

TOCILIZUMAB – A NEW STEP IN RHEUMATOID ARTHRITIS TREATMENT

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Abstract

Rheumatoid Arthritis is a chronic systemic inflammatory disease characterized by joint pain, stiffness and swelling, with progressive destruction of small joints of the hands and feet.

Methotrexate remains the most commonly used therapy and has been the recommended standard against which new drugs should be evaluated and, to date, there is limited evidence that monotherapy with other treatments is superior to MTX.

The introduction of biologic agents, such as TNF α -antagonists, represented an advance in the treatment of RA. However, there are still patients with no or inadequate response, patients in whom responsiveness to treatment is lost over time, and patients in whom safety issues may develop.

Thus, patients may benefit from treatment with newer biologic agents with a different mechanism of action.

Tocilizumab is an IL-6 receptor inhibitor which shows significant (and rapid) clinical efficacy in the treatment of Rheumatoid Arthritis patients, as assessed by ACR responses and DAS remission rates, with an acceptable safety profile.

Keywords: Tocilizumab; Rheumatoid Arthritis; Remission; IL-6.

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory disease affecting appro-

ximately 0.5-1% of the population¹. It is characterized by joint pain, stiffness and swelling due to synovial inflammation, with progressive destruction of the small joints of the hands and feet, accompanied by limitations (or loss) of physical function, fatigue, anemia, increased risk for osteoporosis and coronary heart disease, progressive disability and increased morbidity and mortality^{2,3}. Although the exact cause of the disease is still unknown, insights into its pathogenesis have confirmed the role of pro-inflammatory cytokines – e.g. tumor necrosis factor α (TNF- α), interleukin-1 and interleukin-6 – in disease pathways^{4,5}.

Rheumatoid Arthritis is often treated with disease-modifying anti-rheumatoid drugs (DMARDs) that relieve inflammatory processes and can slow disease progression⁶. Although methotrexate (MTX) is the most commonly used DMARD, other drugs such as leflunomide, sulfasalazine, and anti-malarials, alone or in combination with MTX, are used⁴. For patients with an inadequate response to conventional DMARDs, biologic agents that inhibit the action of cytokines (e.g. tumor necrosis factor α and interleukin-1) or limit B-cell function or T-cell co-stimulation, especially in combination with MTX, are indicated^{4,7-10}. Moreover, in some situations, they are even indicated prior to DMARDs.

Despite the efficacy of these agents, none of them leads to response in all patients, and even among the patients that respond the improvement is sometimes limited^{4,11,12}, as a substantial proportion of patients continue to have active synovitis and/or systemic symptoms or fail to maintain clinical benefit from these therapies^{6,10,13-15}.

Furthermore, with TNF inhibitors (alone or in combination with DMARDs) 20-40% of RA patients show inadequate response¹⁶.

Interleukin-6 and Rheumatoid Arthritis

An alternative target for RA treatment is inter-

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leukin-6, a pleiotropic pro-inflammatory cytokine (IL-6) produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts. It affects the function of neutrophils, T-cells, B-cells, monocytes and osteoclasts - cells that are highly activated in RA - and is involved in diverse immunologic physiological and pathological processes, such as T-cell activation, B-cell proliferation, and stimulation of hematopoietic precursor cell growth, differentiation, and trafficking^{17,18}.

In the joint, IL-6 perpetuates chronic inflammation and autoimmunity via activation of neutrophils, B-cells and T-cells. Synoviocytes are potent sources of this cytokine and produce vascular endothelial growth factor (VEGF) that may contribute to development of pannus¹⁹. This granulation tissue is associated with deterioration of joint surface and releases tissue degrading enzymes, like metalloproteinases that cause joint destruction.

It is also the major inducer of the hepatic acute-phase response, which is also a key feature of RA that is correlated with disease activity and joint destruction²⁰⁻²². IL-6 stimulates hepatocytes to produce C-reactive protein (CRP), fibrinogen, haptoglobin and serum amyloid (SAA)²³. Concurrently, it induces the secretion of the liver hormone hepcidin, which regulates iron metabolism, inhibiting intestinal absorption and impairing its release from macrophages, thus decreasing the iron available for erythropoiesis²⁴.

Interleukin-6 cell signaling is mediated by binding to the IL-6 receptor (CD126, IL-6R α), which is expressed on cell surfaces and as a circulating soluble form. In order to transduce a signal, the IL-6/IL-6R complex must also bind with a ubiquitous trans-membrane protein - glycoprotein 130 (gp130) to activate transcription^{25,26}.

Of particular relevance to RA, IL-6 induces osteoclast differentiation, contributing to joint destruction, bone resorption and osteoporosis¹⁸.

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. Interleukin-6 is over-expressed in synovial tissue in patients with Rheumatoid Arthritis, with raised concentrations in serum and synovial fluid^{27,28}.

IL-6 knockout mice have been shown to be protected from developing joint symptoms in an arthritis model in vivo^{29,30} and we also know that elevated serum and synovial fluid IL-6 levels correlate with disease activity in patients with RA^{31,32}.

Thus, overall, targeting interleukin-6 seems an attractive therapeutic option in this disease, since it has a pivotal role in mediating inflammation, auto-antibody production, joint destruction and also systemic manifestations of RA³³, and some studies suggest that it is the most abundant cytokine in joints and serum of RA patients and its levels are correlated with disease activity³⁴.

Tocilizumab – Clinical Trials in RA

Tocilizumab has been evaluated in several randomized controlled clinical trials, but here we describe only five of the most important, in which it was studied for its efficacy (and safety) in RA patients: OPTION, TOWARD, AMBITION, RADIATE and LI-THE.

Methods

PATIENTS

Adult (≥ 18 years) patients with moderate-to-severe RA of more than six (≥ 3 in the AMBITION study) months' duration, diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA.

At baseline, active disease was defined by a swollen joint count of six (of 66) or more plus a tender joint count of eight (of 68) or more and C-reactive protein over 1 mg/dl or Erythrocyte Sedimentation Rate (ESR) of 28 mm/h or more.

Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and non-steroidal anti-inflammatory drugs (NSAIDs/cyclooxygenase-2 inhibitors were permitted if the doses were stable for ≥ 6 weeks before inclusion).

To minimize MTX-related toxicity, all patients received a stable dose of folic acid (≥ 5 mg/week).

Main exclusion criteria were other autoimmune diseases or significant systemic involvement secondary to RA (eg, vasculitis, pulmonary fibrosis, or Felty's syndrome), functional class IV Rheumatoid Arthritis, previous or current inflammatory joint disease other than RA, currently active or previous recurrent bacterial, viral, fungal, or other infections including, but not limited to, tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-rays, hepatitis B and C, and recurrent herpes zoster. Patients were also excluded if they had active liver disease (indicated by screening and baseline concentrations of aminotransferases of 1-5 times the upper limit of

normal or more), history of malignancies, cytopenias, immunodeficiency (primary or secondary) and treatment with cell depleting agents. Tuberculosis screening was managed according to local practice.

EFFICACY ENDPOINTS

The primary efficacy endpoint was the proportion of patients who had achieved a response according to the ACR criteria for 20% improvement (ACR20) at week 24⁴³. Secondary efficacy endpoints included the proportion of patients with an ACR50 and ACR70 responses, and the time to onset of ACR20/50/70 responses. Changes from baseline at week 24 in disease activity score (DAS28) were also evaluated. The proportion of patients in clinical remission (DAS28 < 2.6), with low disease activity (DAS28 ≤ 3.2), and with EULAR good/moderate responses were assessed^{44,45}. Hemoglobin concentrations were also assessed. Improvement in physical function was assessed by change from baseline at week 24 in Health Assessment Questionnaire-Disability Index (HAQ-DI). Medical Outcomes Study 36 – Item Short-Form General Health Survey (SF36)⁴⁶, and Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue assessment^{47,48}, done at baseline and week 24, were used to assess health-related quality-of-life.

SAFETY ASSESSMENTS

Patients were monitored for adverse events (AEs), serious AEs, infections, infusion reactions, withdrawals due to AEs, deaths, and clinically significant changes in vital signs and laboratory tests.

STUDY DRUG AND DOSE SELECTION

Study drug was Tocilizumab at a dose of 4 mg/kg and/or 8 mg/kg versus placebo administered in a blinded manner, intravenously as a 60-minute infusion every 4 weeks. Dose selection was based on results of the phase II CHARISMA study⁴⁹.

STATISTICAL ANALYSIS

The primary efficacy analysis was done on the intention-to-treat population (ITT) – i.e., all patients randomized who received at least one infusion of study drug – except in AMBITION study where it was done *per protocol* (PP). Safety analysis included all randomized patients who received at least one infusion of study medication and who had at least one assessment of safety after randomization. Patients that withdrew before week 24, who received

rescue therapy and whose data were insufficient to determine endpoints, were classified as non-responders for the ACR20, 50, 70 and EULAR endpoints.

OPTION (Tocilizumab Pivotal Trial in methotrexate Inadequate responders) study⁵⁰

This study was designed to assess efficacy (and safety) of TCZ (either 4 or 8 mg/kg) plus MTX, compared with MTX monotherapy, in RA patients with inadequately response to a stable dose of MTX.

A 24-week, phase III, three arm, randomized, double-blind, placebo-controlled, parallel group study involving patients with RA and inadequate response to MTX for 12 weeks or longer and a stable dose for at least 8 weeks (10 to 25 mg/week).

Patients were randomized to receive placebo, TCZ 4 mg/kg or TCZ 8 mg/kg intravenously every 4 weeks, in combination with weekly stable dose of MTX. All other DMARDs were discontinued before the start of the study, in each case respecting the half-life period for effective washout.

Patients who had not achieved at least 20% improvement in both swollen joint count (SJC) and tender joint count (TJC) by week 16 were eligible for rescue therapy with TCZ 8 mg/kg and, if necessary, intra-articular steroids or an increase in oral corticosteroid dose (maximum 10 mg/day).

The study included 622 patients, in the ITT population, and their baseline characteristics and disease activity were similar in all three groups.

RESULTS

More patients in the TCZ 4 mg/kg group than in the 8 mg/kg group or the placebo group withdrew prematurely from the study, and, overall, the major reasons for withdrawal were AEs, insufficient response and refusal of treatment.

By week 24, ACR20, ACR50 and ACR70 responses (59%, 44% and 22% in the TCZ 8 mg/kg group, respectively; 48%, 31% and 12% in the TCZ 4 mg/kg group, respectively) were significantly more frequent in patients receiving TCZ than in those receiving placebo (26%, 11% and 2%, respectively; $p < 0.0001$), for both individual TCZ groups. A clear difference between the placebo and the TCZ 8 mg/kg group was observed at week 2 for ACR20, at week 4 for ACR50 and at week 8 for ACR70. Significantly superior responses in all variables, including DAS28, were seen with both doses of TCZ versus placebo. DAS28 decreased rapidly with TCZ therapy (two weeks) and DAS28 remission was sig-

nificantly more frequent in the TCZ groups than the placebo group at week 24 (27%, 13% vs. 0.8%, in the TCZ 8 mg/kg and 4 mg/kg vs. placebo groups, respectively). Moreover, 79% of the TCZ 8 mg/kg group had good or moderate EULAR responses.

Mean CRP concentrations normalized by week 2 and remained stable until week 24 of treatment with TCZ 8 mg/kg, but not in the 4 mg/kg group, where the decrease was less evident and not so stable over the 24 weeks. ESR normalized with TCZ 8 mg/kg but not in the 4 mg/kg group.

Mean hemoglobin concentrations increased from baseline by 4 weeks in both TCZ groups and continued to increase until week 24. By contrast, those concentrations did not change in the placebo group during the study.

There were significant greater improvements from baseline in physical function and fatigue with both doses of TCZ, as judged by HAQ-DI, FACIT-Fatigue and SF36 scores.

TOWARD (Tocilizumab in cOmbination With traditional DMARD) study⁵¹

This study was aimed to evaluate efficacy (and safety) of TCZ in combination with a range of DMARDs in RA patients who had inadequate response to at least one conventional DMARD at a stable dose.

It's a 24-week, phase III, randomized, double-blind, placebo-controlled study involving RA patients which had received stable doses of DMARDs (methotrexate, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine or leflunomide) for ≥ 8 weeks prior to study entry.

1220 patients were randomized in a 2:1 ratio to receive either 8 mg/kg of TCZ or placebo, intravenously every 4 weeks, combined with their stable dose of DMARD therapy.

Patients who were unsuccessfully treated with an anti-TNF agent or were previously treated with any cell-depleting therapy were excluded.

Patients who failed to achieve $\geq 20\%$ improvement in both the SJC and the TJC by week 16 could receive rescue therapy consisting of adjustment of the background DMARD dosage and/or a different DMARD, and/or intra-articular/oral corticosteroid. Such patients were non-responders for the analysis of ACR20, 50, 70 and EULAR responses endpoints but remained under study.

The study included 1220 patients, in the ITT population, and the two groups were well balanced

with respect to baseline demographics, disease characteristics, and concomitant DMARD, corticosteroid and NSAID use.

RESULTS

During the study, 96 patients withdrew from initial treatment, 40 of these due to safety reasons. Overall, 76% of patients were treated with 1 DMARD, 23% were treated with ≥ 2 DMARDs and the most commonly used was methotrexate (mean dosage 15 mg/week). The proportion of patients that completed the study, including those who switched to rescue therapy, was higher in the TCZ group.

By week 24, the proportion of ACR20, ACR50 and ACR70 responders was significantly higher in the TCZ group (61%, 38% and 21%, respectively) than in the placebo group (25%, 9% and 3%, respectively; $p < 0.0001$). A clear difference in both the ACR20 and ACR50 responses between the TCZ and placebo groups was apparent at week 2, and by week 4 for the ACR70 response. The mean DAS28 improved incrementally over time and, by week 24, mean changes from baseline were greater in the TCZ group than the placebo group. Rates of DAS28 remission responses were also higher in the TCZ group than the placebo group (30% vs. 3%; $p < 0.0001$).

Moreover, 45% of patients in the TCZ group experienced low disease activity ($\text{DAS28} \leq 3.2$) and 80% had a good or moderate EULAR response.

The levels of inflammation markers (CRP and ESR) decreased significantly in the TCZ group by week 24, with normalization of mean CRP levels as early as week 2.

Mean hemoglobin levels also increased at week 2, with incremental improvement over time in patients with TCZ until week 24. In contrast, the placebo group showed no change in these levels.

There were greater improvements from baseline in physical function and fatigue with the TCZ group than the placebo group, as assessed by HAQ-DI, FACIT-Fatigue and SF36 scores.

AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) study⁵²

This non-inferiority study was designed to assess the efficacy (and safety) of TCZ 8 mg/kg monotherapy compared to methotrexate monotherapy in active RA patients who had not previously failed MTX or biologics treatment.

This 24-week, double-blind, parallel-group

study, randomized patients to either TCZ 8 mg/kg intravenously every 4 weeks, or to MTX oral capsules, weekly (escalating dose regimen: initial 7.5 mg, increasing to 15 mg at week 4 and to 20 mg at week 8). Methotrexate dose reduction to 10 mg weekly was permitted for safety reasons.

Patients were excluded if they had been unsuccessfully treated with an anti-TNF agent, had received MTX in the 6 months preceding randomization or discontinued previous MTX treatment because of clinically important adverse effects or lack of efficacy.

Patients who had temporarily discontinued MTX treatment due to side effects or desired to become pregnant and those who discontinued anti-TNF treatment for reasons other than efficacy (e.g. cost, side effects) could be included in the study.

A total of 673 patients were randomized into the study and most completed 24 weeks' treatment. General demographic and baseline characteristics were well balanced. The majority of patients were MTX-naïve (67% per arm) with mean disease duration of 5 years. The mean weekly MTX dose over 24 weeks was 15.5 mg, with 74% of patients attaining 20 mg weekly at week 8.

RESULTS

After establishing non-inferiority in the PP population (ACR20 at week 24, 71% TCZ vs. 52% MTX), TCZ was confirmed as superior to MTX using the ITT population ($p < 0.0001$). Furthermore, TCZ was superior to placebo at week 8. The proportion of ACR50 (44% TCZ vs. 33% MTX) and ACR70 (28% TCZ vs. 15% MTX) responders at week 24 was also statistically superior for TCZ ($p = 0.0023$ and $p = 0.0002$, respectively).

The proportion of patients in remission at week 24 (DAS28 remission 34% TCZ vs. 12% MTX) was greater in the TCZ group, and TCZ patients were over 5-times more likely to achieve DAS28 remission (odds ratio [95% CI]: 5.8 [3.3, 10.4]).

A clear difference in ACR20 response rate between TCZ and MTX was seen as early as week 2, with the difference between the groups increasing over time. Compared with MTX, ACR50 and ACR70 responses were consistently observed in more TCZ-treated patients from week 4 and week 8 onwards.

A greater improvement in physical function and health-related quality of life was also reflected by the higher mean changes from baseline in HAQ-DI, FACIT-Fatigue and SF36, with TCZ.

Notably, mean CRP levels were within normal range as early as week 2 with TCZ, as well as the improvement in hemoglobin concentrations.

RADIATE (Research on Actemra Determining efficacy after Anti-TNF failure) study⁵³

This study examined the efficacy (and safety) of TCZ (with MTX) in patients with active RA who had failed (or had intolerance to) at least one TNF-antagonist.

This 24-week, phase III, double-blind, placebo-controlled, parallel group study, randomized 499 patients to TCZ 8 mg/kg or 4 mg/kg, or placebo intravenously every 4 weeks (controls). All patients received a stable dose of MTX for 24 weeks and no other DMARDs were allowed.

Patients discontinued etanercept (≥ 2 weeks), infliximab or adalimumab (≥ 8 weeks), leflunomide (≥ 12 weeks) and all DMARDs other than MTX before receiving study medication, and had to be treated with MTX for ≥ 12 weeks prior to baseline (stable dose ≥ 8 weeks).

Rescue therapy of 8 mg/kg TCZ + MTX was offered at week 16 in all cases of treatment failure ($< 20\%$ improvement in both SJC and TJC).

The three groups were reasonably well-balanced for demographics and RA characteristics at baseline.

RESULTS

TCZ treatments showed superior benefits to diminish RA signs and symptoms after a 24-week therapy. At week 24, patients treated with 8 mg/kg of TCZ + MTX achieved significant improvement assessed by ACR20 responses (50% vs. 30.4% and 10.1%, in the 4 mg/kg and placebo groups, respectively), compared to the placebo group ($p < 0.0001$). DAS28 remission rates at 24 weeks were 30.1%, 7.6%, and 1.6% in the 8 mg/kg, 4 mg/kg, and control groups, respectively ($p = 0.0001$ – 8 mg/kg; $p = 0.053$ – 4 mg/kg both vs. control). Patients responded similarly regardless of most-recently failed anti-TNF or the number of failed treatments.

Responses to 8 mg/kg TCZ + MTX were noticeable after 2-4 weeks of treatment and progressively improved until the end of the study.

Health-related quality of life was also better in a higher proportion of patients treated with TCZ + MTX.

By week 24, there were concomitant reductions of CRP and ESR, and elevations of hemoglobin levels, with both TCZ doses starting as early as week 2.

LITHE (Tocilizumab Safety and THE Prevention of Structural Joint Damage) study⁵⁴

This study was aimed at assessing the efficacy (and safety) of TCZ in the inhibition of structural joint damage in RA patients with inadequate response to a stable dose of MTX.

This 2-year, phase III, double-blind, placebo-controlled, randomized 1196 patients into three arms to receive TCZ (either 4 or 8 mg/kg) or placebo, intravenously every 4 weeks, plus MTX weekly (10-25 mg).

From the second year, patients were receiving an open-label treatment with 8 mg/kg TCZ plus MTX, except for those patients achieving a $\geq 70\%$ improvement from baseline in SJC and TJC at two consecutive visits, who had the option to continue their blinded randomized therapy until the end of year 2.

A switch to blinded rescue treatment (TCZ 8 mg/kg) was available at weeks 16 and 28 for patients who had not achieved at least 20% improvement in both swollen joint count and tender joint count.

Patients received MTX as a single DMARD for at least 12 weeks (last 8 weeks prior to baseline at a stable dose – 10 to 25 mg/week) and all other DMARDs were withdrawn prior to randomization. Patients could have been treated with TNF-antagonists (terminated due to cost or discomfort with the subcutaneous injections), but not have failed due to lack or loss of efficacy.

Another inclusion parameter was radiographic evidence of at least 1 joint with an erosion typical of RA.

Beyond ACR20 response at 24 weeks, the primary endpoints also included changes from baseline in Genant-modified Sharp score (linear extrapolation for missing data) and the area under the curve (AUC) in HAQ-DI (standardization for missing data), at week 52.

Additionally, these structural and functional changes were assessed again at the end of year 2.

The analysis population (ITT) included 1196 randomized patients, and the baseline demographics and disease activity were similar in the three groups.

RESULTS

After 24 weeks of treatment, TCZ (8 mg/kg) plus MTX significantly reduced signs and symptoms, compared with MTX monotherapy, assessed by ACR responses (ACR20 57% vs. 27%; ACR50 32% vs. 10%; ACR70 13% vs. 2%, respectively; $p < 0.0001$).

At year 1, mean changes from baseline in total Genant-modified Sharp score was significantly lower in patients treated with both doses of TCZ plus MTX (inhibition of radiographic progression compared to control was 74% in the 8 mg/kg group) indicating a significant delay in the progression of structural joints damage.

By 52 weeks, DAS28 remission rates were significantly higher in the TCZ 8 mg/kg group (47.2% vs. 30.2% and 7.9% in the 4 mg/kg and placebo groups, respectively) compared with control ($p < 0.0001$), and low disease activity rates were significantly higher with both TCZ groups.

By week 52, the mean AUC of the change from baseline in HAQ-DI significantly decreased in TCZ-treated patients compared with control ($p < 0.0001$).

More patients treated with MTX monotherapy (50%) required rescue therapy, compared with the 8 and 4 mg/kg TCZ + MTX groups (15 and 24%, respectively), and withdrawals were also higher in this group.

SAFETY

The overall incidence of AEs was similar in all (TCZ and placebo) groups in the AMBITION and in the RADIATE studies, and most were mild to moderate. In the other three trials, the incidence of AEs was higher in the TCZ groups.

The incidence of serious AEs was similar in the OPTION and in the AMBITION studies.

In the particular case of the RADIATE study, there was no obvious influence of prior type or number of TNF-antagonist treatments, and there were more serious AEs in the control group than in the TCZ treatments groups, primarily related to RA complications.

The most common AEs were infections, with upper respiratory tract, skin and subcutaneous tissue infections being the most frequently reported. There were no cases of tuberculosis detected.

Infusions were generally well tolerated, with minor incidences of nausea, rash or hypertension occurring during or within 24 hours of infusion. In spite of that, some patients had to discontinue the treatment because of hypersensitivity reactions.

The most frequent detected laboratory abnormalities in the TCZ groups were all transient.

A higher proportion of patients in the TCZ groups had a reversible decrease in the neutrophil count, but there was no association with the occurrence of infection-related AEs.

More patients in the TCZ groups had an increa-

se in the aminotransferase levels, however no concurrent increase in total bilirubin or alkaline phosphatase, and no clinical signs of hepatitis or hepatic dysfunction were detected.

Total cholesterol and LDL elevations were observed in more patients in the TCZ groups, but there was no evidence of an increased risk of cardiovascular events, and on average LDL lowered or stabilized with statins.

At 1 year, in the LITHE study, the safety profile was consistent with the other studies and did not change from 6 to 12 months.

Discussion

The data on these five trials provide evidence that inhibition of interleukin-6 pro-inflammatory effects significantly and rapidly improves the signs and symptoms of RA.

Thus, Tocilizumab is an effective agent for the treatment of patients with moderate to severe Rheumatoid Arthritis.

Methotrexate remains the most commonly used therapy and has been the recommended standard against which new drugs should be evaluated and, until recently, there was limited evidence that monotherapy with other treatments is superior to MTX.

The AMBITION study demonstrated superior efficacy of TCZ monotherapy over MTX monotherapy regardless of previous MTX exposure.

It is very difficult to compare results across clinical trials due to different patient populations with varying prior treatment and disease history, however, considering results of other trials comparing anti-TNF agents with MTX, it appears that TCZ is the first biologic treatment to show statistically significant clinical efficacy using standard endpoints, compared with a standard MTX dose regimen in a 6-month study (AMBITION).

Moreover, about 30% (27 to 34%, depending on the trial) of patients treated with TCZ 8 mg/kg achieved DAS28 remission by 24 weeks, so TCZ demonstrates consistent results in achieving the goal of remission in RA patients.

In the LITHE study, at 1 year, 8 mg/kg of TCZ demonstrated 47% of DAS28 remission rates, which suggests an improved response for TCZ treatment compared to placebo (8%; $p < 0.0001$).

We should expect that the long-term extension of these studies - currently ongoing - will clarify on that.

Furthermore, impairment of physical function and health-related quality of life, as well as fatigue (a major debilitating factor in RA), were all improved more with TCZ than with placebo, reflecting substantial functional benefits for the patients.

Rapid and sustained improvements in the acute-phase response markers (the CRP and ESR levels), as well as in hemoglobin concentrations (low levels indicative of severe chronic inflammation), were seen especially with TCZ 8 mg/kg, suggesting a reduction in the severity of systemic inflammation, besides the improvement of synovitis. Particularly in the AMBITION study, TCZ was associated with anemia correction, an effect not seen with MTX in this study.

Clinically relevant improvements with TCZ (DAS28 remission rates and ACR responses) were apparent as early as week 2 to 4, after treatment initiation, and were maintained or further improved over the treatment period (24 weeks), with the dose of 8 mg/kg providing the more rapid, frequent and robust therapeutic effect.

Finally, in the interim analysis of the LITHE study, at 1 year, TCZ therapy significantly inhibited the progression of structural joint damage.

The overall incidence of AEs was very similar (or somewhat higher in the TCZ groups) between treatment groups and controls, and most were mild to moderate in intensity.

The overall incidence of serious infections was increased but in the same range as we can find with the other biologic treatments in RA patients.

In the case of the TOWARD study, TCZ was well tolerated in combination with conventional DMARDs, and the safety profile was not affected by the type or number of DMARDs used.

A greater reduction in the mean number of neutrophils was seen in the TCZ groups compared with the control groups, but the transient decreases were not temporally associated with infection. Some possible mechanisms by which TCZ 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 tissues⁵⁵⁻⁵⁸. The transient nature of neutropenia and the lack of association with infection suggest that this effect is not a significant issue; however, evaluation of the impact of lower neutrophil counts during long-term treatment will require long-term follow up with periodic monitoring.

TCZ therapy was associated with increases in

mean hepatic aminotransferase concentrations, typically single events without concomitant increase in bilirubin, and no patient experienced clinical symptoms of hepatic disease.

In the case of the TOWARD study, there was no evidence that elevations in the hepatic aminotransferase levels were associated with any particular type of DMARD or DMARD combination used.

In the case of the AMBITION study, elevations in the aminotransferases occurred in both treatment groups, and were more common with MTX, leading to more patients discontinuing MTX than TCZ.

Nonetheless, long-term follow up is required to determine the implications of these observations.

In association with the inflammatory process, patients with active rheumatoid arthritis often have lower lipid concentrations than the general population⁵⁹ and increases have been seen with improvement in chronic inflammation⁶⁰. Mean fasting plasma lipid concentrations were raised in the TCZ groups, which coincided with decreases in CRP levels and were stable over the treatment periods. Therefore, the increase in lipid levels may, in part, be a consequence of effective reduction of inflammation. Increases in atherogenic indices were seen in a minority of patients and in the short term there was no indication of an increase in major adverse cardiac events. Nevertheless, monitoring lipid profile, as well as full blood count and aminotransferases, is recommended in all RA patients under TCZ treatment.

Interestingly, increases from lower than normal baseline lipid concentrations, have been observed with other efficacious therapies, including TNF inhibitors⁶¹⁻⁶⁴. Studies in which the inflammatory response in RA was reduced, as with TNF inhibitors, have shown decreased rates of cardiovascular events, despite the increase in lipid concentrations⁶⁵⁻⁶⁹.

Furthermore, considering the recognized higher incidence of cardiovascular (CV) mortality in RA patients^{59-61,70,71}, traditional risk factors for CV disease, including dyslipidaemia, are not necessarily predictive of events for patients with RA.

Nevertheless, there remains a need for longer term follow-up during chronic treatment to determine any implications of this effect and further studies are needed to fully assess the effects of TCZ on cardiovascular risk.

There are several limitations to these studies.

First, although the 6-month trial time is suffi-

cient to judge efficacy, persistence of clinical and functional improvement will need long-term follow-up, as in the case of the LITHE study.

Second, the clinical consequences of the increase in lipid levels observed, together with the significant decreases in CRP and inflammation, are unclear. Long-term studies in this population may determine if the effects of TCZ 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.

Third, these trials did not assess long-term safety and these results will only be available from long-term extension studies. Nevertheless, no new types of adverse events were observed when compared with early phase trials^{49,72,73}.

Conclusions

Tocilizumab, an IL-6 receptor inhibitor, was evaluated for efficacy in several types of RA treatment scenarios, in patients with moderate to severe active disease.

Regardless of the safety profile, with lipid elevations and reversible neutropenia associated with IL-6R inhibition, TCZ's superior efficacy seems to provide evidence of a benefit-risk that supports its use in patients with active moderate to severe RA.

DAS28 remission was evaluated, and overall we could see a proportion of approximately 30% remission rates, at 24 weeks. DAS28 remission scores continued to improve throughout the 24 week period (the LITHE study), which suggests that remission rates with TCZ may continue to improve with longer treatment periods.

The efficacy of TCZ monotherapy in patients with relatively early active RA, who have not previously failed MTX, was superior to that of MTX monotherapy.

The association of TCZ plus MTX provided more efficacy than MTX alone in RA patients with inadequate response to MTX and/or with inadequate response to TNF antagonists, regardless of number of prior failed agents.

TCZ combined with any of the DMARDs was also effective in patients with moderate to severe RA in whom the response to these agents was inadequate.

Finally, TCZ therapy demonstrated significantly inhibition of the progression of structural joint damage at 52 weeks.

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