

Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by articular and systemic manifestations, such as anemia, fatigue, osteoporosis, and increased risk for cardiovascular diseases. The pathogenesis of RA is driven by a complex network of proinflammatory cytokines, with a pivotal role of IL-6 and tumor necrosis factor (TNF). The management of RA has been dramatically changed during the last years by the introduction of a treat-to-target approach aiming to achieve an acceptable disease control. Nowadays, TNF inhibitors (TNFis) are the most frequently prescribed class of biologic therapies, but the significant proportion of patients experiencing the failure of a TNFi led to the development of alternative therapeutic options targeted on different pathways. Considering the increasing number of targeted therapeutic options for RA, there is a growing interest in the identification of potential predictors of clinical response to each available mechanism of action, with the aim to drive the management of the disease toward a personalized approach according to the concept of precision medicine. Tocilizumab (TCZ) is the first humanized anti-IL-6 receptor subunit alpha (anti-IL-6R) monoclonal antibody approved for the treatment of RA refractory to methotrexate or TNFis. TCZ inhibits both the cis- and trans-signaling cascades involving the Janus kinase-signal transducer and the activator of transcription pathway, playing a crucial role in modulating not only joint inflammation but also the previously mentioned extra-articular manifestations and comorbidities of RA, such as fatigue, anemia, bone loss, depression, type 2 diabetes, and increased cardiovascular risk. In this review, moving from pathogenetic insights and evidence-based clinical data from randomized controlled trials and real-life observational studies, we will discuss the drivers for the selection of patient candidates to receive TCZ, in order to clarify the current positioning of this drug in the treatment algorithm of RA.

Keywords: IL-6, profiling, clinical trials, efficacy, real-life

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint disability, systemic inflammation, high morbidity, and increased mortality.^{1,2} Over the last decades, the management of RA has been dramatically changed by the introduction of a treat-to-target approach aiming to achieve an acceptable disease control defined as a state of clinical remission/low disease activity (LDA) in all diagnosed patients.³ The effective application of this strategy in the clinical practice has been facilitated by the increasing knowledge about RA pathogenesis as a process driven by a complex network of proinflammatory cytokines produced by a number of immune cells, leading to joint destruction, loss of function, and systemic manifestations, such as anemia, fatigue, osteoporosis, and increased risk for cardiovascular diseases (CVDs).⁴

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The widespread release of such cytokines, including IL-6 and tumor necrosis factor α (TNF α), plays a crucial role in weighing the balance toward a proinflammatory condition, which can be effectively treated by the use of drugs targeted on the molecules actively involved in the autoimmune process.⁵ To date, according to the most recent international recommendations, the combination of methotrexate (MTX) with a biologic or a targeted synthetic disease-modifying antirheumatic drug (bDMARD or tsDMARD, respectively) represents the most effective approach for treating RA refractory to conventional DMARDs.^{6,7} Nowadays, TNF inhibitors (TNFis) are the most frequently prescribed class of bDMARDs, but the significant proportion of patients experiencing the failure of a TNFi in both randomized controlled trials (RCTs)⁸ and routine care^{9,10} led to the development of alternative therapeutic options targeted on different pathways, such as IL-6 blockade, T-cell co-stimulation inhibition, B-cell depletion, or more recently Janus-Kinase blocking.¹¹ In particular, *in vitro* studies demonstrated the pivotal role of IL-6 in RA autoimmune network by contributing to B and T cells activation, acute-phase proteins and autoantibodies production, and synoviocyte and osteoclast stimulation.¹² This evidence entailed the introduction of TCZ, the first humanized anti-IL-6 receptor subunit alpha (anti-IL-6R) monoclonal antibody,¹³ approved for the treatment of RA refractory to MTX or TNFis and widely used in clinical practice, and the more recent development of other IL-6 receptor blockers such as sarilumab.¹⁴ TCZ targets both soluble and membrane-bound IL-6R, preventing the interaction of IL-6 with both the IL-6R and the signal transducer glycoprotein 130 complex.^{15,16} The result is the inhibition of both the cis- and trans-signaling cascades involving the Janus kinase-signal transducer and the activator of transcription (JAK-STAT) pathway.¹⁷

Considering the abundance of therapeutic options for RA, there is a growing interest in the identification of potential predictors of clinical response to each available mechanism of action, with the aim to drive the management of the disease toward a personalized approach based on the concept of precision medicine.^{18,19} The link between certain disease phenotypic manifestations and specific pathogenetic pathways has been progressively clarified, making the rheumatologist able to choose the right drug for the right patients in an increasing number of patients.^{20–22} As an example, IL-6 has been demonstrated to be deeply implicated not only in joint inflammation²³ but also in the previously mentioned extra-articular manifestations of RA, such as fatigue,²⁴ anemia,²⁵ bone loss,²⁶ mood disorders as depression,²⁷ type 2 diabetes mellitus (T2DM),²⁸ and increased cardiovascular risk.^{29,30}

Moreover, results from RCTs showed the superiority of IL-6 over TNF blockade in the treatment as monotherapy of patients intolerant to concomitant MTX.^{31,32}

In this review, moving from pathogenetic insights and evidence-based clinical data from RCTs and observational studies, we will discuss the drivers for the selection of patient candidates to receive TCZ, in order to clarify the current positioning of this drug in the treatment algorithm of RA.

From pathogenesis to clinical features: the central role of IL-6 in RA

IL-6 is a pleiotropic cytokine mainly produced by monocytes and neutrophils upon toll-like receptors activation, with a predominant proinflammatory activity regulating both the innate and the adaptive immune system.³³ Upon IL-6 stimulation, endothelial cells produce chemokines, which lead to the recruitment of other immune cells and, together with other proinflammatory mediators, to B cells stimulation and T cells differentiation.³⁴ As a consequence, IL-6 promotes antibody production, by causing B cells maturation,^{35,36} and in concert with TGF- β stimulates naïve T cells to differentiate into T helper 17 (Th17) cells^{37,38} and increase IL-17 production via Th17 cells.³⁹ Moreover, IL-6 induces the secretion of acute-phase proteins, such as C-reactive protein (CRP), by hepatocytes^{40,41} and activates fibroblasts-like synoviocytes, which in turn are an important source of the cytokine itself in joint synovia, and it induces autoantibody production by B cells stimulation.⁴² Considering all the aforementioned functions, IL-6 plays a central role in the pathogenesis of RA,⁴³ as clearly confirmed by the massive elevation of its levels both in the serum and synovial fluid of RA patients compared to healthy population,^{44–46} with a clear correlation with disease severity and radiologic joint progression.^{47,48} In particular, just from the very early phase of the disease IL-6 is crucial for the migration of neutrophils into the joints⁴⁹ and for the subsequent transition from acute to chronic inflammation by increasing the recruitment of monocytes and leading to a shift from neutrophil to monocyte infiltration of the synovia.⁵⁰ The persistence of articular inflammation leads to joint damage characterized by osteoclast-dependent bone erosions and cartilage narrowing produced by matrix metalloproteinases. Independent of its inflammatory effects, IL-6 is directly implicated in the activation of osteoclasts by inducing the release of RANKL by fibroblast-like synovial cells.⁵¹

IL-6 action is the result of the interaction with a specific receptor (IL-6R) composed by a non-signaling-receptor subunit existing as both soluble (sIL-6R) and membrane-bound (present only on T cells, hepatocytes, activated

B cells, neutrophils, and macrophages); and two signal-transducing gp130 subunits, which transduce the signal through the JAK-STAT pathway.⁵² IL-6 may interact with the membrane-bound subunit in the classical (cis-) signaling pathway which activates the acute-phase response and is involved in metabolic effects, infection defense, and tissue regeneration. On the other hand, the interaction between the complex IL-6/sIL-6R and the gp130 subunits activates the trans-signaling pathway on different cells (such as endothelial, smooth muscle, and neural cells), resulting in the IL-6 proinflammatory effects.⁵³

Moreover, the central role of IL-6 in a number of RA extra-articular manifestations and comorbidities has been definitely demonstrated. As an example, neuronal cells express gp130 subunits, so they can be stimulated by IL-6 trans-signaling, making IL-6 able to interfere with several nervous functions, such as neuronal development and survival, synaptic plasticity,⁵⁴ and with central pain sensitization through the stimulation of dorsal root ganglia.⁵⁵ Furthermore, hypothalamic–pituitary–adrenal axis can be influenced by IL-6 with a hypersecretion of adrenocorticotrophic hormone without a reciprocal increase of cortisol.^{56,57} Those described effects on central nervous and endocrine systems suggest a direct role of IL-6 in generating/amplifying mood disorders and RA systemic symptoms such as pain and fatigue.⁵⁸

As previously mentioned, IL-6 has been clearly associated with the induction of the acute-phase reaction including the production of hepcidin,⁵⁹ which is a regulator of iron homeostasis by the inhibition of intestinal iron absorption and ferroportin-dependent iron mobilization from macrophages.⁶⁰ Therefore, high IL-6 expression during sustained inflammation is a key driver in the development of anemia of chronic disease.⁶¹

Moreover, IL-6 elevation is involved in atherosclerosis, activation of endothelial cells, pro-thrombotic effects on platelets, and promotion of smooth muscle proliferation and macrophage lipid accumulation.⁶² As a consequence, serum IL-6 and CRP levels are associated with increased cardiovascular risk in both healthy and RA population.^{30,63} Finally, IL-6 has been suggested to be also involved in the pathogenesis of obesity-related and T2DM-related insulin resistance, through a complex effect on glucose homeostasis integrating central and peripheral mechanisms.²⁸

The efficacy of TCZ in the treatment of RA: main evidences from RCTs and real life

TCZ was initially developed as an intravenous (IV) formulation, now firmly established worldwide for the

treatment of RA with different recommended initial dosage regimens between Europe (8 mg/kg body weight every 4 weeks)⁶⁴ and the US (4 mg/kg every 4 weeks with the option of increasing to 8 mg/kg according to clinical response and physician's discretions).⁶⁵ The development program for RA included five main randomized, double-blind, controlled, multicenter, Phase III, clinical trials conducted in different RA subpopulations.^{66–70} More recently, two randomized, double-blind, comparative, Phase III studies demonstrated the noninferiority of the subcutaneous (SC) formulation of TCZ,^{71,72} which is now marketed worldwide with the exception of the US. The study characteristics of main TCZ RCTs are briefly reported in Table 1. Moreover, several observational studies reporting real-life experience with TCZ have been recently published.^{73–76}

1. Use in combination with MTX as the first biologic agent in csDMARDs/MTX failures

The efficacy of TCZ in association with csDMARDs (including MTX) in patients who previously failed a csDMARD was evaluated in the Phase II study CHARISMA⁷⁷ and in three large Phase III RCTs (OPTION, LITHE, TOWARD).^{66,69,70}

The CHARISMA trial included 359 patients with established, active RA refractory to MTX. American College of Rheumatology criteria for 20% improvement (ACR20) response was achieved in 74% of TCZ-treated patients compared to 41% in the MTX arm.⁷⁷ In the OPTION and LITHE trials, inadequate responders to MTX were randomized to receive two different dosages of TCZ (4 and 8 mg/kg) or placebo on top of MTX. The OPTION study⁷⁰ included 623 patients with active, long-standing RA, with 24-week ACR20 response as the primary endpoint, which was achieved by 59%, 48%, and 26% of patients treated with TCZ 8 mg/kg, TCZ 4 mg/kg, or placebo, respectively. The proportion of patients achieving secondary endpoints, such as ACR50, ACR70, and Disease Activity Score 28 (DAS28) remission, was also significantly greater in patients in both TCZ-treated arms.⁷⁰ The LITHE study including 1,196 patients with active, erosive, established RA was designed to evaluate the effect of TCZ on radiographic progression as the primary endpoint.⁶⁶ Patients on TCZ 8 mg/kg achieved the lowest Genant-modified Sharp score at 52 weeks, with a mean change from baseline of 0.29 (vs 0.34 in the TCZ 4 mg/kg and 1.13 in the placebo group) and a progression from baseline reduced by 74% compared to controls.⁶⁶

The efficacy of TCZ in combination with csDMARDs in patients who failed a previous treatment with

Table 1 Main randomized controlled trials with TCZ

RCT	Population	No of patients	Primary endpoint	Treatment arms	ACR response (%)			DAS28-ESR remission (%)	Ref
					ACR20	ACR50	ACR70		
bDMARD-IR and/or csDMARD-IR patients									
RADIATE	TNFi-IR	499	Response rate at week 24 (ACR20)	TCZ 8 mg/kg i.v. plus MTX TCZ 4 mg/kg i.v. plus MTX Placebo plus MTX	50 30.4 10.1	28.8 16.8 4	12.4 5 1	30.1 7.6 1.6	68
ROSE	csDMARD- and/or TNFi-IR	619	Response rate at week 24 (ACR50)	TCZ 8 mg/kg i.v. plus csDMARD Placebo plus csDMARD	45 25	30 11	15 1	38 1	78
BREVEACTA	csDMARD- and/or TNFi-IR	656	Response rate at week 24 (ACR20)	TCZ 162 mg s.c. q2w plus csDMARD Placebo plus csDMARD	61 32	40 12	20 5	32 4	71
SUMMACTA	csDMARD- and/or TNFi-IR	1,262	Response rate at week 24 (ACR20) using a 12% non-inferiority margin	TCZ 162 mg s.c. qw plus placebo plus csDMARD TCZ 8 mg/kg i.v. q4w plus placebo plus csDMARD	69.4 73.4	47 49	24 28	38 36	72
csDMARD-IR patients									
CHARISMA	MTX-IR	164	Response rate at week 16 (ACR20)	TCZ 4 mg/kg i.v. TCZ 8 mg/kg i.v. Placebo	57.4 78.2 11.3	25.9 40 1.9	20.4 16.4 0	NA	77
OPTION	MTX-IR	623	Response rate at week 24 (ACR20)	TCZ 8 mg/kg i.v. plus MTX TCZ 4 mg/kg i.v. plus MTX Placebo plus MTX	59 48 26	44 31 11	22 12 2	27 13 0.8	70
LITHE	MTX-IR	1,196	Radiographic progression at week 52	TCZ 8 mg/kg i.v. plus MTX TCZ 4 mg/kg i.v. plus MTX Placebo plus MTX	57* 51* 28*	32* 25* 10*	12* 11* 2*	47.2 30.2 7.9	66
ADACTA	MTX-IR	326	Response rate at week 24 (DAS28 mean change from baseline)	TCZ 8 mg/kg q4w i.v. Adalimumab 40 mg q2w s.c.	65 49	47 28	33 18	40 11	31
ACT-RAY	MTX-IR	556	Remission rate at week 24 and radiographic progression at week 52	TCZ 8 mg/kg i.v. plus MTX TCZ 8 mg/kg i.v. plus placebo	72 70	46 40	25 25	40 35	110
TOWARD	csDMARD-IR	1,220	Response rate at week 24 (ACR20)	TCZ 8 mg/kg i.v. plus csDMARDs Placebo plus csDMARDs	61 25	38 9	21 3	30 3	69
ACT-ION	csDMARD-IR	1,216	Response rate at week 24 (DAS28 mean change from baseline)	TCZ 8 mg/kg i.v. plus csDMARDs TNFi plus csDMARDs	NA	NA	NA	44.7 29.7	86

MTX-naïve patients												
FUNCTION	MTX-naïve	1,162	DAS28 remission at week 24 and 52	TCZ 4 mg/kg i.v. plus MTX TCZ 8 mg/kg i.v. plus MTX TCZ 8 mg/kg i.v. plus placebo Placebo plus MTX	73* 75* 70* 66*	48* 57* 47* 43*	34* 38* 30* 25*	31.9 44.8 38.7 15	101			
AMBITION	MTX-naïve	673	Response rate at week 24 (ACR20)	TCZ 8 mg/kg i.v. plus placebo Placebo plus MTX	70 53	44 34	28 15	34 12	67			
U-Act-Early	MTX-naïve	317	Persistent DAS28 remission	TCZ 8 mg/kg i.v. plus MTX TCZ 8 mg/kg i.v. plus placebo Placebo plus MTX	63° 65° 61°	49° 55° 48°	36° 39° 35°	86° 83° 44°	103			

Notes: *Data estimated from graph. °At 104 weeks.

Abbreviations: RCT, randomized clinical trial; bDMARD-IR, biologic disease modifying antirheumatic drug insufficient responder; csDMARD-IR, conventional synthetic disease modifying antirheumatic drug insufficient responder; TNFi-IR, tumor necrosis factor insufficient responder; TCZ, tocilizumab; i.v., intravenous; MTX, methotrexate; ACR, American College of Rheumatology; s.c., subcutaneous; q2w, every 2 weeks; q4w, every 4 weeks; qw, every week; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; NA, not available.

csDMARD was demonstrated in the Phase III TOWARD study, which evaluated only the more effective dose of 8 mg/kg in a population of 1,220 patients.⁶⁹ ACR20 response was significantly higher in the TCZ plus DMARD group than in the control group (61% vs 25%; $P < 0.0001$) and good clinical response was also confirmed according to all the considered secondary endpoints.⁶⁹ These findings are consistent with the results of another similar Phase IIIb study (the ROSE trial) conducted in the same kind of RA subpopulation.⁷⁸

A Cochrane systematic review of 8 RCTs including 3,334 patients (2,233 treated with TCZ and 1,101 controls) showed that patients receiving TCZ in combination with MTX were 4 times more likely to achieve ACR50 (38.8% vs 9.3%) and 11 times DAS remission (30.5% vs 2.7%) compared to placebo.⁷⁹ Moreover, a systematic review of similarly designed clinical trial of some of the available bDMARDs (TCZ, infliximab, etanercept, adalimumab, rituximab, and abatacept) provided an indirect comparison showing that TCZ has the greatest estimated relative risk (RR) of ACR response compared to placebo, although the most relevant difference was observed for the ACR70 response (RR 6.8 for TCZ, 3.8 for TNFis, 4.3 for rituximab, and 3.4 for abatacept).⁸⁰

2. Use in TNFi failures

The efficacy of TCZ in combination with MTX in patients who experienced an inadequate response to one or more TNFis was evaluated in the RADIATE study, including 499 patients with active RA randomized in 2 active arms (TCZ 8 or 4 mg/kg) or placebo.⁶⁸ ACR20 response was achieved in 50% and 30.4% of patients treated with TCZ 8 and 4 mg/kg, respectively, and in 10% of those receiving placebo. Similarly, ACR50 and ACR70 response was also greater in patients treated with TCZ and DAS remission was significantly higher in 8 mg/kg group (30%) compared to 4 mg/kg (5%) and placebo (1.3%).⁶⁸

3. SC TCZ in combination with MTX

The noninferiority of SC vs IV formulation of TCZ in combination with MTX or other csDMARDs was analyzed in the SUMMACTA trial, which enrolled 1,262 patients randomly assigned to receive TCZ SC 162 mg weekly or TCZ IV 8 mg/kg every 4 weeks in combination with csDMARDs.⁷² At week 24, 69.4% of TCZ SC-treated patients vs 73.4% of TCZ IV-treated patients achieved an ACR20 response (weighted difference between groups -4.0% , 95% CI -9.2 to 1.2), confirming a comparable efficacy with similar safety profiles.⁷² Subsequently, the BREVACTA study compared TCZ

SC 162 mg with placebo in combination with MTX in a population of 656 RA patients who had an inadequate response to biologic or synthetic DMARDs.⁷¹ TCZ SC was superior to placebo for 24-week ACR20 response (60.9% vs 31.5%; $P<0.0001$) and for all the secondary endpoints such as ACR50 and ACR70 response (40% and 20% for TCZ, respectively, vs 12% and 5% for placebo, respectively; $P<0.0001$ for both) and DAS28 remission (32% vs 4%; $P<0.0001$). In addition, radiographic progression was significantly lower in TCZ compared to placebo group (mean change from baseline in the modified Sharp/van der Heijde score 0.62 vs 1.23; $P=0.0149$).⁷¹

4. Real-life data: observational and pragmatic studies

One of the first relevant real-life experiences with TCZ was reported in an open-label study including 1,681 patients with active RA refractory to previous DMARDs. Authors observed high rates of 24-week DAS28 remission in both TNFi-experienced and TNFi-naïve patients (48.5% and 61.6%, respectively).⁸¹ These findings have been replicated in the German cohort of the ROUTINE study ($n=850$), reporting LDA in 66.4% and DAS28 remission in 55.1% of patients.⁸² Moreover, the ACT-LIFE study showed a similar trend in 379 patients, with more biologics-naïve than biologics-experienced patients achieving 52-week good/moderate EULAR response (95% vs 91.6%, respectively; $P<0.05$).⁸³

Several real-life studies reported higher remission rates in TCZ compared to TNFi-treated patients. A retrospective analysis from the British Society for Rheumatology Biologic Register showed a significantly higher ($P<0.001$) 6-month DAS28 remission in patients who received TCZ (42%; $n=217$) compared to TNFis (28%; $n=2,419$).⁸⁴ Similar results were observed in a German cohort including 1,603 patients refractory to csDMARDs or TNFi. Despite a generally more severe disease, patients treated with TCZ achieved more frequently a clinical remission compared to TNFis, irrespective of the previous treatment (csDMARD failures: 44% vs 29.6%, respectively; TNFi failures: 41.3% vs 19.2%, respectively; $P<0.001$ for both).⁸⁵ Data from the Italian registry GISEA ($n=7,539$, 9.1% treated with TCZ) confirmed these findings, with significantly higher remission rate observed in first-line TCZ users (51%) compared to both abatacept (23.3%) and TNFis (26.2%; $P<0.0001$).⁷⁵ The most relevant evidence about this topic was provided by the prospective, multicenter, comparative study ACT-ION, which enrolled 1,216 RA patients treated with TCZ (35%) or a TNFi (65%).⁸⁶ At week 52, the proportion of patients achieving remission was significantly higher

in TCZ than in TNFi group calculated by both DAS28 (54.3% vs 29.3%, respectively; $P<0.001$) and Clinical Disease Activity Index (27.8% vs 18.3%, respectively; $P<0.001$).⁸⁶ Finally, data from the TOCERRA collaboration of registries (TCZ Collaboration of European Registries in RA) including 1,773 patients receiving TCZ and 4,660 receiving a TNFi showed a significantly higher crude median retention rate in TCZ combination therapy (1.98 years, 95% CI 1.83–2.11) compared to TNFis (1.37 years, 95% CI 1.30–1.45).⁷⁴

Selection of the best patient candidate to TCZ

The increasing number of available options for the treatment of RA within the class of targeted agents has led to the need of identifying potential predictors of clinical response in order to make therapeutic decisions according to specific drivers. However, no significant predictive factors associated with TCZ treatment have yet been demonstrated, with the only exception of the preliminary results of a subanalysis of the ADACTA trial showing that patients with lymphoid synovitis (associated with higher baseline serum C-X-C motif chemokine 13) had a better clinical response to TCZ.⁸⁷ On the other side, elevated body mass index and smoking have been associated with poor clinical response to TNFis^{88,89} and ACPA positivity with a better response to abatacept⁹⁰ and rituximab,⁹¹ but TCZ efficacy seems to be independent by all these factors.^{92–94} The role of serum IL-6 and acute-phase reactants such as baseline CRP as potential biomarkers is still controversial since opposite results were published about this topic.^{95,96} Of note, a recent Spanish study demonstrated that the combination between high levels of IL-6 and low levels of its receptor at baseline seems to predict a better response to TCZ.⁹⁷

Similarly, a scoring system has been recently proposed to predict the efficacy of TCZ based on IL-6 mRNA levels in the peripheral blood of RA patients before therapeutic intervention.⁹⁸ However, considering the overall lack of specific biomarkers,⁹⁹ the place of TCZ in the management of RA can be derived from real-life experience¹⁰⁰ and should be searched in its peculiar mechanism of action and in the role of IL-6 in determining some RA-specific articular and extra-articular manifestations, which could be very useful as drivers for the application of a tailored approach aiming to choose the biologic drug according to clinical features of the disease.

1. Use in very early RA

As previously described, IL-6 has been demonstrated as one of the first proinflammatory cytokines implicated in

the development of RA.^{5,49,50} Thus, from a pathogenetic point of view, the use of IL-6 blockers in the very early phases of the disease could be very effective. Two RCTs have been conducted with TCZ in MTX-naïve early RA patients, demonstrating the impressive effect of IL-6 blockade on clinical response and damage progression in this RA subset. The double-blind FUNCTION study enrolled 1,162 patients (mean disease duration 5 months), randomly assigned (1:1:1:1) to receive 4 mg/kg TCZ + MTX, 8 mg/kg TCZ monotherapy, 8 mg/kg TCZ + MTX, or MTX alone (comparator group).¹⁰¹ The proportion of patients achieving 24-week DAS28 remission (the primary endpoint) was significantly greater ($P < 0.0001$) in all active arms (31.9%, 38.7%, and 44.8% in 4 mg/kg TCZ + MTX, 8 mg/kg TCZ monotherapy, and 8 mg/kg TCZ + MTX, respectively) compared to placebo (15%). The latter group also achieved significantly higher improvement in 52-week radiographic damage progression and physical function compared to placebo (mean change from baseline in van der Heijde–modified total Sharp score [vdH mTSS] 0.08 vs 1.14, respectively; $P = 0.0001$; mean reduction in Health Assessment Questionnaire Disability Index [HAQ-DI] -0.81 vs -0.64 , respectively; $P = 0.0024$).¹⁰¹ In TCZ 8 mg/kg + MTX arm, the inhibition of radiographic progression was also maintained in the 104-week extension (mean change from baseline in vdH mTSS 0.19).¹⁰²

The U-ACT-Early is a multicentric, randomized, double-blind, double-dummy, strategy study that enrolled DMARD-naïve patients who had been diagnosed with RA within 1 year before inclusion (mean disease duration 25 days).¹⁰³ The study population was randomized to start TCZ (8 mg/kg) plus MTX, TCZ (8 mg/kg) monotherapy, or MTX. In the three arms a sustained 2-year DAS28 remission was achieved by 86%, 84%, and 44% of patients, respectively ($P < 0.0001$ for both TCZ groups vs MTX) and the mean change from baseline in vdH mTSS was 1.18 ($P = 0.0207$ vs MTX), 1.45 ($P = 0.0381$ vs MTX), and 1.53, respectively.¹⁰³

2. Use as monotherapy

Several reports confirmed that bDMARDs for RA are more effective when used in combination with MTX rather than as monotherapy.^{104,105} The main reason for this evidence seems to lie in the dampened immunogenic response to the biologic agent provided by the concomitant use of MTX, which is able to reduce the development of antidrug antibodies (mainly targeted on chimeric monoclonal antibodies) through an anti-immunoglobulin effect.¹⁰⁶ As a consequence, international

recommendations for the management of the disease strongly encourage the use of MTX as an anchor drug in association with targeted agents.^{6,7} Despite this clear evidence, data from observational registries suggested an unexpected widespread prescription of bDMARDs as monotherapy (up to 40%) as the result of MTX contraindications and/or poor tolerability.^{107,108} Therefore, in the last decade, the identification of the best biologic treatment option for the management of patients intolerant to MTX has emerged as a crucial unmet need. Three main RCTs explored the efficacy of TCZ as monotherapy, providing the evidence for considering IL-6 blockade as the preferable strategy for this clinical condition. The AMBITION trial is nowadays the only RCT demonstrating the head-to-head superiority of a bDMARD monotherapy over MTX in RA patients who had not previously failed MTX or bDMARDs.⁶⁷ The efficacy of TCZ 8 mg/kg was better than MTX according to all the considered 24-week endpoints, including ACR20 (69.9% vs 52.5%, respectively; $P < 0.001$), ACR50 (44.1% vs 33.5%, respectively; $P = 0.002$), ACR70 (28% vs 15.1%, respectively; $P < 0.001$), and DAS28 remission (33.6% vs 12.1%, respectively).⁶⁷ Long-term results showed that efficacy was maintained or improved for up to 264 weeks in patients receiving TCZ monotherapy.¹⁰⁹ The ACT-RAY trial was conducted in MTX inadequate responders and demonstrated that the strategy of adding TCZ to MTX or switching to TCZ monotherapy was comparable according to both clinical and radiographic endpoints.¹¹⁰ Interestingly, no significant difference in the incidence of anti-TCZ antibodies according to concomitant MTX was observed (1.5% in combination arm vs 2.2% in monotherapy subgroup).¹¹⁰ The ADACTA trial was the first RCT head-to-head comparing two anticytokine agents with different mechanisms of action as monotherapy.³¹ TCZ was superior to adalimumab in both the 24-week primary (mean change from baseline in DAS28 [3.3 to -1.8 , respectively; $P < 0.0001$]) and all the secondary endpoints, with a similar incidence of adverse events (AEs).³¹

Real-life observational experience partially confirms the previously mentioned RCT data. The TOCERRA is a pan-European collaboration including data from ten different registries, with the aim to compare TCZ in combination with MTX vs monotherapy. Although the observed clinical response was similar between the two groups, the retention rate of TCZ as monotherapy was shorter compared to combination group after the first 1.5 years of treatment and the intergroup difference

increased over time. These findings are consistent with the results of the recently published TOZURA trial, a multinational study program including 11 common-framework protocols that evaluated efficacy, safety, and immunogenicity of TCZ as monotherapy or in combinations with csDMARDs in RA patients.¹¹¹ DAS28 remission and ACR20/50/70 response rates were similar in the two arms, but the 24-week retention rate of TCZ was significantly higher in the combination therapy group compared to monotherapy ($P=0.002$).¹¹¹

These clinical findings have been recently confirmed from a pharmacodynamic point of view by a study exploring the effect of the addition of MTX to TCZ, adalimumab, or tofacitinib on translational biomarkers evaluated by a cell-based BioMAP phenotypic profiling platform.¹¹² Authors demonstrated that the BioMAP activity profile was similar for TCZ alone or in combination with MTX, whereas significant differences were observed for both adalimumab and tofacitinib. These results indicated that MTX contributes to the efficacy of adalimumab and tofacitinib, but not of TCZ, suggesting that RA therapies can be affected by factors additional to reduced immunogenicity,¹¹² as previously suggested by the similar incidence of anti-TCZ antibody observed between combination and monotherapy arms in the ACT-RAY trial.¹¹⁰ In particular, considering the central role of IL-6 in the pathogenesis of RA, it is reasonable that IL-6 blockers monotherapy can be effective even without the disease-modifying support of another concomitant drug as MTX. All together, these data strongly suggest the use of IL-6 blockers in patients with contraindications/intolerance to MTX, as recommended by EULAR guidelines.⁶

3. The effect on extra-articular manifestations

Patient-reported outcomes (PROs) are highly valuable indicators of clinical response to therapy as patients can consider measures of health-related quality of life (HRQOL) to be more important than traditional clinimetric endpoints.¹¹³ The pivotal role of IL-6 in the development of RA systemic symptoms like pain, fatigue, and depression has been previously described.¹¹⁴ Two post hoc analyses evaluating the impact of TCZ on HRQOL (including patient global assessment [PtGA], pain, HAQ-DI, Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue, and Short Form-36 [SF-36] physical [PCS] and mental [MCS] components) have been recently published.^{115,116}

In the first one, PROs were explored in clinical trials where TCZ was tested as monotherapy (AMBITION

and ADACTA). In the AMBITION study, 45%–84% of TCZ-treated patients reported MCDI compared with 39.4%–81.8% in MTX group. In particular, compared to the MTX group, patients receiving TCZ showed greater mean improvements in 24-week FACIT-Fatigue (5.7 vs 8.7), HAQ-DI (–0.5 vs –0.7), SF-36 PCS (7.8 vs 9.8), and five SF-36 domains. In the ADACTA trial, significantly greater improvements in PtGA (–42.3 vs –31.8), pain (–40.1 vs –28.7), SF-36 MCS (7.9 vs 5.0), and three SF-36 domains were observed in TCZ group compared to adalimumab. Moreover, TCZ-treated patients reported higher scores \geq normative values across all PROs compared to adalimumab (22.1%–49.3% vs 13.6%–37.8%, respectively).¹¹⁵

When used in combination with csDMARDs, both IV and SC TCZ resulted in higher proportion of patients reporting minimum clinically important differences (MCID) in PRO scores than placebo. In particular, the rates of MCID in TCZ and control groups were 50%–82% vs 31%–57% at week 16 in the OPTION study, and 54%–73% vs 42%–55% at week 12 in the BREVACTA study, respectively. Similarly, in the SUMMACTA trial, 24-week MCID was observed in 61%–84% and 64%–84% of patients receiving IV or SC TCZ, respectively.¹¹⁶

This trend was observed even in the TNFi inadequate responders evaluated in the RADIATE trial, where the improvement of HAQ-DI values from baseline was 20.39, 20.31, and 20.05 in TCZ 8 mg/kg, TCZ 4 mg/kg, and control groups, respectively ($P<0.001$ and $P=0.003$ for 8 mg/kg vs control and 4 mg/kg, respectively).⁶⁸

These findings have been confirmed by the real-life observational experience. In the TAMARA trial (a German multicenter, open-label noncontrolled single-arm study, evaluating RA patients with moderate-to-severe active disease treated with TCZ) HAQ-DI improved from 1.67 to 1.20 in TNFi and from 1.33 to 0.84 in csDMARD inadequate responders.¹¹⁷ Gossec et al performed another multicentric prospective study in RA patients treated with IV TCZ with the aim to evaluate the percentage of variation of the FACIT fatigue scale from baseline to 4 months. Of 719 patients, 378 patients (62%) reached MCDI improvement for fatigue, with a very rapid reduction (within 2 weeks).²⁴ Finally, in the previously described ACT-ION study, the mean change from baseline was significantly greater in TCZ vs adalimumab-treated patients for both HAQ-DI (–0.59 vs –0.43, respectively; $P=0.020$) and VAS pain (–32.96 vs –23.16, respectively; $P<0.001$).⁸⁶

Chronic anemia complicating inflammatory diseases can further affect HRQOL in RA patients and IL-6 blockade has been demonstrated to be crucial for improving hemoglobin level in this condition. A subanalysis of MEASURE trial highlighted that treatment with TCZ was associated with reduction of hepcidin level (evident from day 1, $P < 0.001$ vs placebo) and with the subsequent increase in hemoglobin level (beginning by week 4 and reaching a plateau by week 24).¹¹⁸ These data have been recently confirmed by an analysis of a large US care database including 153,788 RA patients, showing that patients with anemia treated with TCZ were 86% (OR 1.86; 95% CI 1.43–2.00) more likely to increase hemoglobin of at least 1 g/dL at 2 years when compared to other treatments (csDMARDs, bDMARDs, or tofacitinib).¹¹⁹

4. *The effect on comorbidities: CVD risk and T2DM*

The overall impact of IL-6 blockade on CVD risk in RA has been progressively changed during the last decade. In fact, treatment with TCZ since its introduction was known to be involved in the increase of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels, leading to a warning related to the use in patients with dyslipidemia and increased CVD risk.¹²⁰ However, these modifications have been subsequently interpreted in the context of the so-called “lipid paradox” affecting RA patients. The presence in RA of a chronic inflammatory state produces an increased CVD risk that is inversely associated with cholesterol levels and can be effectively treated with bDMARDs, leading to paradoxical elevation of cholesterol levels in response to their anti-inflammatory effect.¹²¹ Indeed, cholesterol elevations generally observed since the first weeks of TCZ treatment are not accompanied by a worsening of the atherogenic index,¹²² which is the most accurate predictor of CVD risk especially in RA patients. Moreover, several analyses demonstrated that therapy with TCZ is associated with a strong decrease in CVD incidence, despite the constant change in lipid profile. A post hoc analysis of clinical trial long-term extensions including 3,986 RA patients treated with TCZ (mean treatment duration 3.7 years, with concomitant use of statins in 11.1%) showed a very low rate (3.4 events per 1,000 patient years) of major adverse cardiovascular event (MACE). Furthermore, in multivariable model, baseline DAS28 score and higher swollen and tender joints count (but not 24-week lipid changes) were the only predictors of MACE.¹²³

Incidence of CV events in TCZ-treated patients was also compared with patients receiving other bDMARDs. The ENTRACTE trial, a Phase IV, multicentric, noninferiority study comparing TCZ ($n=1,538$) and etanercept ($n=1,542$) in RA patients with CVD risk factors, showed no significant differences in MACE occurrence between the two groups (HR 1.05; 95% CI 0.77–1.43) over an average follow-up time of 3.2 years.¹²⁴ Consistently, a recent retrospective cohort study conducted on administrative health care databases of northern Italy showed that TCZ use in RA did not increase the overall risk of acute CV events leading to hospitalization (HR 0.95; 95% CI 0.54–1.66), when compared to etanercept.¹²⁵

Similar results were observed in two retrospective analyses from the same cohort including three large US insurance claims database, which evaluated a composite cardiovascular outcome (hospitalization for myocardial infarction or stroke) by comparing RA patients receiving TCZ with TNFis in bDMARD failures¹²⁶ or with abatacept as first-line biologic agent.¹²⁷ The observed CV incidence rates were 0.52 and 0.59 per 100 person years for TCZ vs TNFi, respectively (HR 0.84; 95% CI 0.56–1.26),¹²⁶ and 0.70 and 0.96 per 100 person years for TCZ vs abatacept, respectively (HR 0.82; 95% CI 0.55–1.22).¹²⁷

Only few studies evaluated the effect of TCZ on T2DM. Wu et al demonstrated in 12 mice the protective effects of TCZ against diabetic renal injury, suggesting a correlation with decreased insulin resistance and inhibition of the inflammasome.¹²⁸ A significant reduction of Homeostasis Model Assessment of Insulin Resistance values (2.97 ± 0.38 – 1.99 ± 0.25 , $P < 0.005$) was observed after 24 weeks of treatment with TCZ in 24 RA patients,¹²⁹ confirming similar results previously reported by a small study involving 11 RA patients treated with TCZ for 3 months.¹³⁰

Taken together, these data seem to confirm the potential role of IL-6 inhibitors in the management of RA-related CV risk, which is clearly not increased by lipids elevation induced by TCZ. Moreover, if confirmed by further analyses, the preliminary data regarding the effect on glucose metabolism seem to be very promising for a preferential future use IL-6 blockade in the management of patients with RA complicated by T2DM.

The role of safety profile

The safety profile of TCZ has been evaluated in several Phase III and IV trials.^{31,66–71,101,110,131} As similarly reported

in RCTs conducted with other bDMARDs, the most common AEs and serious AEs (SAEs) observed in RA patients receiving TCZ in these trials were infections, such as upper respiratory tract infections, nasopharyngitis, pneumonia, and cellulitis. Other SAEs of interest include gastrointestinal perforations (GIPs), myocardial infarction, stroke, and malignancy. In addition, abnormalities in laboratory test results have also been observed, including decreased neutrophil counts, elevated liver enzyme levels, and increase in lipid levels. No other safety concerns were identified in a cumulative analysis of long-term (4.6 years) TCZ exposure (12,293 patient-years) in the pooled population from 5 Phase III trials compared with the placebo-controlled periods.¹³² Despite concerns for the risk for cancer during immunosuppressive therapy, a long-term evaluation of TCZ Phase III trials did not show any additional risk for overall or site-specific malignancies above the increased risk expected in RA patients.¹³³

The comparative safety profile of TCZ against other bDMARDs does not reveal unexpected issues. In a Cochrane meta-analysis evaluating the incidence of AEs in bDMARD-treated patients, the risk for drug withdrawal because of safety issues was similar across all available bDMARDs.¹³⁴ In particular, no significant difference emerged in the incidence rate of serious infections of TCZ compared to main TNFis, abatacept, or rituximab. Similarly, the 6-month rate of serious infections was similar between adalimumab and TCZ (7% for both) in the head-to-head trial ADACTA.³¹ In a retrospective cohort study of patients with rheumatic diseases, a higher incidence of neutropenia was observed in TCZ-treated group compared to both abatacept and infliximab (18.6% vs 3.8% and 2.8%, respectively; $P < 0.001$).¹³⁵ These findings are consistent with the higher incidence of neutropenia reported by comparative analyses of TCZ vs adalimumab from the head-to-head trial ADACTA³¹ and the observational prospective study ACT-ION (12.1% vs 5.7% at 52 weeks, respectively).⁸⁶ However, in the whole experience with TCZ, grade 3 or 4 neutropenia was observed only in a small proportion of patients and the decreased neutrophil count during TCZ treatment has not been associated with serious infections.¹³² A higher incidence of GIPs and especially lower intestinal perforations (LIPs) has been observed in TCZ-treated patients compared to those receiving TNFis (GIPs, 1.8–2.8 vs 0.6–0.9 per 1,000 patient-years, respectively; LIPs, 1.26–2.7 vs 0.2–0.76 per 1,000 patient-years, respectively).^{136–138} In particular, the risk for LIPs seemed to be greater in patients with a history of diverticulitis, suggesting to avoid TCZ in patients carrying this comorbidity.^{136,137}

Conclusion

Extensive experience in RCTs and real-world settings over the last decade has firmly established the short- and long-term efficacy of both IV and SC TCZ in adults with moderate-to-severe RA who failed synthetic or biologic DMARDs. The clinical response and the effect of radiographic progression were consistent across RA subsets, confirming the current main indications of TCZ in MTX and TNFis inadequate responders. Furthermore, the widespread effect on RA pathogenetic network of IL-6 compared to TNF blockade is crucial for the superiority as monotherapy of TCZ over TNFis demonstrated in clinical trials. Based on this clear evidence, IL-6 inhibition along with JAK blockade is now the mechanism of action suggested by EULAR recommendations to be used in patients with contraindications/intolerance to MTX.

The favorable results from TCZ long-term and real-life experiences are reassuring about the initial concerns for safety issues, such as serious infections, liver toxicity, and neutropenia, while history of diverticulitis still remains the major contraindication to the prescription of the drug. Considering the need for strategic tools to be applied in a personalized approach and the lack of specific biomarkers, the central role of IL-6 in the pathogenesis of RA and in the development of articular and extra-articular manifestations of the disease may provide some useful drivers toward precision medicine. The very early involvement of IL-6 in first phase of RA may suggest to anticipate the introduction of TCZ in newly diagnosed disease, as the impressive results of the U-ACT Early trial seem to clearly confirm (more than 90% on remission rate). Moreover, extra-articular features such as pain, fatigue, depression, and anemia seem to be strictly related to IL-6, suggesting the preferential use of TCZ in patients presenting a systemic pattern of RA. In addition, comorbidities such as increased CVD risk and T2DM seem to be effectively managed by the use of IL-6 blockade, giving another potential driver for the choice of TCZ.

Author contributions

EGF designed the review methods and drafted and revised the paper. MB, CC, and AB drafted and revised the paper. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

EGF served as a consultant and/or speaker for BMS, Lilly, Roche, Celgene, MSD, UCB, Pfizer, Janssen, Novartis, Sanofi-Genzyme, and Abbvie. The authors report no other conflicts of interest in this work.

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