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IL-6 Receptor Inhibition with Tocilizumab Improves Treatment Outcomes in Patients with Rheumatoid Arthritis Refractory to Anti-TNF Biologics: Results from a 24-Week Multicentre Randomised Placebo Controlled Trial

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ABSTRACT

Objectives:

The Phase III RADIATE study examined efficacy and safety of tocilizumab, an anti-interleukin-6 receptor monoclonal antibody in patients with rheumatoid arthritis (RA) refractory to TNF-antagonist therapy.

Methods:

499 patients with inadequate response to ≥ 1 TNF-antagonist were randomised to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks. ACR20 responses, secondary efficacy and safety endpoints were assessed.

Results:

ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively ($p < 0.0001$ both tocilizumab groups vs. control). At Week 4 more patients achieved ACR20 in 8 mg/kg tocilizumab vs. controls ($p = 0.0008$). Patients responded regardless of most-recently failed anti-TNF or the number of failed treatments. DAS28 remission (DAS28 < 2.6) rates at Week 24 were clearly dose-related, being achieved by 30.1%, 7.6% and 1.6% of 8 mg/kg, 4 mg/kg and control groups ($p = 0.0001$ for 8 mg/kg and $p = 0.053$ for 4 mg/kg vs. control). Most adverse events (AEs) were mild or moderate with overall incidences of 84.0%, 87.1% and 80.6%, respectively. The most common AEs with higher incidence in tocilizumab groups were infections, GI symptoms, rash, and headache. Serious AE incidence was higher in controls (11.3%) than 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.

Conclusion:

Tocilizumab + MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. ClinicalTrials.gov identifier: NCT00106522.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic disease affecting approximately 1% of the population.[1] It is characterised by pain, swelling and progressive destruction of the small joints of the hands and feet, accompanied by loss of function, fatigue, anaemia and increased risk for osteoporosis and coronary heart disease.

Treatments often include disease-modifying anti-rheumatic drugs (DMARDs, e.g. methotrexate [MTX]) and biologics (e.g. TNF-alpha inhibitors). However, even with TNF inhibitors (alone or with DMARDs), 20-40% of RA patients show inadequate response. In addition, the attrition rate after 2 years nears 20%[2] Switching between anti-TNF treatments, rising patient age and increasing disease duration all increase patients' chances of an inadequate response.[3-9] This partly explains the poor prognosis for, and the difficulty in, treating this population.

An alternative target for RA treatment is the pleiotropic cytokine interleukin-6 (IL-6). Chronic joint inflammation in RA leads to the production of IL-6 and its receptor, IL-6R, which is expressed on effector cells that cause and prolong inflammation. IL-6 also influences B and T-cell development, along with activation of cells involved with the innate immune response.[10,11] IL-6 knockout mice have been shown to be protected from developing joint symptoms in an arthritis model *in vivo*. [12,13]

Tocilizumab is a humanised anti-IL-6R monoclonal antibody that prevents IL-6 from binding to IL-6R.[14] Tocilizumab in combination with MTX or DMARDs exhibits superior clinical efficacy vs. controls in several populations, including patients with an inadequate response to MTX and/or DMARDs.[15-19] The Research on Actemra Determining efficacy after Anti-TNF failures (RADIATE) study examined the efficacy and safety of tocilizumab with MTX in patients with active RA who had failed at least one TNF-antagonist.

PATIENTS AND METHODS

Patients

Patients ≥ 18 years old with moderate to severe active RA and failure to respond or intolerance to ≥ 1 TNF-antagonist within the last year were included. Patients had active RA ≥ 6 months, swollen joint count (SJC) ≥ 6 , tender joint count (TJC) ≥ 8 , and C-reactive protein (CRP) > 1.0 mg/dL or erythrocyte sedimentation rate (ESR) > 28 mm/h at baseline. Patients discontinued etanercept (≥ 2 weeks), infliximab or adalimumab (≥ 8 weeks), leflunomide (≥ 12 weeks) and all DMARDs other than MTX before receiving study medication. Patients had to be treated with MTX for ≥ 12 weeks prior to baseline (stable dose: ≥ 8 weeks).

Exclusion criteria included treatment with cell depleting agents, uncontrolled medical conditions, history of other inflammatory diseases or Functional Class 4 RA, history of malignancies or recurrent infections, primary or secondary immunodeficiency, haemoglobin (Hgb) < 8.5 g/dL, leucopenia, neutropenia, thrombocytopenia, abnormal liver function, triglycerides > 10 mmol/L, or recognised active tuberculosis, hepatitis B, or hepatitis C.

Study design

RADIATE was a Phase III, randomised, double-blind, placebo-controlled, parallel group study conducted throughout North America and Western Europe. Protocol approval by institutional review boards, ethics committees and/or regulatory authorities and written informed consent from each patient were obtained per the Declaration of Helsinki. Participants were randomised to tocilizumab 8 mg/kg or 4 mg/kg intravenously every 4 weeks or placebo intravenously every 4 weeks (controls). Drug/placebo was infused for one hour. All patients received stable MTX (10-25 mg weekly) and folate. No other

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DMARDs were allowed. Patients were allowed to continue stable oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and/or non-steroidal anti-inflammatory drugs.

Rescue therapy of 8 mg/kg tocilizumab + MTX was offered at Week 16 in all cases of treatment failure ($< 20\%$ improvement in both SJC and TJC). Joint assessors were blinded as to other data including CRP, ESR and treatment assignment, thus rescue therapy could be given to patients already receiving 8 mg/kg tocilizumab.

Study endpoints

The primary endpoint was the ACR20 response at Week 24. Secondary endpoints included further efficacy measures. Safety outcomes included adverse events (AEs), infections, and infusion reactions.

Statistical methodology

A sample size of 450 patients was calculated to provide $> 80\%$ power to detect a difference of 20 points between tocilizumab and control arms at Week 24 for the ACR20 response and to enable reporting of safety and efficacy for this unique patient population for registration. Primary endpoint analysis was performed on all participants receiving ≥ 1 administration of study treatment (the Intent to Treat [ITT] population). Safety data are presented using the safety population, comprising all ITT patients with ≥ 1 post-randomisation assessment of safety.

Primary endpoint analysis for ACR20 response (with secondary analyses for ACR50/70, DAS28 and EULAR responses) compared the proportion of patients in each of the tocilizumab + MTX groups vs. controls with a response at Week 24 using a Cochran-Mantel-Haenszel chi-squared test with adjustment for site. Patients on rescue therapy or with insufficient data to calculate the change from baseline ACR score at a specific time point were classified as nonresponders at that time point. Changes from baseline in the individual ACR core set parameters and Hgb were summarised using descriptive statistics, and the difference between treatment groups for each component was compared using an analysis of variance (ANOVA) with adjustment for site.

In case of missing data, SJC, and TJC scores were calculated as last observation carried forward. There was no imputation for missing data for the remaining ACR components. Comparisons between tocilizumab groups and for safety outcomes were not performed.

RESULTS

Patients

The three groups were reasonably well-balanced for demographics and RA characteristics at baseline (**Table 1**).

Table 1: Baseline data

	8 mg/kg tocilizumab + MTX (n=170)	4 mg/kg tocilizumab + MTX (n=161)	Placebo + MTX (n=158)
Age (yr)	53.9 (± 12.7)	50.9 (± 12.5)	53.4 (± 13.3)
% female	84	81	79
Disease duration (yr)	12.6 (± 9.3)	11.0 (± 8.5)	11.4 (± 9.2)
# previous anti-TNFs			
1 (%)	50	47	42
2 (%)	32	41	44
>3 (%)	18	12	14

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Previous anti-TNF therapy (%)

Etanercept	38.3	38.0	30.6
Adalimumab	30.3	34.4	39.4
Infliximab	31.4	26.4	29.4
# previous DMARDs	1.9 (\pm 1.7)	2.0 (\pm 1.6)	2.1 (\pm 1.6)
Baseline MTX dose (mg/week)	15.7 (\pm 4.4)	16.2 (\pm 4.5)	16.5 (\pm 4.8)
% receiving oral steroids	52	58	58
DAS28 score	6.79 (\pm 0.93)	6.78 (\pm 0.97)	6.80 (\pm 1.06)
RF+ (%)	79	73	75
<LLN Hgb n (%)	60 (35.3)	52 (32.3)	57 (36.1)
TJC	31.7 (\pm 15.4)	31.3 (\pm 15.1)	30.4 (\pm 16.8)
SJC	18.9 (\pm 10.9)	19.5 (\pm 10.4)	18.9 (\pm 11.1)
ESR (mm/h)	49.1 (\pm 27.9)	51.3 (\pm 28.3)	54.6 (\pm 32.7)
CRP (mg/dL)	2.80 (\pm 3.37)	3.11 (\pm 3.61)	3.71 (\pm 4.12)
HAQ-DI	1.7 (\pm 0.6)	1.7 (\pm 0.6)	1.7 (\pm 0.6)
Pain VAS (100 mm)	64.7 (\pm 20.6)	63.5 (\pm 22.2)	64.1 (\pm 21.8)
Patient VAS (100 mm)	70.2 (\pm 20.0)	70.4 (\pm 23.8)	70.9 (\pm 21.1)
Physician VAS (100mm)	66.4 (\pm 18.0)	66.5 (\pm 16.1)	67.5 (\pm 16.1)

CRP = C-reactive protein; DAS28 = Disease activity score based on 28 joints; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessments Questionnaire disease index; Hgb = haemoglobin; LLN = lower limit of normal; MTX = methotrexate; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count; VAS = visual analogue score

Patient disposition is shown in **Figure 1**. The major reason for screen failure was a CRP or ESR value below the inclusion limit. This did not skew the populations, which were well balanced. One control patient withdrew after randomisation but prior to receiving any study treatment due to a latex allergy. Also, one patient randomised to the 4 mg/kg + MTX group received 6 mg/kg of tocilizumab at baseline. This patient was assigned to the 8 mg/kg group for safety analyses and to the 4 mg/kg group for ITT analyses but was excluded from PP analyses. The most common reasons for withdrawal were: AEs in 11 (8 mg/kg), 10 (4 mg/kg), and 10 (control) and insufficient therapeutic response in 4, 6, and 19 patients, respectively. More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after Week 16 compared with 11% of patients in the 8 mg/kg group.

Efficacy

Both 8 mg/kg (50.0%) and 4 mg/kg (30.4%) groups exhibited superior ACR20 responses vs. control (10.1%; $p < 0.0001$). ACR50 and ACR70 responses at 24 weeks were achieved by 28.8% and 12.4% of patients in the 8 mg/kg group ($p < 0.0001$ and $p = 0.0002$, respectively vs. control), 16.8% and 5.0% in the 4 mg/kg group ($p < 0.0001$ and $p = 0.1$, respectively vs. control) and 3.8% and 1.3% in the control group. Response to

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tocilizumab treatment was rapid (**Figures 2A-C**). The ACR20 response was comparable irrespective of the type or number of failed TNF-antagonists (**Table 2**). 95% of previous TNF-antagonist failures were due to inadequate efficacy.

Table 2: ACR responses by previous anti-TNF treatment and by number of prior anti-TNF treatments

	8 mg/kg tocilizumab + MTX	4 mg/kg tocilizumab + MTX	Placebo + MTX
ACR response by most recently-failed anti-TNF treatment; n/n' (% responders)			
ACR20			
Etanercept	35/67 (52.2%)	17/61 (27.9%)	8/49 (16.3%)
Adalimumab	26/49 (53.1%)	19/55 (34.5%)	3/62 (4.8%)
Infliximab	24/54 (44.4%)	13/43 (30.2%)	5/47 (10.6%)
ACR50			
Etanercept	19/67 (28.4%)	6/61 (9.8%)	3/49 (6.1%)
Adalimumab	19/49 (38.8%)	13/55 (23.6%)	0/62 (0.0%)
Infliximab	11/54 (20.4%)	8/43 (18.6%)	3/47 (6.4%)
ACR70			
Etanercept	10/67 (14.9%)	0/61 (0.0%)	1/49 (2.0%)
Adalimumab	6/49 (12.2%)	5/55 (9.1%)	0/62 (0.0%)
Infliximab	5/54 (9.3%)	3/43 (7.0%)	1/47 (2.1%)
ACR response by number of prior anti-TNF treatments; n/n' (% responders)			
ACR20			
One	45/92 (48.9%)	28/81 (34.6%)	8/76 (10.5%)
Two	26/52 (50.0%)	17/60 (28.3%)	7/64 (10.9%)
Three	14/26 (53.8%)	4/18 (22.2%)	1/18 (5.6%)
ACR50			
One	28/92 (30.4%)	15/81 (18.5%)	5/76 (6.6%)
Two	16/52 (30.8%)	8/60 (13.3%)	1/64 (1.6%)
Three	5/26 (19.2%)	4/18 (22.2%)	0/18 (0.0%)
ACR70			
One	11/92 (12.0%)	6/81 (7.4%)	2/76 (2.6%)
Two	8/52 (15.4%)	2/60 (3.3%)	0/64 (0.0%)
Three	2/26 (7.7%)	0/18 (0.0%)	0/18 (0.0%)

n = number of patients with ACR response; n' = total number of patients in group

Significant improvements from baseline were observed at 24 weeks for SJC: -7.8 vs. -6.8 vs. -0.5 ($p < 0.0001$ vs. control for both tocilizumab groups) and TJC: -14.8 vs. -10.5 vs. 0.3 in the 8 mg/kg, 4 mg/kg and control groups, respectively ($p < 0.0001$ vs. control for both tocilizumab groups). Likewise, health assessment questionnaire (HAQ) values improved from baseline by -0.39 vs. -0.31 vs. -0.05 in the 8 mg/kg, 4 mg/kg and control groups, respectively ($p < 0.0001$ for control vs. 8 mg/kg and $p = 0.0029$ vs. 4 mg/kg group). Low disease activity (DAS28 < 3.2) was reported at Week 24 in 51.2%, 15.2%, and 4.9% of patients in 8 mg/kg, 4 mg/kg, and control groups, respectively. DAS28 remission (DAS28 < 2.6) rates at 24 weeks were 30.1%, 7.6%, and 1.6% in the 8 mg/kg, 4 mg/kg,

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and control groups ($p=0.0001$ [8 mg/kg], $p=0.053$ [4 mg/kg] both vs. control). The dose response between 8 mg/kg and 4 mg/kg is evident as seen by the proportion of patients achieving DAS28 remission (DAS28 <2.6) as early as Week 4 (**Figure 2D**). Furthermore, there was incremental improvement in this measure in the 8 mg/kg group at each time point, throughout the 24 weeks.

Good or moderate EULAR responses at Week 24 were observed in 67.7%, 46.5%, and 16.5% of the 8 mg/kg, 4 mg/kg, and control groups, respectively ($p<0.0001$ across all categories for both tocilizumab groups vs. control).

CRP levels and ESR dropped markedly by Week 2 in both tocilizumab groups (**Figures 3A-B**). By week 24, mean CRP had normalised (<0.3 mg/dL) in the 8 mg/kg group, but not in the 4 mg/kg or control groups. Mean Hgb levels increased with tocilizumab as early as Week 2, more with 8 mg/kg, with incremental improvements over time (**Figure 3C**).

Safety

The overall incidence of AEs was similar in all groups (**Table 3**). AEs were mostly mild to moderate, with more attributed to study treatment in the tocilizumab groups. There was no obvious influence of prior type or number of TNF-antagonist treatments (data not shown).

Table 3: Summary of safety data

	8 mg/kg tocilizumab + MTX (n=175)	4 mg/kg tocilizumab + MTX (n=163)	Placebo + MTX (n=160)
Overall summary of adverse events, serious adverse events and deaths^a			
Total AEs, n (%)	147 (84.0)	142 (87.1)	129 (80.6)
Severe AE^b	24 (13.7)	22 (13.5)	31 (19.4)
Related AE	111 (63.4)	107 (65.6)	86 (53.8)
Total SAEs, n (%)	11 (6.3)	12 (7.4)	18 (11.3)
Related SAEs	5 (2.9)	3 (1.8)	3 (1.9)
Serious infections	8 (4.6)	3 (1.8)	5 (3.1)
AE leading to discontinuation, n (%)	10 (5.7)	10 (6.1)	8 (5.0)
AE leading to dose modification, n (%)	12 (6.9)	24 (14.7)	13 (8.1)
Deaths	0	0	0
Summary of adverse events by class in >5% of patients			
Infections and infestations, n (%)	86 (49.1)	76 (46.6)	66 (41.3)
Gastrointestinal, n (%)	64 (36.6)	53 (32.5)	31 (19.4)
Skin and subcutaneous tissue,	38 (21.7)	50 (30.7)	23 (14.4)

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n (%)			
Musculoskeletal and connective tissue, n (%)	27 (15.4)	34 (20.9)	34 (21.3)
Nervous system, n (%)	32 (18.3)	32 (19.6)	27 (16.9)
General and administrative, n (%)	21 (12.0)	26 (16.0)	23 (14.4)
Respiratory, n (%)	21 (12.0)	24 (14.7)	21 (13.1)
Injuries and procedural, n (%)	19 (10.9)	11 (6.7)	16 (10.0)
Laboratory investigations, n (%)	14 (8.0)	20 (12.3)	9 (5.6)
Vascular, n (%)	14 (8.0)	18 (11.0)	8 (5.0)
Psychiatric, n (%)	13 (7.4)	16 (9.8)	6 (3.8)
Eye, n (%)	11 (6.3)	11 (6.7)	3 (1.9)
Metabolism and nutrition, n (%)	9 (5.1)	7 (4.3)	7 (4.4)
Haematological, n (%)	9 (5.1)	4 (2.5)	4 (2.5)

Summary of serious adverse events by class in >1% of patients

Infections and infestations, n (%)	8 (4.6%)	3 (1.8%)	5 (3.1%)
Musculoskeletal and connective tissue, n (%)	1 (0.6%)	2 (1.2%)	5 (3.1%)
Gastrointestinal, n (%)	2 (1.1%)	2 (1.2%)	2 (1.3%)

Summary of changes in lipid parameters^c

Total Cholesterol, mmol/L			
Baseline, mean (SD)	5.09 (1.07)	4.96 (1.12)	4.92 (0.99)
Week 24, mean (SD)	5.99 (1.25)	5.38 (1.09)	4.99 (1.07)
HDL, n (%)			
No change	112 (64.7)	100 (61.3)	104 (65.0)
Elevation to ≥60 mg/dL	29 (16.6)	22 (13.5)	6 (3.8)
LDL, n (%)			
No change	90 (51.4)	76 (46.6)	104 (65.0)
Elevation to			

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≥ 160 mg/dL	21 (12.0)	25 (15.3)	6 (3.8)
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^aEvents that occurred on escape therapy were excluded from all treatment groups presented in this table

^bSevere adverse events refer to those resulting in an inability of the patient to work or perform daily activity

^cChanges according to ATPIII guidelines[20] reflect highest elevation of lipid during study

There were more serious AEs (SAEs) in the control group compared to individual tocilizumab treatment arms (**Table 3**). These were primarily related to complications of RA. The incidence of serious related AEs was also higher in the 8 mg/kg group (5) than controls (3). The rate of serious infections per 100 patient years was 9.98, 5.72, and 9.64 in the 8 mg/kg, 4 mg/kg, and control groups, respectively. All but 2 serious infections, staphylococcal polyarthritides in the 8 mg/kg group, and cellulitis in the control group, resolved without sequelae. Five serious infections in 4 patients led to study treatment discontinuation: staphylococcal polyarthritides in the 8 mg/kg group; necrotising pneumonia in the 4 mg/kg group; urosepsis and osteomyelitis/cellulitis in the controls.

Infusion reactions (AEs occurring during or within 24 hours following infusion) occurred in 9.1% (8 mg/kg), 9.8% (4 mg/kg), and 6.3% (control) of patients, resulting in 2 withdrawals: 1 control patient and 1 in the 8 mg/kg group. Most reactions were transient nonspecific symptoms such as headache or hypertension; none were consistent with anaphylaxis.

Mean neutrophil counts decreased within the normal range in patients receiving tocilizumab + MTX. Using Common Toxicity Criteria grades (CTC, version 2.0) to classify neutropenia, 49 patients (28.0%), 33 patients (20.3%), and 1 patient (<1.0%) in the 8 mg/kg, 4 mg/kg, and control groups respectively, had transient neutropenia at some time during the study. Although most changes were CTC Grade 1 or 2, 4 patients in the 8 mg/kg group and 1 in the 4 mg/kg group had Grade 4 neutropenia (absolute neutrophil count <500) requiring withdrawal per protocol. One of the patients in the 8 mg/kg group was inadvertently entered into the study with grade 4 neutropenia and was withdrawn immediately following the first dose. Additionally, 5 patients (4 in 8 mg/kg group, 1 in 4 mg/kg) had transient grade 3 neutropenia. No patients had associated fever or serious infection.

Although transient or recurrent increases in ALT and/or AST above ULN (55 U/L) were common as patients were also receiving MTX, no patients developed evidence of MTX hepatotoxicity. Increases in ALT from normal at baseline to >3x ULN to 5x ULN occurred in 4 patients (2%) in the 8 mg/kg group, 4 patients (2.5%) in the 4 mg/kg group, and 1 control patient (<1%). None of these elevations were sustained for more than 2 consecutive visits. In most patients, values normalised while continuing tocilizumab therapy. Per protocol, 3 patients discontinued study treatment for elevated liver enzymes. Mild to moderate hepatic steatosis diagnosed by imaging methods was recorded in 1 patient each in the 8 mg/kg and 4 mg/kg groups, without clinically apparent hepatitis or hepatic dysfunction.

Elevations in HDL and LDL as defined by ATPIII guidelines,[20] are shown in Table 3. Clinically relevant triglyceride increases without evidence of pancreatitis, were observed in 2 patients in the 4 mg/kg group. Comparable proportions of patients had a >30% increase in the ApoB/ApoA atherogenic index: 11.6% (8 mg/kg), 9.4% (4 mg/kg) and 9.7% (controls). More patients in the tocilizumab groups had a >30% increase in the LDL/HDL index: 22.2% (8 mg/kg), 19.1% (4 mg/kg) and 10.1% (controls). During the study, there were no reported ischaemic cardiac disorders in tocilizumab-treated patients. There was only 1 cardiovascular (CV) event (myocardial infarction), in the control group.

DISCUSSION

RADIATE is the first study demonstrating the efficacy of tocilizumab + MTX in patients with an inadequate response to TNF-antagonist treatment. Treatment with tocilizumab,

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especially at the 8 mg/kg dose, and stable MTX provides rapid and sustained improvement in RA symptoms. Treatment was generally well tolerated, with a comparable incidence of serious infections and withdrawals due to safety issues. These results were consistent with the results obtained in previous trials in different patient populations, including the recently reported OPTION and TOWARD trials.[15,19,21] As observed in these trials, onset of ACR, DAS28 and EULAR responses in RADIATE occurred within 2-4 weeks of tocilizumab 8 mg/kg treatment.

Patients receiving 8 mg/kg tocilizumab + MTX exhibited the greatest ACR20/50/70 responses at 24 weeks; all numerically higher vs. 4 mg/kg and significantly higher vs. control, irrespective of the most recently failed, or number of failed anti-TNF therapies.

Treatment goals for RA have shifted towards achieving remission. Similar to OPTION and TOWARD, in this study over half of patients receiving 8 mg/kg tocilizumab achieved low disease activity (DAS28 <3.2), and nearly a third achieved DAS28 remission (DAS28 <2.6) after 24 weeks of treatment. This is somewhat higher than the ACR50 response rate and may relate to the substantial suppression of acute phase reactants by tocilizumab treatment. DAS28 scores continued to improve linearly throughout the 24 week period in the 8 mg/kg tocilizumab group, which suggests DAS28 remission rates may continue to improve with longer treatment periods. DAS28 improvement was associated with incremental decreases in not only ESR and CRP, beginning by Week 2, but also with improvements in patient global health, SJC and TJC, from Week 4 onwards (data not shown). Collectively, the efficacy data support the use of 8 mg/kg tocilizumab + MTX in this patient population, and together with improvements in HAQ, provide evidence that changing therapy from an anti-TNF biologic to IL-6R inhibition with tocilizumab can improve RA signs and symptoms in inadequate responders (IR) to anti-TNF therapy.

The accumulation of IL-6 and soluble IL-6R prolongs the inflammatory response and produces a variety of systemic conditions which are commonly seen in RA, including anaemia of chronic inflammation.[22,23] Treatment which reduces the severity of inflammation has been associated with an increase in Hgb levels.[22] Indeed, the concomitant reduction in CRP and increase in Hgb observed in this study in the patients receiving 8 mg/kg tocilizumab supports this hypothesis. A proposed mechanism for the increase in Hgb levels relates to the ability of IL-6 to induce hepcidin production as part of the acute phase response.[24] IL-6 signalling activates the JAK-STAT pathway to stimulate production of acute phase proteins, including CRP and hepcidin. Because hepcidin blocks iron transport, inhibition of hepcidin production should lead to the release of sequestered iron in macrophages and alleviation of anaemia. TNF does not stimulate hepcidin production.[25,26] Hence the correction of anaemia seen with TNF-antagonists potentially occurs indirectly via reduction in IL-6 levels,[27] whereas tocilizumab directly inhibits IL-6 signalling for each mechanism.

Although numerically higher in the control group, the incidence of AEs and SAEs was comparable across treatment groups and most AEs were mild or moderate in intensity. Infections were the most frequently reported AE. The rate of serious infections was similar in the 8 mg/kg and control groups and consistent with the OPTION study.[19] These rates are higher than reports in other similar studies, however, it is comparable to rates in a recent large community study and reflects the comorbidities and long disease duration seen in this treatment population,[28-30] as well as concomitant corticosteroid treatment in more than half of the patients. Four patients discontinued study treatment due to serious infections, 1 or 2 from each study group. No tuberculosis or opportunistic infections were observed.

While a higher proportion of patients experienced GI AEs in the 8 mg/kg group, only 2 patients in each treatment group had GI SAEs. One patient in the 8 mg/kg group with history of diverticulosis had an acute diverticular perforation 5 days after her second infusion and recovered fully. Tocilizumab may suppress symptoms and delay detection of diverticulitis; thus patients with a history of diverticulitis must be managed carefully.

Patients treated with tocilizumab in the present study demonstrated reductions in mean neutrophil counts. Although neutropenia was typically transient, not associated with

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infection or fever and of low CTC grade, more patients in this population (TNF antagonist-IR) had transient Grade 3 or 4 neutropenia, compared to reports in the MTX-IR population of the OPTION study.[19] Some possible mechanisms by which tocilizumab may result in lower neutrophil counts include blocking IL-6-induced neutrophil survival, down-regulation of other inflammatory cytokines, and margination of neutrophils from the circulation into tissues.[31-34]

Consistent with prior reports, tocilizumab treatment in this study was associated with episodic increases in hepatic aminotransferases. No patient had both a >3xULN increase in ALT and AST and a clinically relevant (>2xULN) increase in total bilirubin and there were no cases of hepatitis or clinically significant hepatic dysfunction. Nonetheless, long-term follow up is required to determine the implications of these observations.

Increases in total and LDL cholesterol levels in this study were consistent with prior reports[17,19,35] and associated with marked decreases in CRP. Patients with active RA often have abnormal lipid profiles, an inverse relationship that associates low lipid levels with elevated acute phase reactants in some patients.[36,37] Considering the recognised higher incidence of CV mortality in RA patients,[37,38-41] traditional risk factors for CV disease, including dyslipidaemia, are not necessarily predictive of events for patients with RA. Indeed, several studies have provided evidence that despite increases in lipid levels, reduced inflammation markers have been associated with reduced CV mortality.[38,40-43] Interestingly, the ApoB/ApoA ratio is viewed as possibly the more relevant indicator for inflammatory vascular disorders than other atherogenic indices, and this index worsened in a comparable proportion (~10%) of patients in each treatment group in this study.[44,45]

The current study does have limitations. Firstly, the clinical consequences of the increase in lipid levels observed with 24-week tocilizumab treatment, together with the significant decreases in CRP and inflammation, are unclear. Long-term studies in this population may determine if the effects of tocilizumab on lipid levels are clinically meaningful, although it is apparent that this effect may require treatment with statins, according to standards developed to lower CV risk. Secondly, limitation of joint damage with tocilizumab treatment (as shown in the SAMURAI study[18]) needs to be confirmed in patients refractory to anti-TNF treatments.

Conclusion

In patients with moderate to severe active RA responding inadequately or who are intolerant to TNF-antagonists, changing to tocilizumab + MTX is effective, and the safety profile is manageable, regardless of number of prior failed agents.

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FIGURE LEGENDS

Figure 1:

Numbers of patients undergoing enrolment, randomisation and study completion

*One randomised patient was withdrawn from the study prior to receiving any study medication due to a latex allergy

Figure 2:

Clinical response to tocilizumab treatment by visit for (A) ACR20 response, (B) ACR50 response, (C) ACR70 response, (D) % patients achieving clinical remission (DAS28 <2.6)

**p<0.001 vs. placebo

***p<0.0001 vs. placebo

Figure 3:

Changes in haematological and serum proteins per visit for (A) C-reactive protein, (B) erythrocyte sedimentation rate, (C) haemoglobin

*p<0.05 vs. placebo

**p<0.001 vs. placebo

***p<0.0001 vs. placebo

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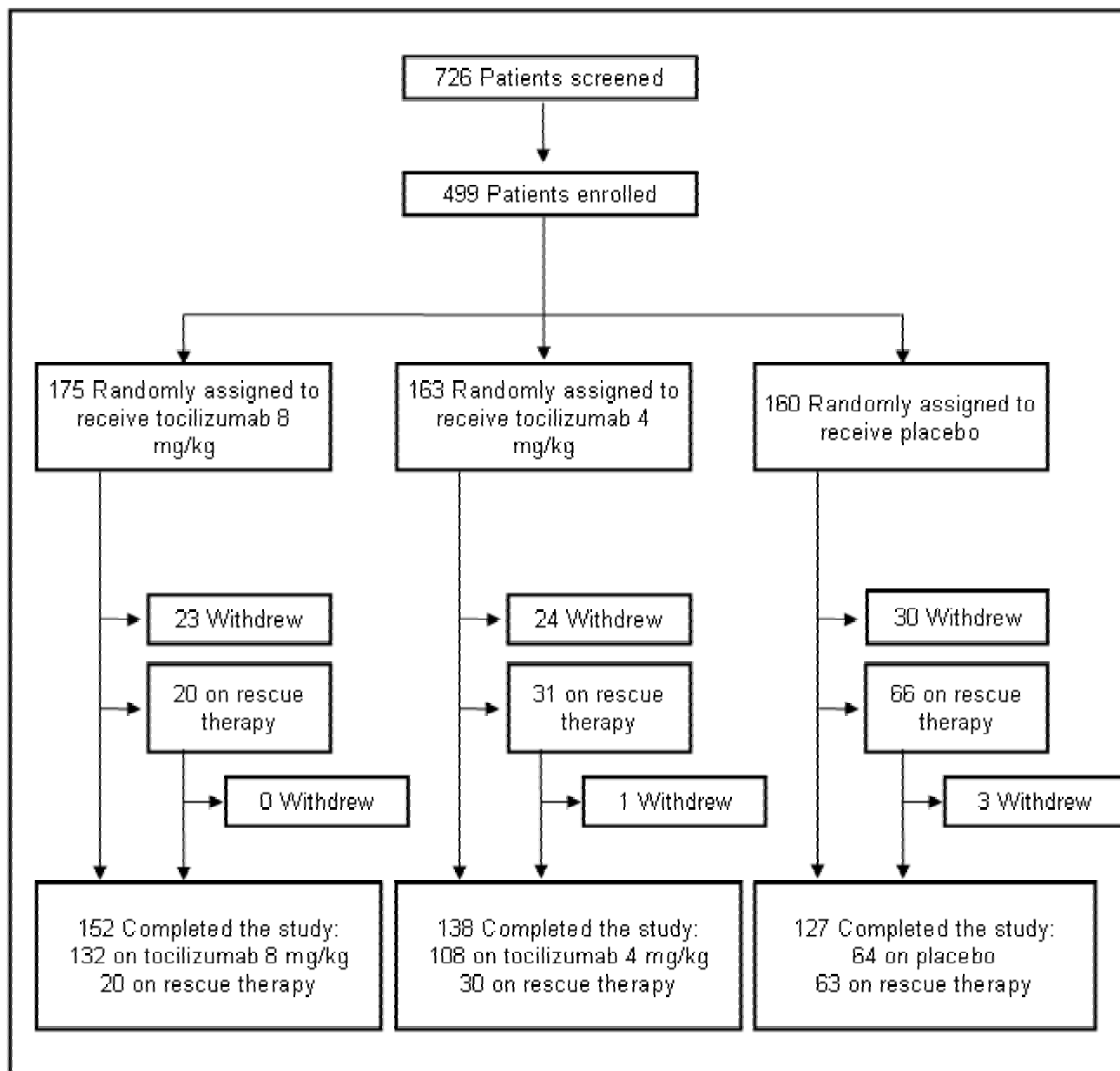
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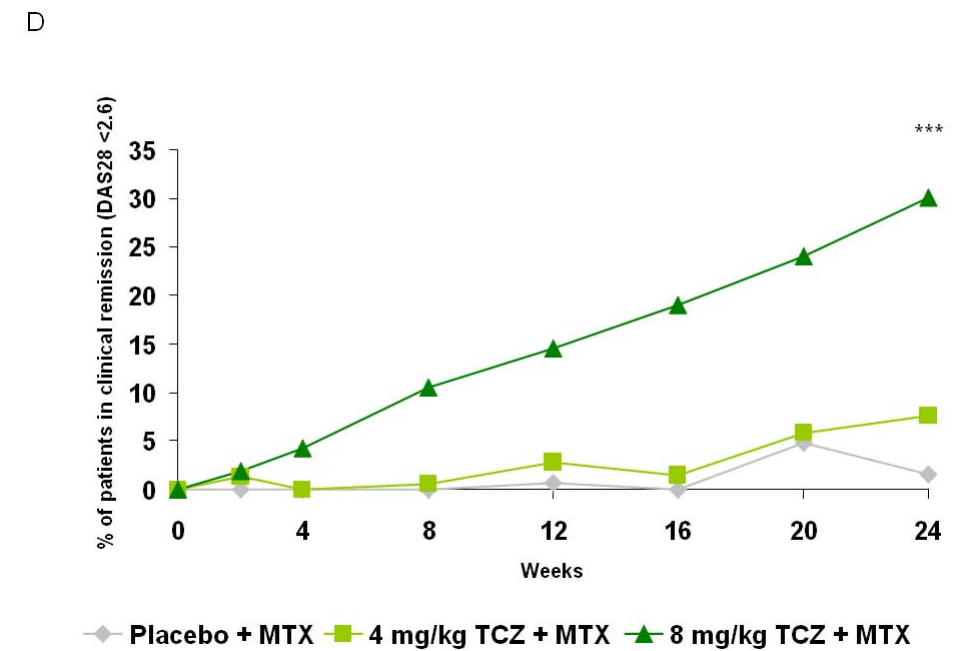
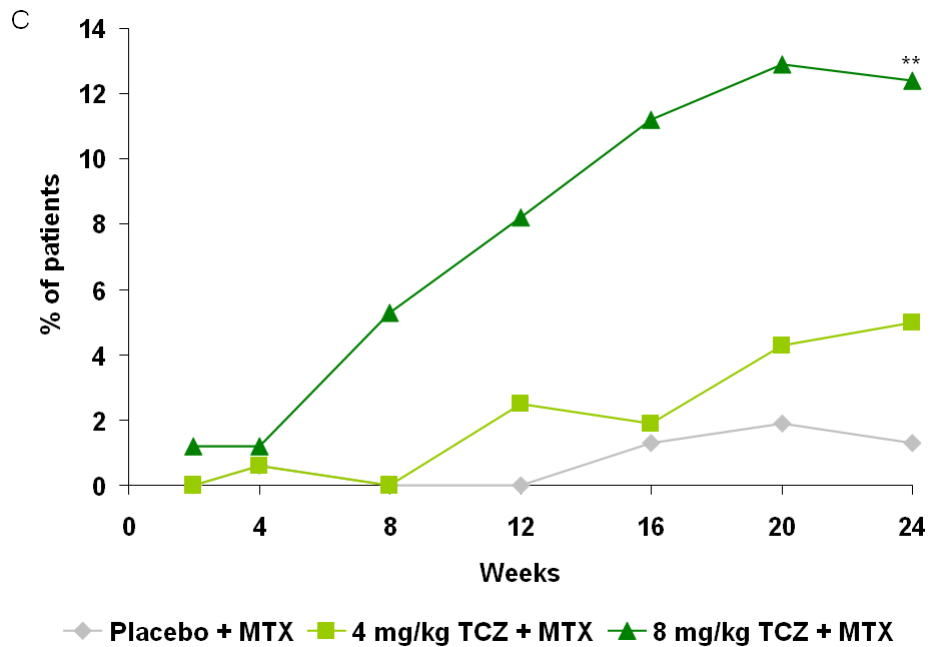
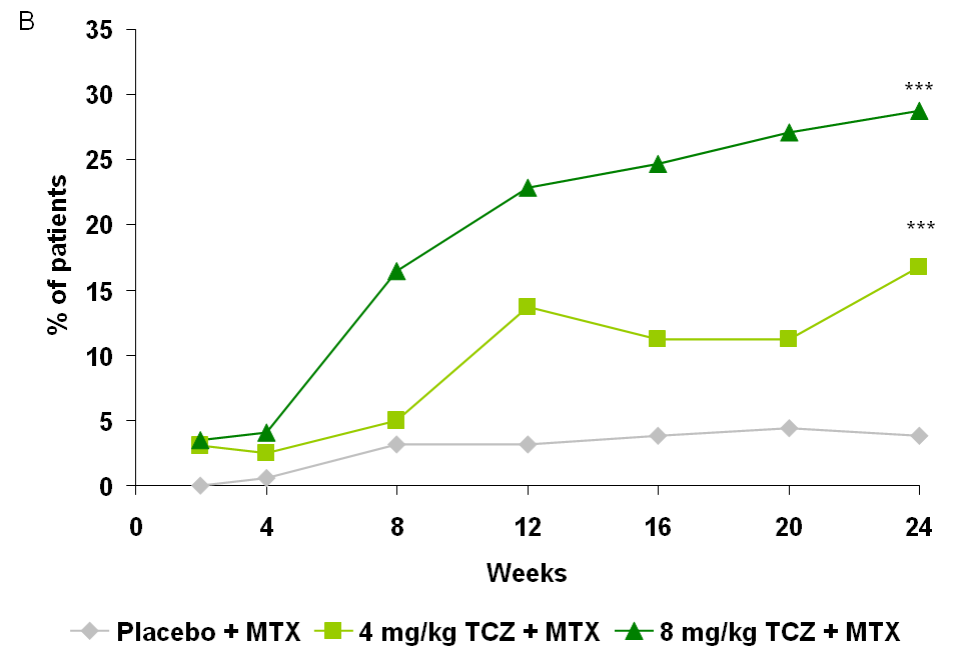
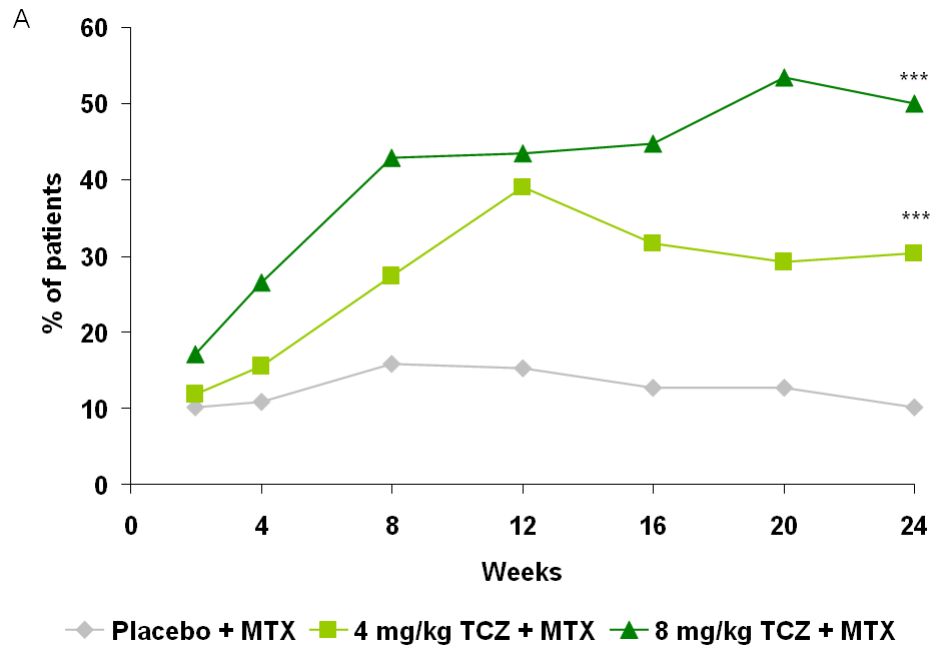
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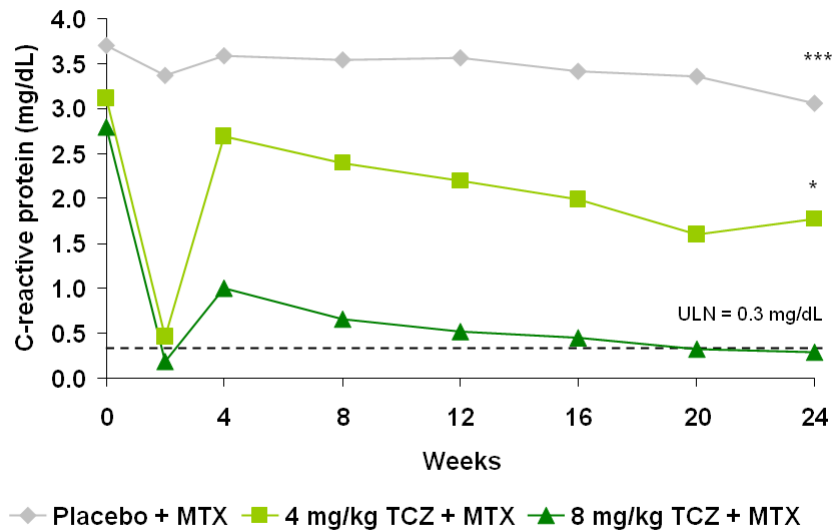
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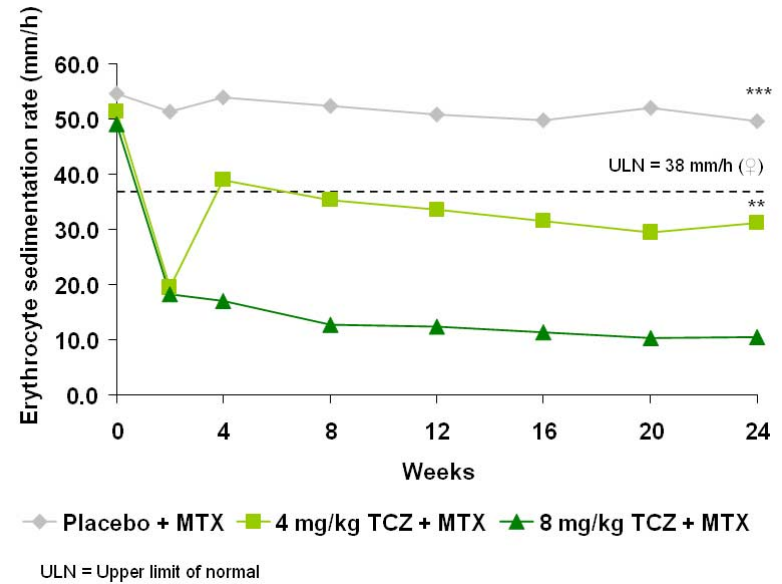




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