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## Tocilizumab: is there life beyond anti-TNF blockade?

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**Abstract**

Anti-TNF- $\alpha$  therapy has become the most effective biologic treatment for rheumatoid arthritis. Despite having changed the prognosis of the disease, establishing new targets for treatment strategy, there are several aspects that still remain unmatched.

About 30% of the patients with rheumatoid arthritis have a less than satisfactory response to anti-TNF therapy, which has led the way for the pursuit of new targets and approaches to treatment. IL-6 is one of these alternative targets and data from the more recent clinical trials involving tocilizumab (an anti-IL-6 soluble receptor antibody) suggest advantages in relation to some clinical aspects which are not addressed by anti-TNF- $\alpha$  treatment.

**Review criteria: how did you gather, select and analyze the information you considered in your review?**

- All the controlled trials with Tocilizumab in Rheumatoid arthritis reported in Medline since 2007 were considered for this review.
- Data regarding the main issues considered for this review was identified and then summarised according to the different subheadings of the manuscript.
- The main / most cited controlled trials using the three most currently used anti-TNF drugs were referred as comparison.

**Message for the clinic: what is the 'take-home' message for the clinician?**

- Anti-TNF therapy has raised the standards of treatment for Rheumatoid Arthritis
- Several aspects are still not fully achieved in the control of the disease such as induction of remission, intolerance to methotrexate, non-responders and safety regarding tuberculosis and other infections.
- Tocilizumab may be a relevant alternative for anti-TNF treatment in patients following any of the previous groups

## Introduction

The last 20 years have shown a remarkable change in overall perspectives on rheumatoid arthritis, from the point of view of both patients and doctors. In the 1990s, methotrexate (MTX) was shown to be the most effective therapy of all the disease modifying drugs (DMARD) (1). By the end of the last decade of the twentieth century, anti-tumor necrosis factor alpha (anti-TNF- $\alpha$ ) therapy raised the standards by achieving impressive results regarding symptom relief, improvement in quality of life and labour hours (2,3) and by preventing the progression of joint destruction (4,5). The power of these new drugs associated with a relatively low incidence of major adverse effects granted them a level of efficacy that allowed, for the first time in this disease, radiographic and clinical long term remission to be considered as a therapeutic target (6). However, after the initial enthusiasm, long term data showed that much had still to be done in order to claim victory over rheumatoid arthritis. Monotherapy with anti-TNF- $\alpha$  is not significantly superior to Methotrexate alone and an association is still needed for optimal results (7). Furthermore, even with combination therapy, a significant proportion of patients still do not achieve satisfactory results (8), and despite some reassuring data put forward by national registries, infections and cancer are still major causes for concern (9,10,11).

Regardless of the undisputed importance of TNF- $\alpha$  as a pro-inflammatory cytokine, directly responsible for joint destruction and the perpetuation of inflammation in rheumatoid arthritis (12), the existence of a significant group of patients who did not respond to anti-TNF- $\alpha$  treatment, led to the search for other potential targets, both molecular and cellular (13,14,15).

More than a decade after the generalization of anti-TNF- $\alpha$  therapy, (and despite the newcomers in this therapeutic group - e.g. golimumab and certolizumab), new challenges have been defined whilst a significant set of problems have still to be overcome.

Common questions on a daily practical basis include: management of patients who do not tolerate methotrexate or with disease refractory to anti-TNF- $\alpha$  treatment, management of extra-articular manifestations, treatment of patients who have a high risk of infection, or with previous or ongoing malignancies, and finally whether remission can indeed be achieved in a greater number of patients. B-cell depletion (16) and blockage of CTLA4-associated lymphocyte co-stimulation (17) have taken the lead

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3 with promising or even good results regarding some of the above items, but much is still  
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5 unknown.

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7 Interleukin – 6 (IL-6), a pivotal cytokine in the inflammatory response has become the  
8  
9 most recent target to be “scrutinised” in clinical trials, through the inhibition of its  
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11 soluble receptor by the monoclonal antibody tocilizumab (TCZ) (18). What news came  
12  
13 from the first major clinical trials using this new drug? Should we expect more in  
14  
15 comparison with what might be already consider as classic biologic therapy (i.e. anti-  
16  
17 TNF- $\alpha$ )? Have the old problems been solved or at least are we getting better results? Is  
18  
19 there life beyond anti-TNF- $\alpha$  blockade?

### 20 21 **Managing patients without methotrexate**

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23 Anti-TNF- $\alpha$  treatment has still to show a clear detachment of its efficacy from the  
24  
25 association with MTX. In fact, the clinical trials regarding the comparison of any of the  
26  
27 anti-TNF- $\alpha$  drugs on monotherapy with MTX has failed to show an outstanding  
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29 difference as far as clinical response is concerned, and in randomized controlled trials  
30  
31 (RCTs) none has actually presented any benefit before the first 6 months. Nevertheless  
32  
33 this data should be read very carefully, because in real life registers, with a large  
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35 number of patients ineligible for RCTs, anti-TNF- $\alpha$  monotherapy showed a clear benefit  
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37 over MTX (7,19,20). Initial studies with infliximab showed an increase of 38-46% of  
38  
39 responders (21) and some studies suggest that the use of this monoclonal in  
40  
41 monotherapy is associated with a relevant increase in acquired resistance to the drug  
42  
43 due to the production of neutralising antibodies (22). Only 46% of patients achieved an  
44  
45 ACR 20 on standard-dose monotherapy with adalimumab during its major phase III  
46  
47 trials (23) and etanercept reached a significant difference only after one 1 year of  
48  
49 treatment (24).

50  
51 This has justified a strong recommendation in most countries for these drugs not to be  
52  
53 used in monotherapy, unless a clear intolerance or contra-indication to the use of  
54  
55 methotrexate is present.

56  
57 Tocilizumab has been tested in monotherapy in a major clinical trial: the AMBITION  
58  
59 study where treatment with tocilizumab 8mg/kg every 4 weeks was compare with MTX  
60  
(up to 20mg weekly). (25)

In the AMBITION study, patients naïve to MTX or anti-TNF agents, who were treated  
with tocilizumab for 24 weeks, showed a significant improvement in clinical parameters  
(ACR20, 50 and 70 and DAS28) at week 24 and a reduction to the normal range of

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3 hsCRP at week 12 and these were statistically different from the placebo group (25). A  
4 clear statistical difference between anti-TNF- $\alpha$  monotherapy and MTX had never been  
5 shown before for a period of time as early as 6 months.  
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### 10 **Additional Therapy for DMARDs – resistant patients**

11 In the large pivotal trials in Tocilizumab's recent history, three randomized controlled  
12 trials have made in MTX and non-biological DMARDs inadequate responders: the  
13 OPTION, TOWARD and LITHE studies. In the OPTION study, an expected result of a  
14 significant improvement of the clinical and biologic response at 24 weeks was found, in  
15 patients treated with TCZ + MTX (8 mg/kg) when compared with MTX alone. In this  
16 setting 27% of the patients achieved DAS remission and 79% good to moderate DAS  
17 responses (26).  
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24 More recently, a structural joint damage study (LITHE) showed remission at 52 weeks  
25 in 47% of patients on TCZ 8mg/kg plus MTX, compared to 8% in a MTX monotherapy  
26 group. This is particularly impressive when one considers the fact that the mean disease  
27 duration in this cohort was 9 years (27). Most of the previous studies looking at  
28 remission with anti-TNF- $\alpha$  treatment used study populations with a much shorter  
29 disease duration, which is known to be associated with a higher possibility of remission.  
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### 37 **Refractoriness to anti-TNF treatment**

38 Multiple studies have addressed the issue of non-responders (or poor-responders) to  
39 anti-TNF- $\alpha$  therapy. Overall, most studies show a benefit of some magnitude when a  
40 different anti-TNF- $\alpha$  is introduced after failure of a first one, regardless of which as  
41 been administered in the first treatment course, specially if there was a loss of efficacy  
42 rather than a primary absence of response (28). The lack of a clear advantage of any of  
43 the anti-TNF- $\alpha$  agents when used as a second course of treatment for non-responders,  
44 with special emphasis for primary non-responders (29), has been somewhat confirmed  
45 by the different national registries, which leads to the general impression that there is no  
46 advantage in switching anti-TNFs in this context.  
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54 The RADIATE study is a controlled study to compare efficacy of tocilizumab vs.  
55 placebo on a MTX background in patients with rheumatoid arthritis refractory to at least  
56 one anti-TNF- $\alpha$  biologic at 24 weeks. A total of 50%, 28.8% and 12.4% of the patients  
57 on TCZ (8mg/kg) achieved ACR20, 50 and 70 responses respectively compared to  
58 10.1%, 3.8% and 1.3% of the placebo group (30). There were no differences regarding  
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3 the type or the number of anti-TNF- $\alpha$  drugs previously used. These data are not  
4 dramatically different from other studies on anti-TNF- $\alpha$  drugs, but allows another  
5 option to be considered in non-responders.  
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### 10 **Extra-articular manifestations**

11 Despite being a systemic disease, the predominance of the articular involvement in  
12 rheumatoid arthritis has determined that the assessment of treatment response should  
13 take into account the changes (either clinical or radiologic) recorded in the joints.  
14 Quality of life and overall patient satisfaction has only been considered as a main  
15 therapeutic target more recently. Anti-TNF- $\alpha$  treatment has provided a relevant  
16 improvement in both those variables. However, other aspects, such as fatigue or other  
17 organ involvement has very rarely been considered. IL-6, being one of the most  
18 important inflammatory cytokines, is directly associated with the systemic features of  
19 the disease. There are no data addressing the response to different treatments regarding  
20 rheumatoid nodules or interstitial lung disease, and, until now, even anaemia was not  
21 thoroughly considered in these patients. Fatigue and inflammatory-disease-related  
22 anaemia are important aspects of the overall burden of rheumatoid arthritis which are  
23 now being addressed by anti-IL6 treatment. In fact, improvement of red blood cell count  
24 in these patients has been consistently shown by TCZ in both the pivotal and follow-up  
25 studies (31). In instance the higher mortality rate among rheumatoid arthritis (RA)  
26 patients in comparison with the general population is largely attributable to  
27 cardiovascular (CV) disease, particularly coronary atherosclerosis, but also non-fatal  
28 myocardial infarction and heart failure. Biological agents such as anti-TNF- $\alpha$  agents  
29 delay and even reverse the progression of endothelial dysfunction and atherosclerosis.  
30 Tocilizumab leads to changes in lipid profiles without increasing adverse vascular  
31 events, however is the dramatic effect on inflammation is long-term potential benefit on  
32 CV disease control (32).  
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### 53 **Remission is the new target**

54 Remission is now being presented as an important endpoint in clinical trials for  
55 rheumatoid arthritis. However, only one study has presented it as a primary endpoint:  
56 COMET. In this study, two groups of approximately 270 patients each were randomised  
57 for a 2 year treatment course with etanercept and MTX vs. MTX alone. All the patients  
58 had been diagnosed with rheumatoid arthritis less than 2 years before. After the first  
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3 year, remission (as measured by DAS28 after one year) was achieved in 50% of the  
4 patients treated with etanercept and MTX vs. 28% in the MTX alone arm. Radiographic  
5 remission (defined by a non-progression in the Total Sharp Score) was achieved by  
6  
7 79.7% of the patients in the etanercept arm, compared with 58.7% of the MTX group  
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9 (33).

10  
11 The BEST program, involving patients treated with infliximab, was a treatment strategy  
12 whereby patients were treated in 4 different groups: sequential monotherapy, step-up  
13 combination therapy, initial combination with prednisone and initial combination with  
14 infliximab. Again the target population was patients with disease duration of less than 2  
15 years. After 5 years, 58% of the group treated with infliximab were off anti-TNF- $\alpha$   
16 treatment and, of those, 19% were off any treatment (34).

17  
18 The PREMIER study comparing adalimumab plus MTX against MTX alone showed a  
19 total of 43 and 49% of patients achieving DAS28 remission at weeks 52 and 104,  
20 respectively. The MTX arm reached 21 and 25%. In this study disease duration could  
21 not be longer than 3 years. Interestingly the remission rate for the patients treated with  
22 adalimumab alone was very similar to the MTX group: 23 and 25% at 52 and 104  
23 weeks (35).

24  
25 Regarding IL-6 receptor blockade, the TOWARD study, involving 1220 patients  
26 already on DMARD treatment for RA, compared a group treated with tocilizumab  
27 8mg/kg in association with any DMARD with a group treated with DMARD only. At 6  
28 months, 30.2% of the patients in the tocilizumab group achieved clinical remission as  
29 assessed by DAS28 $<$ 2.6, a strong result when compared to 3.4% of the placebo group.  
30 The ACR70 response was 21% for the TCZ group vs. 3% for the placebo group) (36).

31  
32 In the AMBITION trial, patients treated with tocilizumab on monotherapy were five  
33 time more likely to reach remission (DAS28  $<$  2.6) than patients on MTX at week 24.  
34 (33.6% vs. 12.1%) (25).

35  
36 Interestingly, a similar result of 30.1% of remissions at 6 months was found when TCZ  
37 was used in patients who did not respond to previous treatments with anti-TNF- $\alpha$  (30),  
38 confirming a remarkable consistency in the induction of remission regardless of the  
39 context or background of where this drug is being used. One could remark that IL-6  
40 blockage dramatically normalizes C-Reactive Protein (CRP) , overestimating the  
41 outstanding DAS remissions achieved by tocilizumab, however acute phase reactants  
42 have little contribution on composite indexes used in clinical practice. In manner of fact  
43 CRP contributes only 5% in DAS28 –CRP score (37).

## Safety

Major safety concerns in the “biologic era” include overall infections and particularly serious infections, tuberculosis and malignancy. International registries have been monitoring these issues and it is now evident that there is an acceptable risk of infections when anti-TNF- $\alpha$  treatment is used, with the exception of a small number of patients who were subjected to high-dose anti-TNF- $\alpha$  therapy (38). Data are not so clear as far as malignancies are concerned, but a large study of the first 6 years after the start of anti-TNF- $\alpha$  therapy in routine care showed no overall elevation of cancer risk and no increase with time of follow up, (with an advantage for the use of etanercept over the monoclonal antibodies for a smaller risk of lymphoma) (39). With regards to high risk cancer patients (patients with personal or strong family history of cancer), there is still no clear data available, and therefore a definitive limitation for the use of these drugs in patients with previous malignancies is the current standard of care (40).

Regarding TCZ the first major set of data from the patients exposed to IL-6 receptor blockade, includes 4700 patients treated for almost 8000 patient-years (41).

Both in the five pivotal studies and in the two long-term follow-up studies, the incidence of serious adverse events (SAE) was low (less than 16 SAE/100pts-yrs) and it did not increase with increasing duration of TCZ exposure (42).

The rate of serious infections in RA patients treated with Tocilizumab inhibitors is 6 events/100 pts-yrs (43). (In patients treated only with DMARDS, it is 2-3 events/100 pts-yrs (44)). Major infections included pneumonia and cellulitis (<1.4% and <0.8% of all the patients exposed in both the pivotal and follow-up studies). For most of the studies, patients were not requested to have a tuberculosis screening test or prophylaxis, in accordance with the relatively low relevance of IL6 in granuloma production. In all of the studies that comprise the TCZ program, only 9 cases of TB were identified, the majority of which presented more than 18 months after the start of the treatment, suggesting a *de novo* infection, rather than the reactivation of a latent one (45).

There was no difference between the expected incidence of malignancies (including non-melanoma skin cancers) and the frequency observed in RA patients, suggesting that TCZ does not appear to implicate an additional risk, as observed in populations with high risk of digestive malignancies (46).

Liver abnormalities are common, particularly in patients treated with the association TCZ + MTX. 5 to 8% of the patients in the pivotal and long-term studies had elevation

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3 of AST levels, and 15 to 20% had elevation of ALT levels. These elevated levels  
4 responded to reduction and/or interruption of TCZ treatment and there were no cases of  
5 hepatic insufficiency or liver failure reported (46).  
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8 Other major concerns during treatment with TCZ seem to be the reduction of  
9 neutrophils and the increase in cholesterol lipids, particularly LDL-cholesterol.  
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11 A reduction in the neutrophil count seems to be associated with a response to treatment.  
12 It is not a real fall in the number of circulating neutrophils but a marginalisation of those  
13 cells in the blood vessel. In fact, there is no relationship between infections and the  
14 neutrophil count, and furthermore, the white cell response to an infection seen in these  
15 patients seems to be similar to the normal population.  
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18 A significant proportion of patients on TCZ show an increase in total cholesterol as well  
19 as in plasma LDL and HDL. Approximately 7% (in the long-term studies) required  
20 statin treatment and showed an appropriate response. There was no increase in  
21 cardiovascular adverse events in patients treated with TCZ, when compared to control  
22 treatments. Finally rare cases of gastrointestinal perforation have been described, and  
23 some of them were fatal, the relative risk is still not well characterized, but caution  
24 should be used in patients with previous diverticulitis or peptic ulcer disease (47).  
25  
26 Overall, the safety profile of this drug seems to be similar (although with a slightly  
27 different adverse event profile) to the other biologic treatments already in use, however  
28 some of the concerning safety problems have to be confirmed in long term studies,  
29 particularly hepatic toxicity and cardiovascular risk (48) (25).  
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#### 42 **Final comments**

43 Anti-TNF- $\alpha$  biologic treatment has started a new era in the management of rheumatoid  
44 arthritis. A remarkable improvement in the outcome of these patients regarding  
45 symptom control and quality of life, alongside the almost complete arrest of joint  
46 destruction, has raised the standards for treating this condition to a different level.  
47 However, some remaining problems have yet to be solved, opening a window of  
48 opportunity for new targets and different drugs. IL-6 blockade is one of the most recent  
49 alternatives. It has shown promising results in the main clinical trials which were  
50 confirmed in long-term follow-up studies and provided new opportunities for solving  
51 some of the issues that were not being particularly well addressed by Anti-TNF- $\alpha$   
52 therapy. Naturally, the lack of head-to-head studies and the inexistence of registry-based  
53 data for this new drug make it difficult to fully endorse all the aspects that individual  
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3 trials with tocilizumab have been showing. However there is sufficient evidence to  
4 consider anti-IL6 receptor blockade as a valid therapy for the treatment of rheumatoid  
5 arthritis. Tocilizumab might have a promising significant advantage over anti-TNF- $\alpha$   
6 treatment, particularly in the management of patients who are non-tolerant or in whom  
7 the use of methotrexate is contraindicated and in patients with significant extra-articular  
8 manifestations. Regarding the treat to target goals, tocilizumab is probably the  
9 biological who achieves the largest number of patients with sustained remission and low  
10 DAS scores, assuming the data of all extended reports of pivotal trials. Nevertheless its  
11 efficacy and security should also be proved in registries, as so far as been done with  
12 anti-TNF- $\alpha$  therapies.  
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Biologic agent	Target/Affinity	Immune actions	Half-life	Administration
<b>Etanercept</b> (humanized fusion protein)	TNF- $\alpha$ , lymphotoxin- $\alpha$ (TNF- $\beta$ ). Soluble TNF- $\alpha$	Decreases circulating TNF- $\alpha$ ; partial blockade; no lysis of TNF-expressing cells	4 days	Subcutaneous injection of 50mg once a week
<b>Infliximab</b> (chimeric mAb <sup>s</sup> )	TNF- $\alpha$ . Soluble and membrane TNF- $\alpha$	Monocyte and T-cell apoptosis; lysis of TNF-expressing cells	9 days	Infusion of 3-5mg/Kg at 0, 2, 6 weeks and then every 6-8 weeks
<b>Adalimumab</b> (humanized mAb)	TNF- $\alpha$ . Soluble and membrane TNF- $\alpha$	ILysis of TNF-expressing cells; possible effects on apoptosis, monocytes and natural killer cells	14 days	Subcutaneous injection of 40mg every 2 week
<b>Tocilizumab</b> (humanized mAb)	IL-6 receptor	Competitive blocking of IL-6 receptor	5-10 days	Infusion of 8 mg/Kg every 4 weeks

**Table 1.** Comparison between tocilizumab and the most used anti-TNF agents in the context of autoimmune rheumatic diseases.