

Original Article

Inhibition of interleukin 6, a new therapeutic option in rheumatoid arthritis

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ABSTRACT

Tocilizumab (TCZ) is a humanized monoclonal antibody which targets the receptor for IL-6, developed by the Japanese pharmaceutical company Chugai and the Swiss company Roche. In Japan it is already under use for Castleman's disease, rheumatoid arthritis (RA), and juvenile idiopathic arthritis. The clinical development outside Japan is very extensive and has shown efficacy in possible RA scenarios; early RA (part of the AMBITION study), established, MTX-resistant RA (OPTION) and RA resistant to other DMARD (TOWARD), and anti-TNF- α resistant RA (RADIATE). Both monotherapy with TCZ (AMBITION) and associated to other background drugs. Radiological efficacy has also been proven (LITHE). So TCZ is probably the biologic therapy with the most extensive clinical development before marketing in the western hemisphere. In this review we will specifically deal with clinical and radiological efficacy, as well as its safety profile.

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La inhibición de la interleucina-6, una nueva opción terapéutica en la artritis reumatoide

RESUMEN

Tocilizumab (TCZ) es un anticuerpo monoclonal humanizado dirigido contra el receptor de la interleucina-6 (IL-6) desarrollado entre la farmacéutica japonesa Chugai y la suiza Roche. En Japón tiene ya indicación para la enfermedad de Castleman, artritis reumatoide (AR) y artritis idiopática juvenil. El desarrollo clínico fuera de Japón es muy extenso y ha demostrado eficacia en los escenarios posibles de la AR, AR precoz (parte del estudio AMBITION), AR establecida refractaria a metotrexato (OPTION) y a otros fármacos modificadores de enfermedad (TOWARD) y AR refractaria a anti-TNF- α (RADIATE), tanto con TCZ en monoterapia (estudio AMBITION) como asociado a fármacos de fondo. También se ha comprobado la eficacia radiológica (LITHE). En consecuencia el TCZ es probablemente el fármaco biológico con el desarrollo clínico más extenso habiéndose aprobado su comercialización por la agencia europea del medicamento con las siguientes indicaciones: TCZ en combinación con MTX está indicado para el tratamiento de la AR activa de moderada a grave en pacientes adultos que han presentado una respuesta inadecuada o fueron intolerantes a terapia previa con uno o más FAMEs o antagonistas del TNF. En estos pacientes TCZ puede ser administrado en monoterapia, en caso de intolerancia a MTX, o cuando el tratamiento prolongado con MTX es inapropiado. En esta revisión nos centraremos especialmente en la eficacia clínica, radiológica, así como en el perfil de seguridad

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Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the receptor, both soluble as well as membrane bound, of interleukin-6 (IL-6). It has been jointly developed between the University of Osaka, the Japanese pharmaceutical company Chugai, and the Swiss Roche. In Japan it has been indicated for Castleman's

disease since April 2005 and for rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) since April 2006. This implies that for RA there are clinical trials developed both in and out Japan (Table 1).¹⁻¹² The clinical development of TCZ in RA in Japan is sensibly different for example, and is generally done as monotherapy.²⁻⁶

In change, outside of Japan, the clinical program is more extensive,^{1,7-12} having shown clear efficacy in the 3 scenarios of RA; early RA (arm of AMBITION), established RA resistant to methotrexate (MTX) (CHARISMA, OPTION) and to other disease modifying anti-rheumatic drugs (DMARD) (TOWARD), and anti-TNF- α resistant RA (RADIATE), both with TCZ in monotherapy (AMBITION), as associated to MTX or other DMARD.

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All of this leads to TCZ probably being the biologic drug with a greater clinical development program for RA (Table 1), showing a good efficacy and safety profile. In this review we will center on the more relevant aspects on clinical efficacy, as well as its safety profile.

Clinical efficacy: pharmacokinetics and phase I-II, II, and III trials

Pharmacokinetics and phase I-II trials

The first randomized, double blind trial, with TCZ was a phase I/II carried out in the United Kingdom for RA and efficacy was seen after 2 weeks with a single intravenous infusion (IV) of TCZ at different doses.¹ But in the initial pharmacokinetic studies, especially those designed to determine the most adequate dose and frequency, come from a Japanese phase I-II open trial.² This was performed in patients with RA who had been prescribed 3 IV repeated doses of 2, 4, and 8 mg/kg body weight of TCZ at 2 week intervals. The half life ($t_{1/2}$) of TCZ increased with dose increments and with the repetition of the dose. Therefore, after the third infusion of 8 mg/kg of TCZ the $t_{1/2}$ reached 240 h, close to the $t_{1/2}$ of human immunoglobulin G1. In addition, only with these higher doses the acute phase reactants were normalized, as well as C-reactive protein (CRP) and amyloid A. Serum CRP and amyloid A are acute phase proteins produced by the liver as a response to the stimuli of IL-6, IL-1, and TNF.^{13,14} TNF inhibitors such as infliximab and etanercept, also reduce the CRP but only in a limited proportion of patients does it reach normality.¹⁵ This is probably due to the fact that the production of a lot of the acute phase reactants need IL-6, and that this is the most important mediator in their regulation.^{13,14} A certain serum concentration of TCZ is necessary to inhibit the actions of IL-6 and in this sense the CRP can serve as an indicator of the plasma TCZ concentrations.² Therefore, from the pharmacokinetic standpoint, repeated and high dose TCZ infusions (8 mg/kg) seem to be the most adequate.²

Phase II trials

As a complement of the preceding study, a double blind, randomized, phase II trial in Japan was carried to prove the efficacy and safety of 3 IV infusions of 4 and 8 mg/kg of TCZ, but every 4 weeks.³ The conclusion was that even as monotherapy, a 8 mg/kg IV dose every 4 weeks seemed to be the optimal therapeutic regimen.

But it is the phase II CHARISMA (Chugai Humanised Anti-human Recombinant Interleukin-Six Monoclonal Antibody) trial which was more relevant.⁷ Multicentric, double blinded, randomized in design, it is the only one that, as shown on Table 1, was carried out exclusively in Europe. All of the patients had MTX resistant RA, having taken that drug at a stable dose for at least 4 weeks before randomization to correct the possible therapeutic effect of the placebo group (MTX group) observed in the CHARISMA trial. From the standpoint of efficacy and safety, CHARISMA reaches very interesting conclusions by having 7 therapeutic arms: 6 with different doses of IV TCZ (2, 4, and 8 mg/kg) every 4 weeks as monotherapy or in combination with MTX and a placebo group with only MTX (comparative group).

The primary objective of the study was the ACR (American College of Rheumatology) 20 response at week 16, resulting significantly superior with respect to patients treated with placebo plus MTX when applied as monotherapy at a 4 and 8 mg/kg dose of TCZ and in the 3 groups with MTX and TCZ combined (2, 4, and 8 mg/kg). But the ACR50 and ACR70 were significantly more effective only in the combined 8 mg/kg of TCZ plus MTX group. Therefore, the infusions of TCZ (8 mg/kg) every 4 weeks combined with MTX achieved a significant improvement in all of the ACR20, ACR50, and ACR70 responses. In parallel, all of the groups treated with TCZ alone or combined with MTX had a larger descent in the DAS28 with, once

again, the TCZ (8 mg/kg) plus MTX group the one that had a maximal DAS28 improvement, with 34% of patients achieving the DAS28 remission criteria (Figure 1).⁷

Laboratory alterations in RA are mainly related to the capacity of proinflammatory cytokines, especially IL-6, in producing hepatic acute phase reactants.^{13,14} The correction of the CRP demonstrated an almost mathematical “sawtooth,” model, clearly related to the TCZ dose and independent of MTX (Figure 2). A rapid descent was observed after the administration of TCZ at 2 weeks, which was the minimal period of time in which data was available. Once again, it was seen that the 8 mg/kg dose of TCZ (independent of MTX) is the one associated to a maintained reduction of this. Changes in ESR, as was to be expected, although effective, were less sudden than CRP and were also better with larger doses of TCZ.¹³ With respect to anemia in RA, it is believed that one of the essential mechanisms is the hyperproduction of hepcidin, also an hepatic acute phase reactant which is essential in iron physiology, blocking ferroportin which is the “portal” of entry of iron into the blood, both from the intestine, once it has been absorbed, as from bodily reserves or iron (reticulo-endothelial system) for marrow erythropoiesis.¹⁶ The correction of anemia using TCZ is probably due to the correction of hyperhepcidinemia. Other analytical parameters were also progressively normalized, such as serum ferritin, amyloid A, complement fraction 4 (C4), fibrinogen, neutrophils, and platelets. The safety profile of TCZ was also observed to be adequate, as will be commented later.⁷

Phase III trial

This preliminary phase I-II data was ratified in the phase III study. Outside of Japan there are 5 double blind trials in Japan (Table 1).^{8–12} of which 3 have already been published (OPTION, TOWARD, and RADIATE)^{8–10} and the last 2 (AMBITION and LITHE)^{11,12} have been communicated during Rheumatology meetings. As mentioned, there are studies of the possible scenarios of RA. The efficacy of TCZ combined with MTX or other DMARD or in monotherapy both in early RA as in established RA has been demonstrated. In the phase III trials, the therapeutic arms were restricted to those of greater efficacy and, apart from the placebo group, the TCZ therapeutic arms were only the 8 mg/kg IV every 4 weeks in the TOWARD and AMBITION trials, and, on the other hand, 4 mg/kg in the OPTION, RADIATE, and LITHE trials. In general, after 24 weeks the primary objective, which was the ACR20 response oscillated around 70% in the AMBITION trial and 50% in the RADIATE study (Figure 3), something which was expected, considering that that the RA populations were different (Table 1). The clinical remission results, which in the studies with TCZ have used a DAS28 of less than 2.6, are equally optimal, oscillating around 30% after 24 weeks including the patients with anti-TNF resistant RA in the RADIATE trial (Figure 4). Another peculiarity of TCZ is its relatively precocious clinical response after 2 weeks, which is the first clinical and analytical evaluation and which, with the passage of time, efficacy data measured as ACR improvement as well as remission indexes can progressively increase.^{7–12,17} Other common parameters measured were improvement in the HAQ (Health Assessment Questionnaire) and FACIT (Functional Assessment in Chronic Disease Therapy) also showed therapeutic efficacy.^{7–12}

The results of the OPTION and TOWARD trials overlap to those of the CHARISMA trial. The RADIATE trial reached remissions in the TCZ therapeutic group (8 mg/kg) associated to MTX in a 30% of anti-TNF resistant patients (Figure 4), even in those resistant to 2 or 3 anti-TNF drugs.¹⁰ Up to the moment, the biologic drugs indicated in anti-TNF resistant RA (Rituximab and Abatacept), independent of whether they were different studies, obtaining results which were significantly less at least regarding remission (around 10%)^{18,19}. The AMBITION trial also obtains interesting results¹¹. TCZ in monotherapy demonstrates a clinical efficacy (ACR20, ACR50, ACR70, HAQ, and DAS28 remission) clearly superior to MTX, which is different than that which occurs

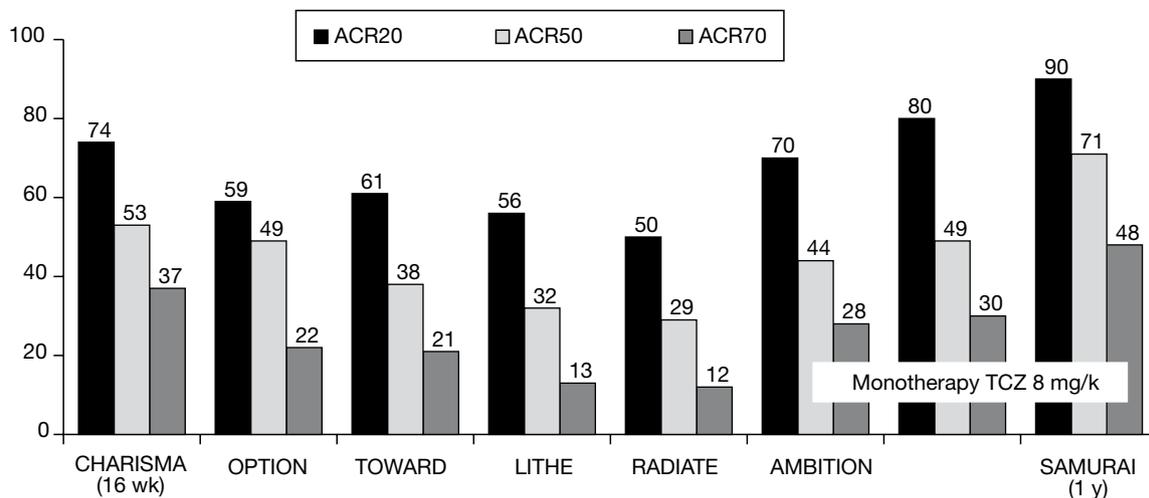


Figure 3. Proportion of patients with ACR (American College of Rheumatology) responses 20, ACR50, and ACR70 in different studies with tocilizumab (TCZ) in rheumatoid arthritis. The results were observed after 24 weeks except in the CHARISMA trial which was performed after 16 weeks and in the SAMURAI trial which performed it after a year. The results of the best therapeutic group of each study is shown, TCZ (in a dose of 8 mg/kg every 4 weeks IV) associated to methotrexate or in the case of disease modifying anti-rheumatic drugs. The AMBITION, SATORI, and SAMURAI trials, because they were monotherapy, express the results of the TCZ at a dose of 8 mg/kg.

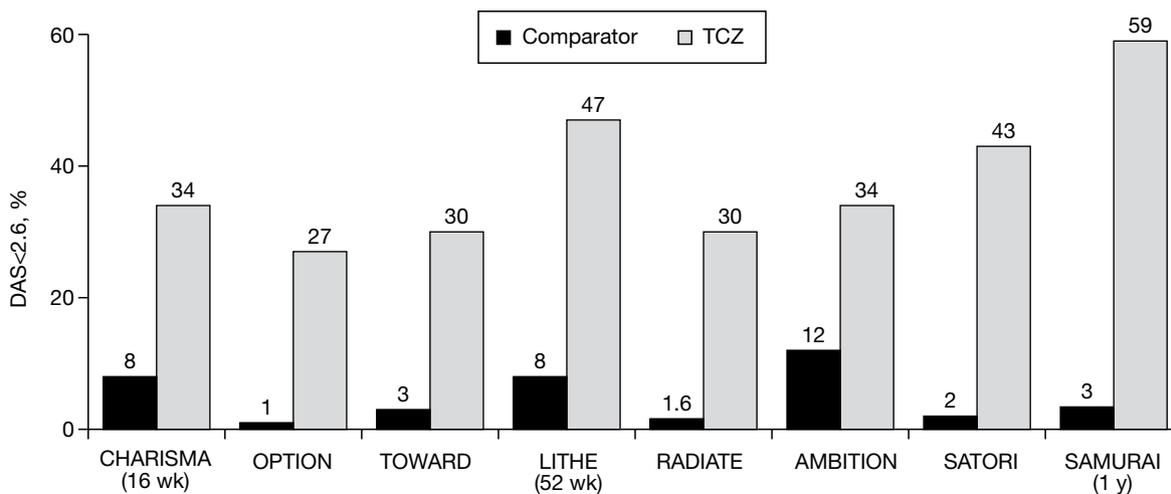


Figure 4. Proportion of patients in clinical remission (disease activity score 28 < 2.6). The results were observed after 24 weeks, except in the CHARISMA trial which was performed after 16 weeks and in the LITHE and SAMURAI trials which were done after 1 year. The results of the best therapeutic group for each study are shown, tocilizumab (TCZ) (at a dose of 8 mg/kg every 4 weeks IV) associated to methotrexate or in its case to disease modifying anti-rheumatic drugs. The AMBITION, SATORI, and SAMURAI trials, in monotherapy, express the results of the TCZ groups at a dose of 8 mg/kg.

lower progression both by the total Sharp score as in its erosion and joint space narrowing components (Figure 5A). In addition, less patients of the TCZ group showed radiological progression.⁵ These beneficial results were maintained for 3 years.⁶ In LITHE, 2 treatment arms were observed for 52 weeks, (4 and 8 mg/kg) combined with MTX compared with the placebo group (MTX). The Sharp index as modified by Genant was employed. There is also less statistically significant progression in the 2 TCZ therapeutic groups regarding the total score as well as its components (Figure 5B).¹²

In parallel, in the OPTION trial it was shown that TCZ, especially at a dose of 8 mg/kg and combined with MTX, reduces rapidly and effectively biochemical markers of bone resorption, cartilage exchange and type 3 matrix metalloproteinases.²³

Adverse events

The results of the different clinical trials demonstrate that TCZ is a safe and well tolerated drug.⁴⁻¹² Most of the adverse events were mild to moderate, with those most frequent being upper airway infections. The combined safety results from the 5 phase III trials performed outside Japan, with a duration of 24 weeks, have been recently published (Table 2).²⁴ There is also combined data of 4 of these clinical trials, in their open phase, after a longer period (median follow up 18 months).²⁵ The data below ratifies the safety results of each individual trial and also proves that adverse events are not increased and can even be reduced starting at 24 weeks.²⁵ In any case, there are no differences in the rate of serious adverse events between

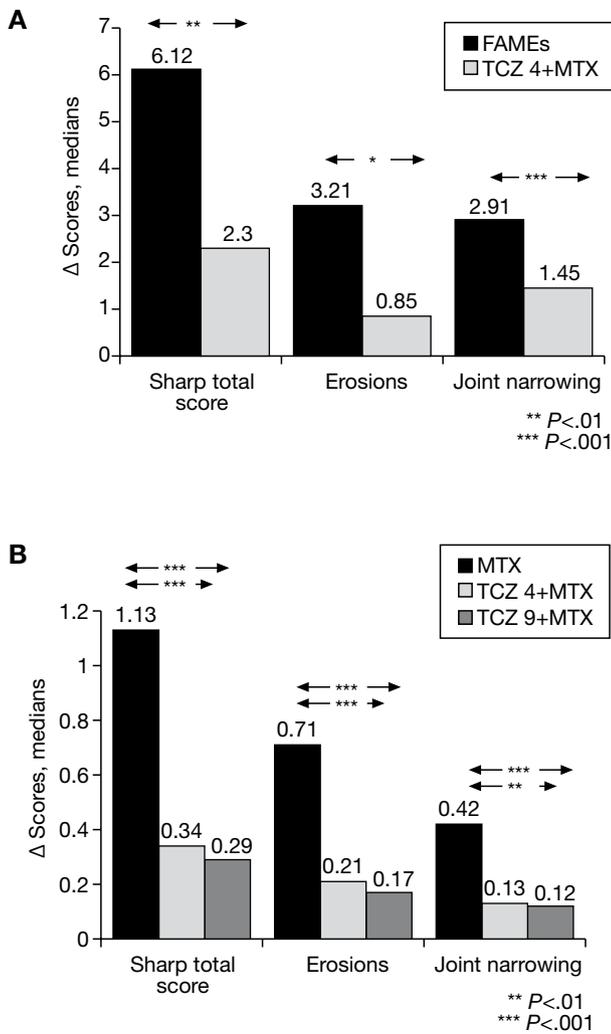


Figure 5. A) Increase in the Sharp score modified by van der Heijde in the SAMURAI trial at 52 weeks. Tocilizumab (TCZ) at a dose of 8 mg/kg in monotherapy is compared with traditional disease modifying drugs. B) Increase in the Sharp score modified by Genant in the LITHE trial at 52 weeks. TCZ at a dose of 4 mg/kg and 8 mg/kg combined with methotrexate (MTX) is compared to placebo (MTX).

groups treated with TCZ and control groups.^{4-12,24,25} Isolated cases of intestinal perforation have been described and are currently under study.²⁵ The most relevant adverse event data is commented below.

Infections

Serious infection is the most common severe adverse event; however, its frequency was relatively low in all of the therapeutic groups (Table 2).^{24,25} A discreet increase in the TCZ combined with DMARD group was seen, although the confidence intervals (CI) overlapped between the different groups. The index of severe infection [100 patients-years (95% CI)] is 5.2 (range, 3.7-7.1),²⁴ which is similar to that communicated with anti-TNF agents.²⁶ With the 18 month available data there is no visible increase in this risk by increasing the time of exposure to TCZ, even being reduced.²⁵ The only factors that predispose to the development of serious infection were an age of 65 years or older, diabetes mellitus, a history of prior infection, and the use of steroids.²⁷ The most serious infections were pneumonias, cellulitis, herpes zoster, gastroenteritis, and diverticulitis.²⁵ Infections by opportunistic germs, even mycobacteria, were exceptional.^{24,25,27} Studies in JIA have shown that patients with TCZ therapy can be effectively immunized with the influenza vaccine.²⁸

Neoplasia

The combined analysis of the available data does not show an increase in neoplasia related to TCZ (Table 2).^{24,25}

Infusion reactions

Infusion reactions to TCZ were generally mild, well tolerated and did not lead to abandonment of the trial. Nausea, exanthema, hypertension, headache, and pruritus were the most frequently observed reactions. On the other hand, TCZ was associated to a low production of autoantibodies and immunogenicity.²⁹ The presence of HAA (human anti-human antibodies) was rare and its presence was not increased in TCZ monotherapy.

Analytical alterations

1. Neutropenia

A peculiar effect of TCZ is neutropenia, which is usually mild, transient, and not associated to infection.^{24,25,27} It was relatively

Table 2

Main adverse events of the different clinical trials of tocilizumab in rheumatoid arthritis. The combined data of 5 clinical trials in phase III after 24 weeks is shown: OPTION, TOWARD, RADIATE, AMBITION, and LITHE

	Combined treatment		Monotherapy groups	
	TCZ (8 mg/kg) + DMARD, n=1582	Placebo + DMARD, n=1170	TCZ (8 mg/kg), n=288	MTX, n=284
Total patients per year	754	507	140	134
100 patients per year index (95% CI)				
Total AE	462 (447-478)	377 (361-395)	492 (456-530)	450 (414-487)
Severe AE	15 (13-18)	15 (12-18)	9 (4-15)	11 (6-19)
Infections	118 (110-126)	104 (95-113)	106 (90-125)	109 (92-128)
Severe infections	5.2 (3.7-7.1)	3.8 (2.3-5.9)	2.9 (0.8-7.3)	1.5 (0.2-5.4)
Neoplasia	1.3	1.4	1.4	2.2
Incidence, n (%)				
Reacciones infusionales	6 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
AE that did not lead to drug suspension	74 (4.7)	28 (2.4)	11 (3.8)	15 (5.3)
AE related to the drug	756 (47.8)	401 (34.3)	163 (56.6)	141 (49.6)

Abbreviations: AE, adverse events; DMARD, disease modifying anti-rheumatic drugs; CI, confidence interval; MTX, methotrexate; TCZ, tocilizumab.

frequent and 38% of patients on TCZ had a number of less than $2.0 \times 10^9/L$, although in less than 1% it was under $0.5 \times 10^9/L$. In any case, the analysis of patients with neutropenia demonstrated that it is not related to an increase in infections.²⁷ Neutropenia is related with the dose of TCZ and independent of MTX.⁷ It is believed that more than one adverse effect is pharmacodynamic, because IL-6 physiologically increases the number of circulating neutrophils by reducing its marginal reserve,³⁰ and its inhibition with TCZ can lead to the opposite effect.

2. Elevation of liver enzymes

Transient elevations of alanine- ALT, AST, and total bilirubin can be seen. The increase in ALT and AST is observed more frequently in the high dose TCZ group, especially when combined with MTX.^{7,31} On the contrary, the elevation with TCZ monotherapy is similar to that observed with MTX monotherapy.³¹ Most of the increases in aminotransferases were mild (less than 3 times their limit), isolated, and unrelated to bilirubin increases. No cases of hepatitis of liver dysfunction were seen. Although the mechanism is unknown, IL-6 is known to have an antiapoptotic physiological action on the liver, leading to its regeneration.³²

3. Alteration of the lipid profile

Treatment with TCZ was associated to an increase in total cholesterol, LDL, HDL, triglycerides, apolipoprotein A1 and B, and the LDL/HDL quotient.^{24,25,33} This increase is early and maintained and with no further elevation. The simultaneous elevation of HDL is a differential fact used with the lipid pattern of common dyslipidemia in which it is reduced, and contributes to the correction of the atherogenic profile. Concomitant statin treatment improves the lipid profile.³⁴ The elevation of the different lipids is parallel to the descent of inflammation markers such as CRP, amyloid A, haptoglobin, and lipoprotein A.³³ It is a well known fact that inflammation is related to the development of atherosclerosis. The balance of all of these factors (lipid alterations and improvement on inflammatory parameters) in strokes is currently unknown. Although in the results of the different trials, patients with TCZ did not present more strokes.^{24,25} Similar alterations in the lipid profile and in correcting the inflammatory process are well described with anti-TNF agents.^{35–37} The global effects of these last drugs are also under study, but a substantial reduction in strokes is well documented, as well as in myocardial infections, in patients with therapeutic response.³⁸

In conclusion, at the time of this review, after the approval by the European drug agency and awaiting the publication of more long-term data, a new biologic is added to the therapeutic arsenal for RA, against a new therapeutic target. Eight mg/kg TCZ IV infusions every 4 weeks in monotherapy or combined with MTX or other DMARD seem to be the most adequate way to administer it, with an adequate safety profile. It is as effective in traditional DMARD resistant patients as well as those resistant to anti-TNF, with clinical remission scores at 6 months of 30%.

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