Review

Pros and cons of TNF inhibitors and tocilizumab in the treatment of large-vessel vasculitis

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ABSTRACT

Large-vessel vasculitides (LVVs) include giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Even if similar, these two entities differ in terms of treatment and outcomes.

High doses of glucocorticoids (GCs) are still the first choice for the treatment of both conditions. However, adjunctive therapies are recommended in selected patients in order to decrease the risk of relapse and the amount of side effects related to GCs. Tumour necrosis factor α inhibitors (TNFis) and tocilizumab (TCZ) are used for the treatment of LVVs, with some differences. In GCA, TCZ has been proved to be effective and safe in inducing remission with some open questions still remaining, whereas data about TNFis are scarce and non-conclusive. On the contrary, in TAK either TNFis or TCZ seem to be able to control symptoms and angiographic progression in refractory forms.

However, their place in the management of treatment must still be clarified, and as a result the American College of Rheumatology and EULAR guidelines slightly differ in the recommendations about when and what treatment to start. Thus, the aim of this review is to look at the evidence on the use of TNFis and TCZ in LVVs, outlining the pros and cons of both therapies.

Introduction

Large-vessel vasculitides (LVVs) are conditions affecting mainly the aorta and its major branches and include giant cell arteritis (GCA) and Takayasu's arteritis (TAK) (1). Both entities are granulomatous diseases that share several similarities in the clinical presentation, imaging features, and histologic hallmarks. Women are more affected than men, with a ratio of 2–3:1 and 12:1 for GCA and TAK, respectively; however, GCA is more common among the elderly (>50 years old), whereas TAK is a disease of younger patients (2, 3)

Despite the aforementioned similarities, some differences should be outlined between the two LVVs. GCA may involve cranial arteries, large vessels, or both. The involvement of extracranial branches of the carotid arteries may lead to the most feared complication of anterior ischaemic optic neuropathy with consequent irreversible blindness (4). On the other hand, large-vessel involvement could lead to inflammatory aneurysms or dilations that may require surgical repair (5). Differently, vascular inflammation in TAK is characterised by a thick periaortic tissue and intimal proliferation that more often cause stenoses rather than dilation of large arterial vessels (6).

In both cases, the goal of treatment must be targeted to stop the ongoing inflammatory process, thus halting vascular damage progression.

The American College of Rheumatology (ACR) and EULAR guidelines still suggest glucocorticoids (GCs) at high doses (up to 1 mg/kg daily) as the mainstay of treatment. Although GCs are initially effective in controlling symptoms and short-term complications, at lower doses they are less effective in preventing disease flares, and up to 50% of patients may benefit from the addition of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (7-9). Furthermore, long-term courses of GCs are associated with significant side effects, and recently attention has been raised to save GCs to decrease their potential harmful toxicity. Consequently, biologic therapy is becoming a first-line treatment, particularly in relapsing forms of GCA and TAK (5, 7, 8, 10-14).

This review aims to give an overview of the pros and cons of tumour necrosis factor α inhibitors (TNFis) and tocilizumab (TCZ) in GCA and TAK, evaluating all the different aspects of these diseases in terms of outcomes.

TNF inhibitors in GCA

The role of TNF-α in the pathophysiology of GCA is still an open question (15). A study demonstrated a strong tissue expression of pro-inflammatory cytokines, particularly IL-1β, TNF-α and IL-6, in arterial wall samples of temporal artery biopsy (TAB) of GCA patients with sustained systemic inflammatory response and resistance to steroid therapy; besides, longer corticosteroid therapy was associated with higher TNF-α tissue production (16). Furthermore, there are some data on the association between elevated tissue TNF-α concentrations and disease activity (15).

Three RCTs and a few other observational studies have investigated the use of TNFis in GCA, with negative or non-conclusive results (14, 17), whereas some case series reported efficacy of TNFis (18, 19).

The first RCT was designed to evaluate the role of infliximab in maintaining remission in GCA (20). Forty-four patients with newly diagnosed GCA after GC-induced remission were enrolled. Participants were randomly assigned in a 2:1 ratio to receive GCs plus infliximab (at a dosage of 5 mg/kg at week 0, 2, 6 and then every 8 weeks) or placebo. After an interim analysis, the initially planned 54-week trial was interrupted at week 22. At that time, infliximab was unable to reduce both the number of relapses and the cumulative GC dose. The authors concluded that the experimental period was too short to take conclusive remarks, but no evident benefit from infliximab therapy was observed.

Another RCT on 17 patients with a biopsy-proven GCA assessed the efficacy of etanercept (8 received etanercept and 9 placebo) combined with GCs (21). The ability to withdraw the GC therapy and control the disease activity at 12 months was the primary outcome. No significant differences were observed, however the patients in the etanercept group had a significantly lower cumulative dose of GCs during the first year of treatment. There were no differences in the number and type of adverse events.

The third RCT enrolled 70 patients with newly diagnosed GCA and assessed the effect of adding a 10-week treatment with adalimumab (40 mg every other week) to a standard course of prednisone therapy (22). The results highlighted that adding adalimumab did not increase the number of patients in remission on less than 0.1 mg/kg of GCs at six months (primary endpoint). In addition, the decrease in prednisone dose and the proportion of relapse-free patients did not differ between the two groups.

Taken together, these results indicate that an efficacy of TNFis cannot be exluded, since the number of patients with relapsing GCA included in the RCTs was too small.

Tocilizumab in GCA

Interleukin (IL)-6 has a key role in the pathogenesis of GCA. Elevated serum levels of IL-6 are present and correlate with disease activity; furthermore, IL-6 is strongly expressed in temporal arteries of GCA patients (23, 24). It also seems that IL-6 driven inflammatory environment can induce the production of IL-17A from regulatory T cells, which may therefore lose their immunosuppressive role (25).

Two double-blind RCTs demonstrated the efficacy of TCZ compared to GCs monotherapy in GCA (9, 26).

A single-centre, phase 2, randomised, double-blind, placebo-controlled trial involving 30 patients with new-onset or relapsing disease assessed the role of TCZ in inducing remission, along with a standard regimen of GCs (26). Patients were randomly assigned (2:1) to receive either TCZ (8 mg/kg) or placebo intravenously monthly until week 52. The primary endpoint was the proportion of patients who achieved complete remission, defined as the absence of GCA clinical signs and symptoms and normalisation of CRP and ESR, at a prednisolone dose of 0.1 mg/kg per day at week 12. Seventeen (85%) of 20 patients treated with TCZ and four (40%) of 10 patients in the placebo group reached complete remission by week 12 (p=0·0301). Relapse-free survival was achieved in 17 (85%) patients in the TCZ group and 2 (20%) in the placebo group by week 52 (p=0·0010). The mean cumulative prednisolone dose was of 43 mg/kg in the TCZ group *versus* 110 mg/kg in the placebo group (p=0·0005) after 52 weeks. No differences in the frequencies of serious adverse events were observed between the two groups.

After 52 weeks, all treatment was stopped in 17 patients randomised to TCZ in complete remission, and 8 (47%) patients relapsed after a mean of 6.3 months (26).

These data show that a 52-week treatment with TCZ induces a lasting remission that persists in half of the patients after treatment stop. None of the clinical, serological or MRA findings were able to predict relapse.

A second multicentre randomised, double-blind, placebo-controlled, phase 3 trial (the Giant-Cell Arteritis Actemra; GiACTA) trial was published in 2017 (9). In this trial, 251 patients were randomly assigned in a 2:1:1:1 ratio (four groups) to receive subcutaneous TCZ at a dose of 162 mg weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over either 26 weeks or 52 weeks. The primary outcome was the rate of sustained GC-free remission at week 52 in each TCZ group as compared with the rate in the placebo group that underwent the 26-week prednisone taper, while the comparison between each TCZ group and the placebo group that underwent the 52-week prednisone taper was the key secondary outcome. Sustained remission at week 52 occurred in 56% of the patients treated with TCZ weekly and in 53% of those treated with TCZ every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper (p<0.001 for the comparisons of either active treatment with placebo). Tocilizumab had also an important GC sparing effect. The cumulative median prednisone dose over the 52-week period was 1862 mg in each TCZ group, as compared

with 3296 mg in the placebo group that underwent the 26-week taper ($p<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($p<0.001$ for both comparisons).

No differences in the occurrence of serious adverse events were noted in the four groups (9).

In the open-label extension of the GiACTA trial 81 patients, who were randomly assigned to TCZ once a week in part one, were in clinical remission after 1 year, and 59 of these 81 patients started part two without treatment (27). Only 25 of these 59 patients (42%) maintained TCZ-free and GC-free clinical remission in the following 2 years. However, patients' cumulative prednisone doses over 3 years were strictly related to their original treatment assignment: patients randomly assigned to placebo with a 52-week prednisone taper received more than twice the amount of cumulative prednisone as those randomly assigned to once-a-week TCZ (28). Furthermore, weekly TCZ delayed time to first flare and reduced GC exposure in new-onset and relapsing GCA to a greater degree than every-other-week TCZ (27, 28).

These two RCTs clearly demonstrated that TCZ is highly effective in GCA, has a powerful steroid sparing effect, and is well tolerated. Considering the high prevalence of GC-related side-effects (86% of patients) in GCA and the correlation between the cumulative GC dose and the development of side effects, an early initiation of TCZ therapy in all new GCA patients could represent a reasonable option (29).

However, some open questions on the use of TCZ in GCA remain, particularly regarding the duration of TCZ treatment, its long-term safety, the persistence of remission after TCZ suspension and whether TCZ is able to prevent vascular damage, particularly ascending aorta aneurysms.

The extension of the two RCTs answered to some of these questions and showed that one year of TCZ therapy did not completely suppress the inflammation and in more than half of the patients, apparently in clinical remission, the arteritis still persisted (27, 28).

Interestingly, in the GUSTO (GCA treatment with Ultra-Short GCs and TCZ) trial, the authors evaluated the safety and efficacy of isolated TCZ after an ultra-short course of GCs in naive GCA patients in inducing and maintaining remission (30). The study was a single-arm, single-centre, open-label, proof-of-concept trial. Eighteen participants received steroid pulses (500 mg methylprednisolone intravenously for three consecutive days) followed by TCZ monotherapy without oral GCs until week 52. The results showed remission in 14 (78%) of 18 patients within 24 weeks, and 13 of 18 showed no relapses up to 52 weeks (72%). The mean time to first remission was 11 weeks. Three of the 18 patients did not respond to treatment, and two discontinued the treatment due to adverse events. Anterior ischaemic optic neuropathy occurred in one patient. The authors concluded that after an initial 3-day glucocorticoid pulse treatment, TCZ monotherapy can induce remission in many patients with newly diagnosed GCA, albeit its action in suppressing clinical manifestations was very slow (30).

As a proof-of-concept study these data must be confirmed in RCTs, furthermore an ethical issue is the lack of data about the ability of ultra-short GCs and TCZ to prevent severe ischaemic complications in GCA. Therefore, this treatment should probably be limited to GCA patients without cranial manifestations, such as PMR patients with LV involvement or GCA patients presenting with systemic manifestations.

The efficacy of TCZ alone in maintaining remission has also been evaluated in a multicentre study on 134 patients with refractory GCA (31). TCZ in monotherapy (TCZMONO) was compared with TCZ therapy combined with conventional immunosuppressive drugs (TCZCOMBO) over 12 months. TCZ was prescribed IV (8 mg/kg monthly) or SC (162 mg weekly). 82 patients were enrolled in the TCZMONO group and 52 in the TCZCOMBO (methotrexate n=48, azathioprine n=3, and leflunomide n=1). Therapy was effective in determining a rapid improvement in both groups, but the frequency of prolonged remission at 12 months was higher in the TCZCOMBO group where methotrexate was frequently associated. Relapses and serious adverse events were similar in both groups, supporting the use of a combination therapy with methotrexate and TCZ in patients with refractory GCA (31).

Ongoing RCTs are planned to clarify the efficacy of sequential or alternative use of methotrexate and TCZ. In METOGiA trial (NCT03892785), TCZ will be compared to methotrexate in maintaining remission after induction with scheduled tapering prednisone regimen.

Pros and cons of TNF inhibitors *versus* tocilizumab

Due to the scarce data and inconclusive results in most studies, TNFis are not considered for the therapy of GCA (7, 8). However, increased expression of TNF-α in TAB specimens at diagnosis was associated with persistent disease activity and tissue production of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in GCA (16), therefore the efficacy of these biological agents in patients with relapsing disease cannot be excluded.

In the most recent EULAR guidelines for the management of GCA, TCZ is considered as an adjunctive therapy to GCs in selected cases, such as patients at increased risk of developing GC-related side effects or complications, or for relapsing or refractory disease requiring long-term GC therapy (7); whereas in the ACR guidelines, TCZ with GCs is considered as a first-line therapy in all patients (8). Although there is no clear evidence that TCZ is able to reduce GC-related side effects, particularly in the subgroup of patients without increased risk factors, early initiation of TCZ could represent a reasonable option in all new GCA patients (14). Indeed, TCZ has proven a powerful steroid sparing effect, much higher than that of methotrexate.

In terms of safety, TCZ is well tolerated in most cases. Side effects associated with therapy more commonly include elevations in transaminases (particularly if in combination with methotrexate), but without a clear correlation with

hepatic adverse events; and eventually, a transient reversible neutropenia that however does not appear to be associated with severe infections (32).

Compared to other therapies (TNFis, csDMARDs, abatacept or rituximab) TCZ may lead more frequently to diverticular perforations in patients with diverticulitis. In addition, perforations may be asymptomatic and without increased acute phase reactants, rendering a prompt diagnosis more challenging (33). Thus, the addition of TCZ in an elderly population should be considered carefully, if any of these risk factors are present.

Another point to consider in managing patients with TCZ is the abrogation of the hepatic synthesis of the acute phase reactants. As a result, the need for reliable biomarkers in the assessment of disease activity becomes even more urgent. Osteopontin and Pentraxin-3 could be promising molecules for this purpose (34, 35).

TNF inhibitors in TAK

TNF-α is implicated in the pathogenesis of TAK, given the granulomatous nature of this vasculitis.

Differently from GCA, many observational prospective/retrospective studies have shown that TNFis are effective in inducing complete or partial remission in refractory TAK (36-41). However, no RCTs have been published. Infliximab is the most used TNFi because the dose-escalation allows optimising infliximab treatment in the case of refractory vasculitis (42).

A recent retrospective multicentre study on 209 TAK patients, conducted by the French Takayasu Network, evaluated the efficacy of TNFis (total n=132, infliximab n=109, adalimumab n=45, golimumab n=8, certolizumab n=6, and etanercept n=5). Disease activity was assessed according to the National Institutes of Health (NIH) criteria, which, among the other features, incorporated imaging findings in terms of new angiographic progression as a marker of disease activity (6). Complete response, defined as a NIH score <2 and a dose of prednisone <10mg daily, was seen after six months in 101/152 (66%) of patients (6, 43).

A study on infliximab on 12 patients with newly diagnosed or relapsing TAK used the PET vascular activity score (PETVAS) among the outcomes of remission and found a decrease in median (interquartile range) of PETVAS from 12 (11–15.5) to 11 (8–12) over a follow-up period of 30 weeks (39). In another observational study including 21 TAK patients, of whom 7 treated with infliximab, a normalisation of ^{18}F-FDG-PET was reported in only two patients (19). In an open label monocentric study, 23 TAK patients were treated with infliximab biosimilar for 52 weeks and at one-year evaluation ^{18}F-FDG-PET showed in all patients neither new vascular uptake, nor worsening of previously detected vascular uptake. MRA disclosed disease stability in 9 (47%), worsening in 2 (11%), and improvement in 8 (42%) patients. Only one patient was active at MRA assessment (44).

Quartuccio *et al*. assessed the improvement in health-related quality of life measures using the 36-item short-form (SF-36) questionnaire in ten patients before and after infliximab and observed a significant improvement in body pain, general health, and vitality components of the SF-36 (45).

Taken together, these results indicate that TNFis can induce clinical remission in TAK and also improve the quality of life. Angiographic progression seems rare when patients are treated with TNFis, despite ^{18}F-FDG-PET may apparently remain active, even if improved. However, these results should be analysed in a prospective context and in RCTs.

In a meta-analysis, relapses after a course of TNFi were seen in 32% of patients (46). Therefore, in patients who failed a first-line TNFi, an open question remains whether to use a biological agent with a different mechanism of action or to switch to another TNFi. In a retrospective study on 24 patients who failed a TNFi, 13 were swapped to another mechanism of action (mainly TCZ), and 11 were switched to a different TNFi. At 12 months relapse-free survival and vascular progression evaluated on MRA were comparable between the two groups (47).

Tocilizumab in TAK

As in GCA, IL-6 has a pivotal role in the pathogenesis of TAK. Levels of circulating IL-6 are higher in active than in inactive TAK, and increased levels of IL-6 in peripheral blood correlate with a greater risk of future relapses (48).

A double-blind, phase 3 trial on TCZ (the TAKT study) in TAK was published in 2017. Thirty-six patients with relapsing TAK were included: 18 received TCZ subcutaneously every week, and 18 placebo. Relapse was defined as the presence of 'signs of relapse' as judged by the investigator in the primary endpoint and according to the NIH criteria in the secondary endpoints. Vascular progression on imaging (either CT or MRA) was also explored. In the intention-to-treat analysis, the hazard ratio for time to relapse of TAK was 0.41 (95.41% CI 0.15 to 1.10; p=0.0596). However, in the per-protocol set sensitivity analysis, the hazard ratio was 0.34 (95.41% CI 0.11 to 1.00; p=0.0345), favouring TCZ for a longer time to relapse. The results were not different when considering the NIH criteria, and no significant differences in vascular damage were reported (49).

In the trial extension, 28 of the 36 enrolled patients received subcutaneous weekly TCZ 162 mg for up to 96 weeks or longer. A GC-sparing effect was observed in TAK patients treated with TCZ. Furthermore, during long-term TCZ treatment, no vascular progression was detected (50).

In the above-mentioned retrospective study on 209 patients with refractory TAK, 121 patients were treated with TCZ intravenous (n=95) or subcutaneous (n=26). 75/107 patients obtained a complete clinical response (NIH score <2 and GCs dose <10 mg daily) (43).

Since TCZ is often used in clinical practice after at least one TNFi or other csDMARD failure, patients included in observational studies often had a disease more difficult to treat since the beginning. An open-label multicentre prospective trial assessed the efficacy of TCZ in inducing and maintaining remission in treatment naive TAK. TCZ was given for seven months intravenously at a dosage of 8 mg/kg monthly to 13 patients. The primary endpoint

was the discontinuation of GCs, which was achieved by half of the patients; however, half of them relapsed in the 12-month follow-up after TCZ discontinuation (51). In a retrospective study conducted by the same group and including 46 patients with TAK, remission, defined as an NIH score <2, was achieved by 80% of patients on TCZ. Eighteen patients (39%) were treated concomitantly with other csDMARDs, however, event-free survival was similar in patients under TCZ with and without csDMARDs (log-rank p=0.25) (52).

Three studies compared the efficacy and safety of TCZ to other csDMARDs, particularly cyclophosphamide, and reported a more frequent complete clinical response in patients treated with TCZ, together with a lesser number of adverse events. The risk of angiographic progression was similar between the two groups, indicating that TCZ may be a good option in refractory patients (53-55).

In terms of response assessed by ^{18}F-FDG-PET, 19 refractory TAK patients were treated with TCZ subcutaneously and at one-year remission (defined as absence of clinical symptoms and reduction of GCs) was achieved by the 70.6% of patients. ^{18}F-FDG-PET was inactive for all patients who responded to treatment (56).

Pros and cons of TNF inhibitors *versus* tocilizumab

The ACR guidelines favour TNFis over TCZ in refractory TAK. On the other hand, EULAR recommendations stated that either TCZ or TNFis could be used as treatment options in refractory TAK. The reason why ACR prefers TNFis over TCZ is the presence of a negative RCT and the scarce literature on TCZ in TAK patients (7, 8, 49). However, in terms of efficacy, a recent meta-analysis, including six studies that directly compared TCZ with TNFis and were amenable to meta-analysis, reported a similar capacity of inducing remission (defined as clinical response and/or angiographic stabilisation) (57). Two multicentre retrospective cohorts involving 111 and 209 refractory TAK, respectively did not detect any differences in terms of risk of relapse, GC dose decrease and drug retention rate (43, 58).

Safety seems also to be comparable between TCZ and TNFis. However, adverse events, including infections may account for a sizeable proportion of decreased drug persistence. In a study on 20 patients, 73.8% were still receiving TNFis after one year and just 55.4% after two years, and in 20% of cases, the suspension was due to side effects (59). In the study by Mekinian *et al*., 37 (21%) adverse events (mainly infections) occurred on TNFis and 21 (17%) on TCZ. The frequencies of severe adverse events requiring drug suspension in this study were similar: 6 (5%) cases treated with TCZ and 20 (11.5%) with TNFis (43). Another retrospective study assessing the drug retention rate in TAK patients treated with csDMARDs or biologic agents stated that the percentages of discontinuation and the rate of adverse events between TNFis and TCZ were similar (60).

A point to consider is that TAK affects young women in reproductive age, making the management of these patients more complex. EULAR recommendations prefer TNFis over TCZ during pregnancy due to scarce literature on the latter. Register and cohort data support the use of all TNFis up to the 20th gestational week, and, if indicated, throughout pregnancy (61). However, among the TNFis, certolizumab pegol is the safest since it lacks Fc-fragment and has a low potential to cross the placenta. A retrospective case series support its role in maintaining remission. Ten patients with refractory TAK were treated with certolizumab pegol and response was defined as a NIH score <2. Seven patients were still in remission after two years without signs of vascular progression (62). Thus, in young women with a desire of pregnancy TNFi should be preferred over TCZ.

RCTs comparing TCZ *versus* TNFis are needed to define their place in the treatment of TAK. INTOReTAK (NCT04564001) is an ongoing trial comparing infliximab *versus* intravenous TCZ in refractory TAK. At this time, recruitment is not started yet.

Conclusions

The mainstay of treatment for LVVs is high doses of GCs; however, research is focused on finding new molecules to treat refractory patients and those at major risk of developing GC-related side effects. TNFis and TCZ have been widely used in other rheumatological conditions and are safe and well-tolerated overall. In GCA, TCZ has now been approved for inducing and maintaining remission. ACR guidelines suggest it as a first-line treatment, whereas EULAR recommends its use in a selected population of patients. Indeed, there are still open questions about the full GC-sparing effect of TCZ, its capacity to prevent severe ischaemic complications (particularly anterior ischaemic optic neuropathy) and ascending aorta aneurysms, and the optimal duration of treatment.

In TAK, both TNFis and TCZ may be used in inducing and maintaining remission. ACR guidelines favor TNFis over TCZ; however, results are still controversial, and head-to-head RCTs are urgently needed.

Indeed, even if the RCT on TCZ failed to achieve the primary endpoint, similar clinical responses, angiographic stabilisation, and safety profile were observed comparing TCZ and TNFis in observational studies. However, TNFis may be preferred in young females with a desire for pregnancy, since they present a safer profile in this setting.

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