The role of tocilizumab monotherapy in the management of rheumatoid arthritis: a review

A major advance in the treatment of rheumatoid arthritis has occurred following the introduction of tocilizumab (TCZ), an anti-IL-6 receptor antibody, into the therapeutic armory. Improvements in multiple aspects of the disorder including signs and symptoms, radiographic damage, disability and quality of life have been seen following its use. Extensive trial data revealed both the efficacy and safety of TCZ. Although methotrexate remains the foundation drug for rheumatoid arthritis, up to 30% of patients do not tolerate this disease-modifying antirheumatic drug. The following article will therefore focus on the current knowledge regarding TCZ as monotherapy, which to date, appears to be the most effective biologic agent administered in this way.

KEYWORDS: biologics ■ efficacy ■ monotherapy ■ rheumatoid arthritis ■ tocilizumab ■ tolerability

Muhammad K Nisar* & Andrew JK Östör

Rheumatology Research Unit, Box 194, Addenbrooke's Hospital, CUHNHSFT, Cambridge, CB2 2QQ, UK
**Author for correspondence:*
Tel.: +44 1223 217457
Fax: +44 1223 217838
muhammad.nisar@addenbrookes.nhs.uk

Rheumatoid arthritis (RA) is a chronic, systemic, disabling disease of unknown etiology affecting up to 1% of the population [1]. Its onset is most frequent in the fifth and sixth decades of life and occurs more commonly in females. The chronic inflammation associated with RA leads to a number of sequelae including reduced joint function, disability and premature mortality [2]. Radiological damage may occur early, and up to a third of patients stop work within 2 years of disease onset [3]. Hence the condition has major economic implications with an estimated cost to the European economy of €45.3 billion in 2006, a third (€16.6 billion) of which was attributed to lost productivity [4].

It is clear that immune dysfunction forms the cornerstone of the etiopathogenesis of RA. An uncoupling of the tightly regulated balance between pro- and anti-inflammatory mediators occurs in RA, ultimately leading to chronic inflammation. This manifests principally as synovitis and destruction of cartilage and bone. Although the initiating factor is unknown, both the innate and adaptive arms of the immune system are involved. The $CD4^+$ T cell holds primacy in the cell-mediated immune response stimulating the production of cytokines including TNF-α, IL-1 and IL-6 [5].

Although the optimal management of RA requires a multidisciplinary approach, biologic disease-modifying antirheumatic drugs (DMARDs) have truly revolutionized treatment of the condition. Following the success of TNF antagonists, a number of newer biologics have been trialed in RA including tocilizumab (TCZ), a humanized monoclonal antibody to the IL-6 receptor. Despite the success of biologics however, methotrexate (MTX) remains the benchmark drug for RA against which other agents are compared. As such, most guidelines recommend MTX as the first-line DMARD either as monotherapy or in combination with other DMARDs [6,7,101,102].

From the current evidence MTX improves the efficacy of most biologics when given concurrently [8]. However, approximately 30% of RA patients are MTX intolerant chiefly due to side effects [9]. In addition, although combination therapy is widely viewed to be more effective, the side-effect profile may be augmented limiting this paradigm in certain patients such as the elderly or those with comorbidities. Hence, it is imperative to determine how individual biologic agents perform when given as monotherapy.

Biologics that have been approved as monotherapy to date are etanercept, adalimumab, certolizumab, TCZ and abatacept in the USA. This review will focus specifically on the role of TCZ monotherapy in the treatment of RA, including its efficacy and safety, and compare it with other biologic agents used in this way.

Chemistry, pharmacokinetics & pharmacodynamics

IL-6 is a pleiotropic cytokine with a wide range of biological effects (Figure 1). IL-6 binds to both soluble and membrane-bound receptors, which then couple with the cell-surface molecule (gp130) resulting in cellular activation [10]. IL-6

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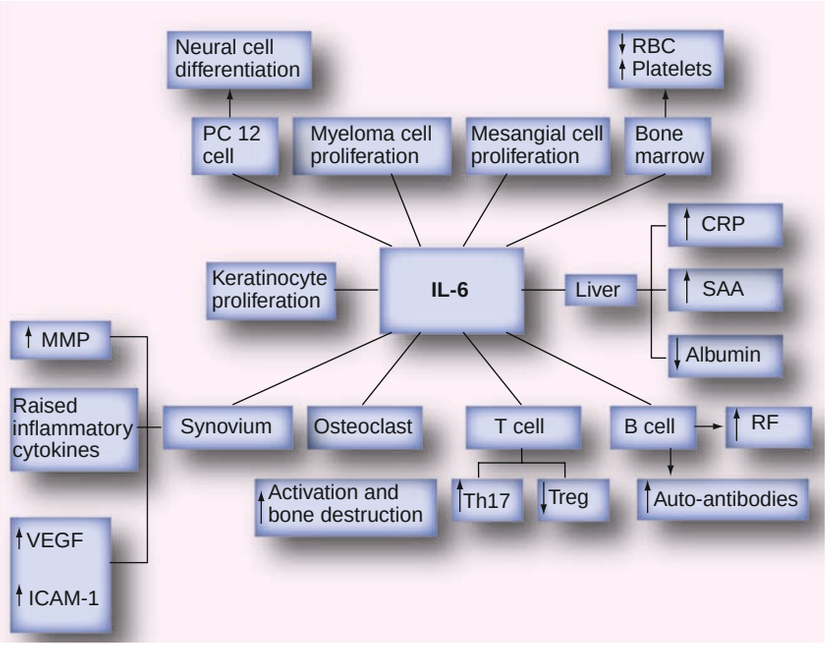

Figure 1. Actions of IL-6.
CRP: C-reactive protein; MMP: Matrix metalloproteinase; RBC: Red blood cell; RF: Rheumatoid factor; SAA: Serum amyloid A.

is produced by a variety of cells including T cells, B cells, fibroblasts and synoviocytes.

Amongst its many actions IL-6:

- Stimulates B cells to produce immunoglobulins;
- Induces T-cell growth and differentiation;
- Induces the acute-phase response;
- Activates hepatocytes to produce C-reactive protein and fibrinogen;
- Influences the hypothalamic–pituitary–adrenal axis causing fever and fatigue;
- Promotes the formation of osteoclasts;
- Plays a major role in the pathogenesis of osteoporosis;
- Regulates physiological metabolism and body weight [11].

IL-6 has been found to be a pivotal cytokine in the pathogenesis of RA. It is found abundantly in the joints and serum of patients with active disease and serum IL-6 concentration correlates with disease activity and radiological joint damage [12]. High levels of synovial IL-6 promotes osteoclast activation with the degree correlating with joint damage [13]. As IL-6 upregulates the expression of ICAM-1, it recruits immunocompetent cells into sites of inflammation [14]. Interestingly, it has emerged that IL-6 may have both pro- and anti-inflammatory properties suggesting a differential role of classic and trans-signaling mechanisms, however the clinical implications of this remain unclear [15].

Chemistry

TCZ is a recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1κ subclass with a molecular weight of 148 kDa (Figure 2). TCZ binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) thereby preventing the binding of IL-6 to IL-6 receptors and inhibiting IL-6-mediated signaling [16]. It helps prevent accumulation of high serum levels of IL-6 as might be found with anti-IL-6 antibody treatment. However, high IL-6 levels are seen following TCZ therapy possibly reflecting variable levels of endogenous IL-6 production in individual patients. Proposed explanations include sIL-6R/TCZ immune complex formation or inhibition of IL-6 clearance from the serum [17].

Pharmacodynamics

Using functional assays, TCZ binds competitively to IL-6 receptors thereby inhibiting the growth of IL-6-dependent cells *in vitro* [16]. In clinical studies of TCZ (both in a 4 and 8 mg/kg dose regimen) improvement in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate, C-reactive protein, serum amyloid A and increases in hemoglobin) with both doses, however the 8-mg/kg dose was more effective [103]. Healthy individuals and RA patients given TCZ (2–28 mg/kg) showed a decrease in absolute neutrophil counts (nadir 3–5 days) [103]. Thereafter, neutrophils recovered towards baseline in a dose-dependent manner. TCZ was also found to alter liver function tests (LFTs) and lipid levels.

Pharmacokinetics

The pharmacokinetics (PK) of different TCZ dosing regimens used for the treatment of RA patients were extracted from a population analysis of 1793 RA patients treated with TCZ (4 and 8 mg/kg every 4 weeks for 24 weeks). The clearance of TCZ decreased with increasing doses. At the 10 mg/kg single dose in RA patients, mean clearance was 0.29 ± 0.10 ml/h/kg with a terminal half-life of 151 ± 59 h (6.3 days). PK parameters did not change over time.

The PK profile is similar between RA patients and healthy individuals. Age, gender and race do not appear to affect TCZ PK nor does concurrent MTX use or alcohol consumption. The main

differences in PK between the 4 and 8 mg/kg dosing regimens (administered by a 1-h infusion) is that the area under the plasma concentration time curve, the minimal plasma concentration and the maximal plasma concentration appear to increase in a dose proportional relationship over the limited dose range. Comparing the 8 mg/kg with the 4-mg/kg dose, the former showed an area under the plasma concentration time curve 2.7-fold higher, and trough levels 6.5-fold higher than the latter. At steady state, the elimination half-life varies from 11 days (4 mg/kg every 4 weeks) to 13 days (8 mg/kg every 4 weeks) and is therefore concentration dependent.

No formal studies exist of the effect of renal or hepatic impairment on the PK of TCZ, however dose adjustment does not appear to be required for mild renal impairment.

As IL-6 downregulates CYP isozymes, blockade of IL-6 signaling may alter PK interactions with hepatically metabolized drugs [103].

Clinical efficacy

The pivotal trial program for TCZ has been extensive, thus only the larger studies will be summarized below, followed by an in-depth discussion of TCZ used as monotherapy.

Phase I/II studies

In a Phase I/II 12 week, double-blind, placebo (PBO)-controlled study, 162 patients with active RA were randomized to PBO or TCZ (4 or 8 mg/kg). The primary end point was the American College of Rheumatology (ACR)20 response. At 3 months, a dose-dependent reduction in the ACR20 response for the 8-mg/kg dose (78%; $p < 0.001$) was higher than for the 4-mg/kg dose (57%; $p = 0.02$) or PBO. Similarly, superior response was seen in the 8-mg/kg group for the ACR50 and ACR70 compared with PBO [18]. In the 5-year long-term extension of this trial (STREAM, n = 143), the serious adverse event (SAE) rate was 27.5 events/100-patient years, with 5.7 serious infections/100-patient years. At 5 years the ACR20, 50 and 70 responses were 77, 59 and 38%, respectively. Disease activity score-28 (DAS28) remission was achieved in 55% of patients with a decrease in corticosteroid use in 89% of patients. This was the first study to demonstrate the safety and efficacy of TCZ monotherapy in DMARD-resistant disease in the long term [19].

In the Phase II CHARISMA study, a 16-week, randomized controlled trial (n = 359), a statistically significant ($p = 0.05$) change in the ACR20 response was seen in 61 and 63% of those on monotherapy (TCZ 4 and 8 mg/kg, respectively) and in 63 and 74% of those with the same TCZ dose plus MTX, respectively, compared with 41% receiving MTX plus PBO. The TCZ 8-mg/kg dose achieved the best results for monotherapy. Remission rates (DAS28 <2.6) were 34% with the TCZ 8 mg/kg combination therapy, 17% with the TCZ 8 g/kg monotherapy and 8% among those receiving PBO plus MTX [20].

Phase III studies

TCZ combination therapy

The OPTION study was a 24-week double-blind, randomized, PBO controlled trial of 622 patients with moderate-to-severe RA, who were MTX inadequate responders (IR). In this study, 59% ($p = 0.001$) in the 8-mg/kg group, 48% ($p = 0.001$) in the 4-mg/kg group and 26% of those in the PBO group achieved the primary end point of ACR20 response. Significantly more patients receiving TCZ also achieved ACR50 and 70 responses compared with patients in the PBO group [21]. It is important to note that patients in this trial were receiving MTX as the study was not designed to assess TCZ monotherapy.

The RADIATE trial assessed the combination of TCZ with MTX in RA patients refractory to TNF antagonists. Patients received TCZ 8 mg/kg (n = 170) or 4 mg/kg (n = 163) or PBO, plus MTX (10–25 mg/wk, n = 158). Both TCZ groups (8 and 4 mg/kg) achieved significantly higher ACR20 responses than the PBO group (50, 30.4 [$p < 0.001$ for both doses] and 10.1%, respectively). Significantly greater ACR50 and 70 responses were also seen in the TCZ 8-mg/kg group at 24 weeks. Improvement was rapid in the TCZ groups (often within 2

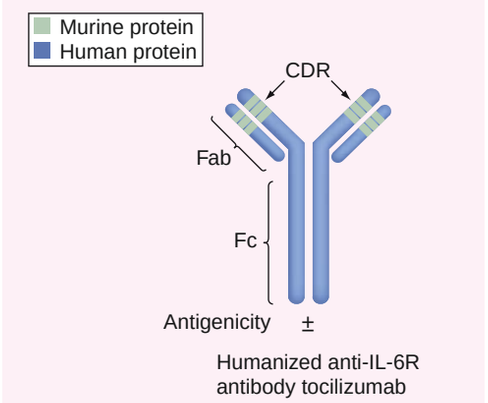

Figure 2. Tocilizumab: humanized anti-IL-6R monoclonal antibody.
CDR: Complementarity-determining region.

weeks) and at 24 weeks DAS28 remission rates for the 8, 4 mg/kg and PBO groups were 30.1, 7.6 and 1.6%, respectively [22].

TOWARD was a randomized, double-blind, PBO-controlled trial evaluating 1216 RA patients who were DMARD IR (~75% were MTX IR) and were treated with TCZ 8 mg/kg. All patients were receiving background DMARDs. At 24 weeks, the TCZ group had significantly improved ACR20 responses (61 vs 25% for PBO; $p < 0.0001$) and more patients in the TCZ group achieved improved DAS28 scores and DAS28 remission as compared with the PBO group. Significantly greater responses were also seen in assessments of function, fatigue and markers of inflammation in the TCZ group [23].

LITHE was a 2-year study (n = 1190) comprising approximately 400 RA patients with an IR to MTX. Patients were randomized to TCZ 4, 8 mg/kg or PBO with the primary end point being the ACR20 response at week 24. The coprimary end points were the prevention of joint damage and improvement in physical function at weeks 52 and 104. All patients were on combination therapy with background MTX. Compared with controls, patients in the TCZ 8 mg/kg plus MTX arm had superior ACR20 (56 vs 25%), ACR50 (36 vs 10%) and ACR70 (20 vs 4%) responses ($p < 0.0001$ for each) with more patients achieving DAS28 remission at 1 year ($p < 0.0001$). Significantly less progression of structural joint damage and an improved physical function (health assessment questionnaire disability index) was seen in the TCZ 8 mg/kg group being maintained for 2 years (Table 1) [24].

TCZ monotherapy

AMBITION was a randomized, double-blind study over 24 weeks evaluating the efficacy and safety of TCZ monotherapy versus MTX in patients with moderate-to-severe RA for whom previous therapy with MTX and/or biologic agents had not failed. Approximately 66% of patients were MTX naive and 8% had prior anti-TNF agent exposure. Six hundred and seventy three patients were randomized to receive TCZ 8 mg/kg every 4 weeks, MTX (titrated to 20 mg weekly, by week 8) or PBO for 8 weeks followed by TCZ. The primary end point was the ACR20 response at week 24. The primary efficacy analysis was a noninferiority comparison using the established per-protocol population (ACR20 70.6% for TCZ vs 52.1% for MTX; weighted difference 0.21, CI: 0.13–0.29). In the intention-to-treat (ITT) population superiority of TCZ to MTX was seen as early as week 2, which increased over time (ACR20 69.9% for TCZ versus 52.5% for MTX, $p < 0.001$ at week 24). ACR50 and ACR70 responses at week 24 were also greater for TCZ vs MTX (44.1 vs 33.5%, $p = 0.002$ and 28.0 vs 15.1%, $p < 0.001$).

Improvement in DAS28 at week 24 (ITT) was superior in the TCZ group and the proportion of patients in DAS28 remission at week 24 (ITT) was higher with TCZ than with MTX (33.6 vs 12.1%). Patients in the TCZ-treated groups were five-times more likely to achieve DAS28 remission than in the MTX-treated group at 24 weeks (odds ratio vs MTX: 5.83; 95% CI: 3.27–10.40). TCZ monotherapy also showed greater improvements in inflammatory markers, health assessment questionnaire disability index, European

Table 1. Efficacy data of Phase III trials using tocilizumab 8 mg/kg combination therapy.

	OPTION (24 weeks) [21]		RADIATE (24 weeks) [22]		TOWARD (24 weeks) [23]		LITHE (52 weeks) [24]	
	MTX (n = 204)	*TCZ + MTX (n = 205)*	*MTX (n = 158)*	*TCZ + MTX (n = 170)*	*DMARD (n = 413)*	*TCZ + DMARD (n = 803)*	*MTX (n = 393)*	*TCZ + MTX (n = 398)*
ACR20 (%)	26.0	59.0 ($p < 0.0001$)	10.1	50.0 ($p < 0.001$)	24.5	60.8 ($p < 0.0001$)	25.0	56.0 ($p < 0.0001$)
ACR50 (%)	11.0	44.0 ($p < 0.0001$)	3.8	28.8 ($p < 0.001$)	9.0	37.6 ($p < 0.0001$)	10.0	36.0 ($p < 0.0001$)
ACR70 (%)	2.0	22.0 ($p < 0.0001$)	1.3	12.4 ($p < 0.01$)	2.9	20.5 ($p < 0.0001$)	4.0	20.0 ($p < 0.0001$)
DAS28 remission (%)	0.8	27.0 ($p < 0.0001$)	1.6	30.1 ($p < 0.01$)	3.0	30.0 ($p < 0.0001$)	8.0	47.0 ($p < 0.0001$)
EULAR response (%)	35.0	79.0 ($p < 0.0001$)	16.5	67.7 ($p < 0.001$)	38.0	80.0 ($p < 0.0001$)	–	–
HAQ-DI (%)	-0.34	-0.55 ($p < 0.01$)	-0.05	-0.39 ($p < 0.001$)	-0.2	-0.5 ($p < 0.0001$)	-0.39	-0.58

ACR: American College of Rheumatology; DAS28: Disease activity score-28; DMARD: Disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; HAQ-DI: Health assessment questionnaire disability index; MTX: Methotrexate; TCZ: Tocilizumab.

League Against Rheumatism response, pain and patient's global assessment of disease activity. It is worth highlighting that this study is the first and only randomized controlled trial to show superiority of a biologic agent as monotherapy compared with MTX [25].

SATORI was a 24-week, randomized, double-blind, PBO-controlled Japanese study evaluating the efficacy and safety of TCZ monotherapy in MTX IR RA patients with active disease. Subjects received either TCZ 8 mg/kg intravenously (iv.) every 4 weeks plus MTX PBO weekly (n = 61) or TCZ PBO iv. every 4 weeks plus MTX 8 mg orally weekly (n = 64). The primary end point was the ACR20 response at week 24 (80.3% for TCZ vs 52.5% for PBO, $p < 0.001$). At 24 weeks, the ACR50 response was 49.2 vs 10.9%, and ACR70 was 29.5 vs 6.3% in the TCZ versus MTX monotherapy, respectively. DAS28 remission was achieved in 43.1 vs 1.6% (TCZ vs MTX) patients [26].

SAMURAI was a 52-week, Phase III, multicenter, randomized controlled Japanese study evaluating the ability of TCZ monotherapy to inhibit progression of structural joint damage in patients with early RA. Patients received either TCZ 8 mg/kg iv. every 4 weeks (n = 157) or conventional DMARD therapy (n = 143). The primary end point was a change in radiographic disease progression at 12 months. In the TCZ group significantly less radiographic progression was seen compared with the DMARD group. At week 52, patients achieving ACR20, 50 and 70 responses were 78, 64 and 44% in the TCZ group and 34, 13 and 6% in the DMARD group, respectively, indicating the superiority of TCZ monotherapy to conventional DMARD therapy ($p < 0.001$ for each comparison). DAS28 remission was achieved in 59% of patients receiving TCZ, but only 3% of patients receiving DMARDs ($p < 0.001$) at week 52 [27].

ACT-RAY was a double-blind 2-year study evaluating the efficacy and safety of adding TCZ 8 mg/kg iv. every 4 weeks to MTX versus switching from MTX to TCZ monotherapy (same dose regimen) in 556 MTX-inadequate responder, biologic naive patients with moderate-to-severe active RA (DAS28 >4.4). The primary efficacy outcome of this superiority study was DAS28 remission rate (DAS28 <2.6) at week 24. This was found to be 40.4% for TCZ + MTX and 34.8% for TCZ + PBO ($p = 0.19$, difference was not significant). No difference for ACR scores and core set components were seen between the two groups. ACR20, 50 and 70 were 71.8, 45.1 and 24.9% for the TCZ + MTX group compared with 70.7, 40.9 and 25.7% for the TCZ alone group, respectively. 18.1 and 15.2% of patients achieved DAS28 remission at week 8 in the TCZ + MTX and TCZ + PBO groups, respectively [28].

ACT-SURE was a 6-month, single-arm, open-label study of DMARD-IR or TNF inhibitor-IR patients receiving TCZ 8 mg/kg every 4 weeks, alone or in combination with one or more DMARDs. The study was designed to approximate a real-life clinical setting. Subanalysis was performed to compare the safety and efficacy in patients who received TCZ monotherapy versus patients receiving combination treatment. Of 1681 patients in the safety and ITT populations, 14% (n = 239) received TCZ monotherapy and 72% of these were anti-TNF-IR. The most commonly used DMARD was MTX (81%). Overall, patients had high disease activity with baseline DAS28 being similar in the two groups (6.2 and 5.9). ACR50 (43.5 vs 47.2%, $p = 0.80$) and ACR70 (23.8 vs 26.8%; $p = 0.75$) responses were similar between the cohorts as were DAS28 remission rates (49.8 vs 57.9%; $p = 0.70$) **(Table 2)** [29].

Safety & tolerability

As with all biologic agents, safety remains our chief concern. In relation to this, TCZ has been found to have acceptable safety and tolerability in both the combination and monotherapy trials. The following section will focus on the safety in the monotherapy studies.

In AMBITION, the overall incidence of adverse events (AEs) was similar in both groups (79.9% TCZ vs 77.5% MTX; $p = 0.484$), as was the incidence of SAEs. Infectious complications were the most common AEs (TCZ 34.4% vs MTX 37.3%). A higher frequency of skin and subcutaneous infections were reported in the TCZ (4.1%) than in the MTX group (0.7%). Other common AEs were gastrointestinal disorders which occurred with similar frequency in both groups. Infusion reactions (occurring during or within 24 h after infusion) occurred in 5.6% of patients with TCZ and 1.8% with MTX ($p = 0.016$). The majority of these occurred during the first two infusions (TCZ: 10/16; MTX: 3/6); however no serious infusion reactions were reported. More patients had reversible neutropenia (3.1 vs 0.4%) and lipid abnormalities with TCZ compared with MTX; however, alternations in LFTs were similar between the two groups [25].

In SATORI, nasopharyngitis was the most common AE in both groups; TCZ vs PBO (18 vs 10.9%), respectively. SAEs were reported in 4.7% (three of 64 patients) and 6.6% (four of

Table 2. Efficacy data of tocilizumab 8 mg/kg monotherapy.

	SAMURAI (52 weeks) [27]		SATORI (24 weeks) [26]		AMBITION (24 weeks) [25]		ACT-RAY (24 weeks) [28]		ACT-SURE (24 weeks) [29]	
	DMARD (n = 143)	*TCZ (n = 157)*	*MTX (n = 64)*	*TCZ (n = 61)*	*MTX (n = 284)*	*TCZ (n = 286)*	*TCZ + MTX (n = 277)*	*TCZ + placebo (n = 276)*	*TCZ + DMARDs (n = 1442)*	*TCZ (n = 239)*
ACR20 (%)	34.0	78.0 (p < 0.001)	52.5	80.3 (p < 0.001)	52.5	69.9 (p < 0.001)	71.8	70.7 (p = 0.86)	–	–
ACR50 (%)	13.0	64.0 (p < 0.001)	10.9	49.2 (p < 0.001)	33.5	44.1 (p = 0.002)	45.1	40.9 (p = 0.43)	47.2	43.5 (p = 0.80)
ACR70 (%)	6.0	44.0 (p < 0.001)	6.3	29.5 (p < 0.001)	15.1	28.0 (p < 0.001)	24.9	25.7 (p = 0.67)	26.8	23.8 (p = 0.75)
DAS28 remission (%)	3.0	59.0 (p < 0.001)	1.6	43.1 (p < 0.001)	12.1	33.6	40.4	34.8 (p = 0.18)	57.9	49.8 (p = 0.70)
EULAR response (%)	–	–	39.7	96.6	64.8	82.2	89.5	85.8 (p = 0.19)	83.6	82.0 (p = 0.65)
MHAQ improvement (≥0.22) (%)	40.0	68.0	34.0	67.0 (p < 0.001)	–	–	–	–	73.4	68.4 (p = 0.03)

ACR: American College of Rheumatology; DAS28: Disease activity score-28; DMARD: Disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; MHAQ: Modified health assessment questionnaire; MTX: Methotrexate; TCZ: Tocilizumab.

61 patients) in the MTX and TCZ groups, respectively. More patients who received TCZ had laboratory test abnormalities (56 vs 23%) although all of these were mild and did not require withdrawal from the study [26].

In SAMURAI, nasopharyngitis again was the most common AE, but the incidence was similar in both groups. SAEs were reported in 18 and 13% in the TCZ and DMARD groups, respectively. Laboratory test abnormalities were reported in 61% of those receiving TCZ and 31% of those in the DMARD group however were mild in severity [27].

In ACT-RAY, rates of AEs, SAEs and serious infections per 100-patient years were 491, 21 and 6 for TCZ + MTX; and 467, 18 and 6 for TCZ + PBO, respectively, with the most frequent being infections. Alanine aminotransferase (ALT) elevations >60 upper limit were observed in 16 and 6% of TCZ + MTX and TCZ + PBO patients, respectively [28].

Finally, the safety comparison of monotherapy versus add-on DMARDs in the ACT-SURE trial suggested that the two groups were very similar. Withdrawal rates (5 vs 5%), AEs (77 vs 82%), SAEs (8 vs 8%), AEs leading to withdrawal (5 vs 5%), infections (35 vs 38%) and serious infections (2 vs 2%) were all similar between the groups. Laboratory investigation abnormalities such as neutropenia, lipid changes and alternation in LFTs were also comparable [29].

As the data regarding side effects is limited from the TCZ monotherapy trials we will summarize the currently available TCZ combination and monotherapy safety data from pivotal trials and postmarketing studies.

In all the 6-month controlled studies using TCZ, the rate of all infections and serious infections reported with TCZ 8 mg/kg plus DMARD treatment was 127 and 5.3 events per 100-patient years, respectively, compared with 112 and 3.9 events per 100-patient years in the PBO plus DMARD group. In the long-term exposure population, the overall rate was 108 and 4.7 events per 100-patient years, respectively. The rate of infections in the monotherapy group was 119 events per 100-patient years and was similar to the MTX monotherapy group. Similarly, the rate of serious infections in the monotherapy group was 3.6 per 100-patient years compared with 1.5 per 100-patient years in the MTX group [24–29,103].

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100-patient years with TCZ therapy and 0.28 events per 100-patient years in the long-term exposure population. This is slightly higher than the rate reported for traditional DMARDs and anti-TNF agents but less than that for corticosteroids [30].

Infusion reactions were reported by 6.9% of patients in the TCZ 8 mg/kg plus DMARD group and 5.1% of patients in the PBO plus DMARD group in the 6-month controlled trials.

However, clinically significant hypersensitivity reactions requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with TCZ during the controlled and open-label clinical studies [103].

A reduction in neutrophil count below 1×10^9/l occurred in 3.4% of patients on TCZ 8 mg/kg plus DMARDs compared with <0.1% of patients on PBO plus DMARDs in the 6-month controlled trials. Approximately half of these patients did so within 8 weeks after starting therapy. Decreases below 0.5×10^9/l were reported in 0.3% patients receiving TCZ 8 mg/kg plus DMARDs [104]. Despite this no increase in infectious complications was seen in these patients.

Transient elevations in ALT/aspartate aminotransferase more than three-times the upper limit of normal were observed in 2.1% of patients on TCZ 8 mg/kg compared with 4.9% of patients on MTX and in 6.5% of patients who received 8-mg/kg TCZ plus DMARDs compared with 1.5% of patients on PBO plus DMARDs. The addition of potentially hepatotoxic drugs (e.g., MTX) to TCZ monotherapy resulted in increased frequency of these elevations. Elevations of ALT/aspartate aminotransferase more than five-times the upper limit of normal were observed in 0.7% of TCZ monotherapy patients and 1.4% of TCZ plus DMARD patients, the majority of whom were discontinued permanently from TCZ treatment. These elevations were not associated with a clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment [103].

Abnormalities of lipid parameters have been frequently reported in the 6-month trials. Approximately 24% of patients receiving TCZ experienced sustained elevations in total cholesterol ≥6.2 mmol/l, with 15% experiencing a sustained increase in low density lipoprotein to ≥4.1 mmol/l. These elevations in lipids responded to treatment with lipid-lowering agents [31]. No increase in cardiovascular events was seen in patients with a rise in lipid parameters.

Data are now available from the long-term extension studies of patients who had received at least one dose of TCZ (n = 4009) in the double-blind control period or open-label extension phase of the five Phase III studies (only one monotherapy study – AMBITION). The most commonly reported AEs (occurring in ≥5% of patients treated with TCZ monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT (Table 3) [32].

Clinical applicability

Data from the monotherapy trials have shown that TCZ is superior to MTX monotherapy in those who had not previously failed on MTX and was significantly more effective than DMARDs alone in those who had failed prior treatment [25–29]. In the studies where DAS28 remission data was provided, TCZ again displayed its superiority when compared with MTX at 6 and 12 months [25–27]. Similarly, ACR response rates were also greater with TCZ [25–29]. This contrasts with the anti-TNF agents approved for monotherapy (adalimumab, etanercept and

Table 3. Safety data of tocilizumab 8 mg/kg monotherapy.

	SAMURAI (52 weeks) [27]		SATORI (24 weeks) [26]		AMBITION (24 weeks) [25]		ACT-RAY (24 weeks) [28]		ACT-SURE (24 weeks) [29]	
	DMARD (n = 143)	*TCZ (n = 157)*	*MTX (n = 64)*	*TCZ (n = 61)*	*MTX (n = 284)*	*TCZ (n = 286)*	*TCZ + MTX (n = 277)*	*TCZ + placebo (n = 276)*	*TCZ + DMARDs (n = 1442)*	*TCZ (n = 239)*
AE (%)	82.0	89.0	72.0	92.0	78.0	80.0	491†	467†	82.0	77.0
SAE (%)	13.0	18.0	4.7	6.6	3.0	4.0	21.0†	18.0†	8.0	8.0
AE leading to discontinuation (%)	–	–	–	–	5.0	4.0	3.9	2.9	5.0	5.0
AE leading to dose modification (%)	–	–	–	–	22.0	19.0	27.4	18.5	–	–
Infections (%)	–	–	–	–	37.3	34.4	–	–	38.0	35.0
Serious infections (%)	5.5	7.6	1.6	3.3	0.7	1.4	6.0†	6.0†	2.0	2.0

†*Per 100-patient years.*
AE: Adverse event; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; SAE: Serious adverse event; TCZ: Tocilizumab.

certolizumab), which have not shown superiority when compared with MTX monotherapy. Etanercept 25 mg subcutaneously twice weekly showed similar clinical outcomes to MTX monotherapy at 6 months in two studies involving patients with early RA [33,34]. In one of these the difference between MTX and etanercept was only visible for ACR70 ($p < 0.05$) but not for the ACR20 or 50 responses [33]. Similarly, the TEMPO study failed to show any statistically significant difference in ACR responses or DAS28 remission rates between etanercept and MTX at 24 weeks [34,35]. The COMET study, comparing etanercept + MTX versus MTX monotherapy for 1 year followed by etanercept monotherapy in the second year, showed that removing MTX resulted in a decline in clinical and radiographic outcomes at week 104 [36,37]. The ADORE study at week 16 also failed to show any major ACR response difference in etanercept monotherapy versus etanercept + MTX [38].

In relation to adalimumab, the PREMIER study showed that MTX monotherapy achieved numerically but not statistically higher ACR responses at all major study time points compared with adalimumab monotherapy. Similarly, DAS28 remission on adalimumab versus MTX monotherapy was similar (23 vs 21%) [39]. No comparative data exist for certolizumab, however golimumab (although not approved as monotherapy) even when given at high dose (100 mg monthly; licensed dose 50 mg monthly) was not superior to MTX monotherapy at any time point [40,41].

The improvement in radiographic outcomes with TCZ monotherapy versus MTX appears similar to adalimumab and etanercept although may be better than that for golimumab monotherapy [33,34,39,41]. In both SAMURAI (52 weeks) and LITHE (2 year), radiographic outcomes were greater following TCZ therapy as compared with golimumab [24,25,27].

A potential advantage of TCZ over TNF inhibition is that tuberculosis (TB) infection does not appear to be an issue. IL-6 has little, if any role in granuloma formation thus the likelihood of recrudescence of latent TB in patients with previous infection is minimal. It is important to note however that TB screening was undertaken in all patients included in the TCZ trials. Additionally, the emergence of antinuclear antibodies or anti-DNA antibodies observed with TNF inhibition was also not evident in any TCZ study [32].

In addition, comparing TCZ with other biologics across studies is problematic due to the differences in the trial designs including study populations, procedures and outcome measures. Several of the TCZ studies reviewed used varying doses of MTX and the lower remission rates in the MTX arms of the Japanese studies reflect the lower approved doses of MTX in Japan. A head-to-head trial comparing IL-6 inhibition with TNF antagonism would be extremely helpful in answering the question as to which agent is preferential following failure of conventional DMARDs. Currently, two such studies are underway comparing TCZ 8 mg/kg versus adalimumab in patients who are either DMARD-IR or anti-TNF-IR [105].

It is clear that TCZ monotherapy, as well as when used in combination, improves both clinical and patient-reported outcomes and that the response is sustained in the extension trials. Most of the AEs were mild-to-moderate and comparable with PBO. Additionally, the study populations reported did not suffer from serious comorbidities as these patients were excluded from the trials. Vigilance for AEs will be critical therefore when treating patients in the 'real world'.

One potential safety issue is the effect of TCZ on lipids with an increase in total cholesterol, low density lipoprotein and high density lipoprotein. As coronary artery disease is a leading cause of mortality in RA and a well-known extra-articular feature of the condition, the true safety of TCZ in this population requires further investigation. Current recommendations state that lipids should be checked every 6 months, however this may require modification in those with established, or with risk factors for coronary artery disease. Similarly, deranged LFTs associated with TCZ therapy is another area where caution is required although it appears to be more of an issue when TCZ is combined with MTX.

Regulatory affairs

TCZ has been approved in Europe for the treatment of RA in those who have either responded inadequately to, or who were intolerant of, previous therapy with one or more DMARDs or anti-TNF-α inhibitor. It may also be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate [106]. The medication is also approved in the USA as monotherapy and in combination with MTX for the treatment of moderate-to-severely active RA in patients who have had an inadequate response to one or more TNF-α inhibitors [107]. The recommended dose in the USA is 4 mg/kg iv., with an increase to 8 mg/kg based on response, given every 4 weeks. NICE in

the UK however recommends TCZ, in combination with MTX, for the treatment of moderate-to-severe active RA in those who have responded inadequately to one or more TNF-α inhibitors and who have responded inadequately to rituximab, or in whom rituximab is contraindicated or withdrawn due of an adverse effect [108]. TCZ is also approved in a number of other countries in Asia and South America.

Conclusion

TCZ monotherapy has consistently shown superiority over MTX for both clinical outcomes and radiographic progression. Its clinical efficacy appears to be superior to other biologics when used as monotherapy, especially TNF inhibitors; however, the radiographic improvement appears similar. Hence TCZ may be the treatment of choice where MTX coprescription is inappropriate due to either intolerance or contraindication. Currently, TCZ is well placed for use following DMARD or anti-TNF failure, as monotherapy or as part of combination treatment. Head-to-head trials would help discriminate between biologic agents however none have been published to date. Finally long-term studies with robust safety data are required to help identify the precise position TCZ should take in the RA treatment algorithm.

Future perspective

The last decade has seen a sea change in the treatment of RA. Therapies have evolved rapidly with targeted intervention, in the form of biologics, becoming well established in the therapeutic arsenal. TCZ has shown efficacy and tolerability both as monotherapy and combination with DMARDs in a number of clinical settings. However, it is unlikely to replace TNF antagonists wholesale as the first-line biologic due to the long term and vast experience with TNF inhibitors.

Over the next few years, treatment to target strategies will ensure brisk escalation of agents in

Executive summary

Mechanism of action

- Tocilizumab (TCZ) is a recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1κ subclass with a typical H_2 L_2 polypeptide structure.
- TCZ binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.

Pharmacokinetic properties

- TCZ is administered intravenously once a month with excellent bioavailability.
- Its terminal half-life is 151 ± 59 h (6.3 days) and pharmacokinetic (PK) parameters do not change with time.
- The PK profile is similar between healthy individuals and rheumatoid arthritis patients with no effect seen with age, gender or race.
- Concurrent methotrexate (MTX) use or alcohol consumption have not been found to alter the PK.
- There does not appear to be a need to adjust the dose for mild renal impairment.

Clinical efficacy

- TCZ monotherapy has consistently shown superiority over MTX for the signs and symptoms of rheumatoid arthritis and for radiographic progression.
- The monotherapy data are better for clinical outcomes as compared with anti-TNF agents although the radiographic data are similar.
- It may be the treatment of choice in patients with MTX intolerance or a contraindication to its use.

Safety & tolerability

- TCZ monotherapy is generally well tolerated.
- Most commonly reported adverse reactions are upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased alanine aminotransferase.
- General and serious infections are higher than with MTX but comparable to other biologics.
- Neutropenia, mild-to-moderate elevations in liver function tests and lipid profile have been observed in trials although drug discontinuation was rarely required.

Drug interactions

- MTX, NSAIDs and glucocorticoids do not appear to have any interaction with TCZ.
- As IL-6 downregulates major CYP isozymes, blockade of IL-6 signaling with TCZ may alter PK interactions with drugs metabolized hepatically.

Dosage & administration

- TCZ is licensed to be administered as 4 mg/kg and 8 mg/kg intravenously every 4 weeks as monotherapy or in combination with traditional disease-modifying antirheumatic drugs.

order to achieve disease remission by 'switching off' the aberrant inflammatory process. A further advance will be to offer 'personalized' biologic therapy according to clinical features or biomarkers. Studies aimed at identifying prognostic factors in RA, and subsets of patients with a higher likelihood of responding to particular drugs, will hopefully become available to guide therapeutic decisions. Drugs with greater efficacy that target the deleterious proinflammatory properties of various cytokines without compromising their protective role in host defense will be the next great step forward.

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