influence the timing of response.

Non-response to tocilizumab was identified early (week 16) after the start of tocilizumab therapy in the current study. Based on published data (14, 15, 19), a non-responder rate of approximately 25% was expected in the MIRAI study. However, only 27 of 519 patients (5.2%) overall were considered primary non-responders to tocilizumab at week 16 and switched to rituximab (ITT3 population). These patients received higher weekly doses of concomitant methotrexate and experienced substantially longer durations of RA and higher TJC68 at baseline than did early/partial responders. Although results indicate that approximately one-third of tocilizumab non-responders benefitted from a switch to rituximab, the number of week 16 tocilizumab non-responders was lower than expected, and the small sample size of the ITT3 subpopulation means that these results should be interpreted with caution. Further investigation into the efficacy of switching biologicals is needed (20).

This lower than anticipated non-responder rate supports the efficacy of initial tocilizumab therapy in biological-naïve RA patients, as reported in DMARD-naïve patients with recently diagnosed RA (18), and it provides additional evidence that a 'hit hard and early' approach may be effective. Further studies are required to investigate biological-switching regimens for non-responders according to EULAR/ACR treatment algorithms, which are based primarily on a larger magnitude of non-responders in anti-TNF-treated patients with RA (6, 21).

Tocilizumab was generally well tolerated in the MIRAI study, and the safety profile was consistent with that of previous reports from randomised controlled trials and open-label extensions (22). Patients receiving concomitant leflunomide appeared to have a slightly higher incidence of serious infections (5.1%) than those receiving concomitant methotrexate (1.8%); however, more patients receiving concomitant leflunomide than concomitant methotrexate previously received two or more csDMARDs, which could have contributed to toxicity. Tocilizumab and rituximab sequential therapy was well tolerated, and no new safety signals were detected after patients switched to rituximab 4 weeks

after the last tocilizumab infusion. The small patient numbers should be taken into consideration, however; longer-term data on larger patient populations are needed to evaluate the safety of switching biologicals. Overall safety profiles of tocilizumab and rituximab were similar to those observed in earlier studies of each agent (7, 12-17, 23, 24) and were consistent with the expected profile in an RA population.

The non-randomised, open-label design was a limitation of this study and introduced the potential for selection bias and assessment bias because of an unblinded joint assessor. Although DAS-ESR provides a good indication of the magnitude of treatment response and the degree of residual inflammation, particularly when acute phase reactants (APRs) are involved, it may introduce bias when evaluating agents that have a direct impact on APRs, such as tocilizumab (25). Therefore, another limitation is the possibility that the DAS28-ESR results could be driven by the normalization of ESR because of the pharmacodynamic effect of tocilizumab on APRs. Similar results were obtained for CDAI, however, which does not include an APR component.

In conclusion, results from the MIRAI study support early improvement in RA disease activity with tocilizumab treatment in patients with inadequate response to csDMARDs. Later response at week 32 was observed in early week 16 partial responders who continued tocilizumab treatment, suggesting that longer duration of treatment might be considered for patients who initially experience only partial response. Switching to another biological, such as rituximab, appears to be safe for early non-responders and provides some benefits. Results of this open-label trial support further investigation of early and late responses to biological treatment and prospective studies of biological switching.

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Competing interests

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M.A. Peters is an employee of Roche and reports personal fees from Roche both during the conduct of the study and outside the submitted work.

H.-P. Tony received personal fees from Roche Pharmaceuticals during the conduct of the study and personal fees from AbbVie, BMS, Chugai, Janssen, Novartis, Pfizer, Sanofi, Lilly, MSD and Astra-Zeneca outside the submitted work.

The other co-authors have declared no competing interests.

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