Five-year Efficacy and Safety of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Who Were Methotrexate- and Biologic-naive or Free of Methotrexate for 6 Months: the AMBITION Study

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ABSTRACT. ***Objective.*** To report on the 5-year efficacy and safety results of the AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) monotherapy study (ClinicalTrials.gov: NCT00109408, NCT00720798).

Methods. Patients with rheumatoid arthritis for whom biologics had not failed or who did not discontinue methotrexate because of lack of efficacy or tolerability were followed up for 5 years to assess the efficacy and serious adverse events (SAE) of tocilizumab (TCZ) monotherapy.

Results. Longterm efficacy results showed that efficacy was maintained or improved for up to 264 weeks in patients receiving TCZ monotherapy. Serious infection was the most frequent SAE; no new safety signals were reported.

Conclusion. Longterm monotherapy with TCZ demonstrated continuing efficacy and safety. (J Rheumatol First Release December 1 2016; doi:10.3899/jrheum.160287)

Key Indexing Terms:
BIOLOGICAL THERAPY CLINICAL TRIALS DISEASE ACTIVITY
METHOTREXATE RHEUMATOID ARTHRITIS

Methotrexate (MTX) or a combination of oral conventional synthetic disease-modifying antirheumatic drugs (csDMARD)[1] is recommended as first-line treatment for adult patients with rheumatoid arthritis (RA)[2,3]. However, because of adverse events (AE) or other issues, about 30% of patients receiving biological DMARD do not take them in combination with csDMARD[4]. Use of MTX, the most studied drug in combination therapy, is required to enhance the maximal efficacy and to suppress the immunogenicity of antitumor necrosis factor (anti-TNF) agents in the treatment of most patients with RA[4]. However, side effects involving gastrointestinal (GI), respiratory, hepatic, blood, neurologic, or dermatologic conditions, and fatigue, can cause patients to stop taking MTX[5], which could lead to suboptimal treatment of clinical disease activity and radiographic progression.

Tocilizumab (TCZ), the first drug approved for adult RA and for systemic and polyarticular juvenile idiopathic arthritis, blocks the interleukin 6 receptor [IL-6R; also known as IL-6Rα or CD126; National Center for Biotechnology Information (NCBI) gene ID 3570] and is linked to the signal transducer molecule gp130 (also known as IL-6Rβ or CD130; NCBI gene ID 3572). A study in patients with active RA for whom previous treatment with MTX/biologics had not failed showed that TCZ monotherapy had statistically significantly higher efficacy than MTX monotherapy[6]. Other TCZ studies showed that TCZ + MTX was not superior to TCZ monotherapy in patients with RA with inadequate response to MTX, with a trend favoring combination therapy[7], and that TCZ monotherapy had statistically significantly superior efficacy in all variables compared with adalimumab monotherapy in patients with RA who were intolerant of MTX or for whom MTX was inappropriate[8]. Among targeted csDMARD, 1 study[9] reported that tofacitinib monotherapy was superior to MTX monotherapy in patients

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with RA who had not previously received MTX. Among biological original DMARD, only TCZ has consistently shown efficacy similar to that of monotherapy and as part of combination therapy for the treatment of RA[4]. Potential loss of efficacy is a concern when a biologic is used without MTX over a long period. The purpose of this article is to report on the longterm efficacy and safety of TCZ monotherapy in patients who were part of the AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) study. Month 6 results from AMBITION have been published[6].

MATERIALS AND METHODS

AMBITION was a 24-week, randomized controlled trial in patients with active RA who were either MTX-naive or MTX-free for 6 months before study entry[6]. Patients were originally randomly assigned to receive TCZ 8 mg/kg intravenously (IV) every 4 weeks or oral MTX weekly (initial dose 7.5 mg, escalating to 20 mg). This randomized, blinded treatment was maintained for 24 weeks. A subset of patients was enrolled in a placebo-controlled substudy in which they received, on a weekly basis, placebo oral MTX and placebo IV infusions at weeks 0, 4, and 8, followed by TCZ 8 mg/kg for 16 weeks. At 24 weeks, patients had the option to enroll in a longterm extension (LTE) study. Ethics approval was granted by the Human Research Ethics Committee (Tasmania) Network, Tasmania, Australia (reference number H0010842), and ethics approval was obtained from 124 additional centers. Written informed consent was obtained from each participating patient before the start of the study and after adequate explanation of the aims, methods, anticipated benefits, and potential hazards. The study was performed in compliance with the principles of the Declaration of Helsinki and its amendments and with the applicable laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

The objective of our LTE study was to evaluate longterm efficacy and safety in patients treated with TCZ from their first dose up to 264 weeks. Followup safety assessments continued for up to 276 weeks. In the LTE study, patients at Week 24 who achieved ≥ 50% improvement from baseline in tender joint count (TJC) and swollen joint count (SJC) at weeks 20 and 24 could opt to continue their current blinded treatment in a transition phase until the last patient from AMBITION completed the 24-week core study, or they could move into the LTE study at any time during the transition phase if ≥ 50% improvement in active TJC and SJC was not maintained. All other patients who completed the planned course of assigned therapy or who escaped before 24 weeks could enroll in the LTE study and receive open-label TCZ 8 mg/kg IV every 4 weeks. During the LTE study, if a patient did not achieve ≥ 50% improvement in TJC and SJC from baseline of the AMBITION core study, MTX or another allowable DMARD could be added according to investigator practice and as tolerated by the patient.

Efficacy assessments included the Disease Activity Score at 28 joints (DAS28), American College of Rheumatology (ACR) 20/50/70 responses, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). Remission was defined as DAS28 < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8. Serious AE (SAE) were evaluated and summarized by MedDRA (Medical Dictionary for Regulatory Activities) version 10.0 superclass term and weeks since first TCZ exposure. SJC and TJC data were analyzed as observed. For disease activity measurements, the last observation carried forward method was used for SJC and TJC; however, the remaining components had to be present for the disease activity score to be calculated. Otherwise, the disease activity score was considered missing for that visit. For categorical disease activity summaries, observed data scores and nonresponder imputation were analyzed. No imputation was completed for missing data.

RESULTS

Two hundred eighty-six patients received TCZ 8 mg/kg monotherapy in the AMBITION core study[6]. Of these, 243 patients transitioned to the LTE study. One hundred thirty-four patients (55%) continued with monotherapy (Table 1), and 109 patients (45%) had added a DMARD. By the end of this LTE period, 94 of the 134 monotherapy patients (70.1%) remained in our study; therefore, 94 of 243 patients (39%) initially assigned to TCZ monotherapy who entered the LTE completed 5 years of TCZ monotherapy treatment. Withdrawals for safety reasons were reported for 19 patients (14.2%), and 21 patients (15.7%) withdrew for nonsafety reasons, including 6 who refused treatment, 3 who failed to return, 3 who withdrew consent, 1 who withdrew because of insufficient therapeutic response, 1 who had a protocol violation, and 7 for other reasons. Baseline DMARD history (DMARD-naive or DMARD-free for 6 mos) did not determine which patients needed a DMARD; 41.0% of DMARD-naive monotherapy patients and 40.4% of DMARD-experienced patients each received a DMARD.

In patients who continued to take TCZ monotherapy throughout the core and LTE studies, the time to maximum response according to the proportion of patients who achieved remission (DAS28 < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8) was about 130 weeks, which was maintained through Week 264 (Figure 1). The proportion of patients achieving DAS28 clinical remission at 24 and 264 weeks was 40.2% and 65.2%, respectively (Figure 1). ACR20/50/70 responses at 24 and 264 weeks were 85.8%/56.7%/35.8% and 90.5%/77.9%/60.0%, respectively. CDAI and SDAI remission rates were 16.5% and 20.3% at 24 weeks and 43.0% and 46.2% at 264 weeks. Therefore, TCZ monotherapy showed durable and increasing efficacy over time.

Table 1. Baseline demographics of TCZ monotherapy patients who transitioned to LTE. Values are mean (SD) unless otherwise specified.

Demographic	TCZ Monotherapy, n = 134
Age, yrs	51.1 (12.3)
Female, n (%)	111 (82.8)
Baseline oral corticosteroid use, n (%)	60 (44.8)
No. previous DMARD	0.9 (1.0)
No. previous anti-TNF	0.1 (0.3)
RA duration, yrs	5.9 (7.4)
CRP, mg/dl	3.0 (3.3)
ESR, mm/h	51.3 (26.0)
TJC68	32.3 (14.3)
SJC66	18.7 (9.9)
VAS PtGA, mm*	62.5 (19.2)
DAS28*	6.8 (0.9)

* n = 133. TCZ: tocilizumab; LTE: longterm extension; DMARD: disease-modifying antirheumatic drug; anti-TNF: antitumor necrosis factor; RA: rheumatoid arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC68: tender joint count at 68 joints; SJC66: swollen joint count at 66 joints; VAS: visual analog scale; PtGA: patient's global assessment; DAS28: Disease Activity Score at 28 joints.

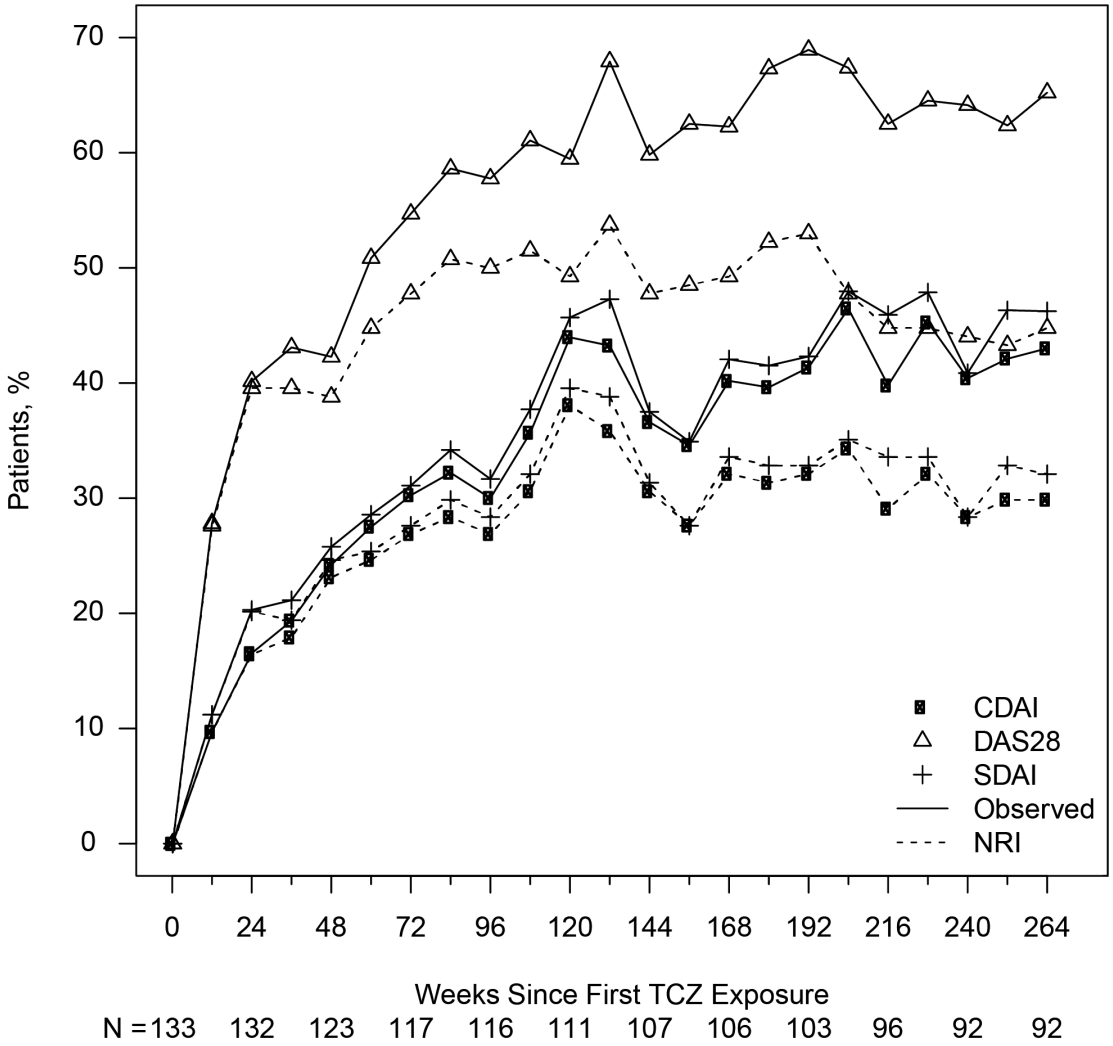

Figure 1. Proportion of patients who continued TCZ monotherapy achieving remission up to Week 264. Remission criteria were DAS28 < 2.6, CDAI ≤ 2.8, and SDAI ≤ 3.3. TCZ: tocilizumab; DAS28: Disease Activity Score at 28 joints; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; NRI: nonresponder imputation.

No trends were seen in SAE type reported over time (Figure 2). The overall cumulative SAE rate per 100 patient-years (PY; 95% CI) was 14.96 (12.16–18.22). The most common SAE for monotherapy patients was infection, and the most frequent infection was pneumonia. The overall serious infection event rate was 5.74 (4.06–7.88) per 100 PY, and the overall longterm infection rate remained stable. Few serious GI disorder events occurred, and 2 serious cases of diverticulitis were reported; no perforations occurred. Five patients died: 2 of pneumonia, 2 of malignant disease, and 1 (unexpectedly) of an unknown cause. Two occurrences of myocardial infarction were reported in 2 patients by 276 weeks. Eight occurrences of stroke were reported in 7 patients, with a rate per 100 PY (95% CI) of 1.21 (0.52–2.38) over the 276-week study period. Malignancies were infrequent and included lung cancer (n = 3), carcinoma of colon (n = 1), anorectal cancer (n = 1), and thyroid nodule (n = 1). Serious renal disorders occurred and included nephrolithiasis (n = 3) and calculus ureteric (n = 1); no patients experienced renal failure. No obvious associations between SAE and duration of TCZ exposure were observed, and no new safety signals were detected. Three patients experienced serious hypersensitivity reactions, but none experienced anaphylaxis. Of the 129 patients screened for anti-TCZ antibodies, postbaseline confirmation assay results were positive for 2. Neither of these patients experienced serious hypersensitivity events or anaphylaxis.

DISCUSSION

AMBITION was the first trial to show the clinical efficacy and superiority of a biologic monotherapy compared with MTX monotherapy for typical MTX dosing regimens[6]. Results of the 5-year LTE study of AMBITION confirm the continued efficacy and safety of TCZ as monotherapy that has been demonstrated previously[10]. The risk for serious

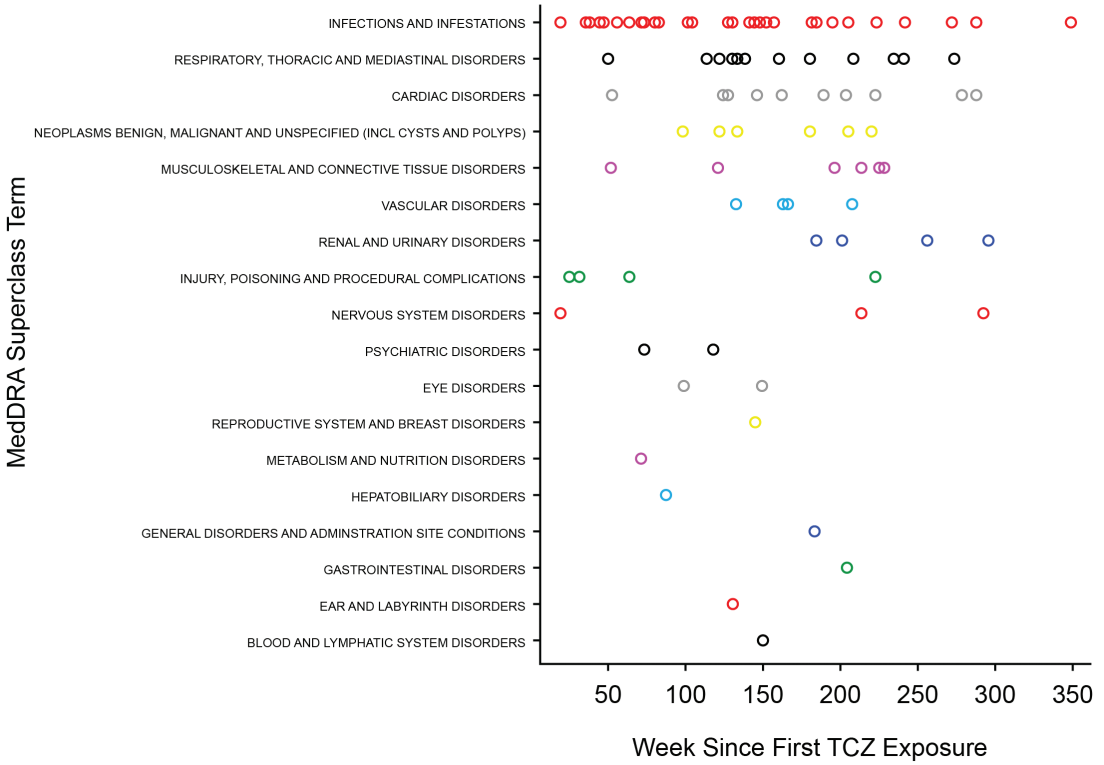

Figure 2. All SAE* over time in 5 years. Each open circle represents a single SAE by MedDRA superclass term and time since first TCZ exposure. * SAE from patients randomly assigned to TCZ monotherapy in AMBITION who entered the LTE study. SAE: serious adverse event; MedDRA: Medical Dictionary for Regulatory Activities; TCZ: tocilizumab; AMBITION: Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy; LTE: longterm extension.

infections remained stable over time in the AMBITION LTE. Registry data have shown a decrease in the risk for serious infection over time in patients with RA treated with TNF inhibitors; however, this may be influenced by tapering of corticosteroids[11].

Limitations typically associated with LTE include a population that is enriched for patients who respond to treatment and those who do not experience tolerability issues[12]. To minimize bias associated with LTE, efficacy results in our current study show nonresponder imputation as well as observed data, and the absolute numbers of patients remaining in the study are shown at each timepoint (Figure 1). However, the results should be interpreted with the understanding that the monotherapy patient population may be enriched for responders, especially because patients who did not achieve ≥ 50% improvement in TJC and SJC could add MTX or other DMARD.

In the AMBITION study, up to 264 weeks of therapy showed the continuing efficacy and safety of TCZ, which is consistent with the efficacy and safety results of 7 other TCZ monotherapy studies, and suggested a sustained effect even without MTX. Longterm treatment of RA with TCZ monotherapy is an important option for patients who are unable to tolerate MTX or for whom MTX is otherwise inappropriate.

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