Editorial

Interleukin-6 inhibition for Takayasu's arteritis: before or after tumour necrosis factor inhibitors?

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Takayasu's arteritis (TAK) is a chronic relapsing large-vessel vasculitis (LVV) characterised by granulomatous inflammation affecting the aorta and its branches (1). TAK can cause large-artery stenosis and occlusions with resultant ischaemic manifestations, as well as aortic aneurysms or stenosis (2). Unfortunately, nearly 90% of patients already have evidence of damage at the time of diagnosis with additional items of damage, including vascular damage occurring in 42% (3). As a result, early diagnosis, and, treatments that minimise risk of relapse and glucocorticoid exposure remain important. While glucocorticoids are effective treatment, their use is associated with adverse events, underscoring the important role of other glucocorticoid sparing medications. However, there are no medications that have been approved by the U.S. Food and Drug Administration for TAK. Additionally, until the fairly recent publication of clinical trials evaluating abatacept and tocilizumab, there were no randomised clinical trials in TAK to inform therapeutic decision making. Indeed, much of the data on use of immunosuppressive agents was based on observational studies or open-label trials (4, 5).

The American College of Rheumatology and Vasculitis Foundation (ACR/VF) and the European Alliance of Associations for Rheumatology (EULAR) have published guidelines on the treatment for TAK (6, 7). Both recommend initiation of adjunctive immunosuppression at diagnosis rather than glucocorticoids alone (6, 7). EULAR recommendations are for conventional immunosuppressive therapy as first-line with addition of biologic therapy in cases of refractory disease (6). In contrast, the ACR/VF guideline considers biologic therapy with tumour necrosis factor inhibitors (TNFi) along with conventional immunosuppressive therapy as first-line (7). This difference may reflect factors including cost and access to biologic therapies. With respect to biologic agents, EULAR recommends TNFi or tocilizumab (TCZ), an interleukin-6 (IL-6) receptor antagonist for refractory disease, whereas ACR/VF favoured TNFi over TCZ in TAK based on the data available at the time (7).

Since then, there have been many studies reporting efficacy of TCZ in TAK. In this editorial, we review the current evidence for TCZ use in TAK, as well as data evaluating TCZ *versus* TNFi, potential drawbacks of treatment with TCZ and ongoing uncertainties.

Rationale for tocilizumab

The pathogenesis of TAK shares many similarities with giant cell arteritis (GCA) where tocilizumab is an approved and efficacious therapy. T-helper (Th) 1/Th17 cell activation and increased expression of NOTCH1 in CD4(+) T cells have been reported in TAK (8, 9). The Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway may also play a role (10). The cytokine milieu drives differentiation of naive T-cells toward either a T-helper 1 (Th1) (via interleukin (IL)-12) or Th17 (via IL-6 and tissue growth factor β) pathways (11, 12). Th1 commitment is linked with STAT1 and STAT3 mediated gene induction, whereas Th17 differentiation, via IL-6, is mediated through the surface protein STAT3 (11, 12). In TAK, the Th1 pathway is suppressed by glucocorticoid therapy while the cytokines driving Th17 persist (9). Additionally, elevated serum IL-6 levels have been associated with active disease in TAK (13-15) providing a rationale for IL-6 inhibition in TAK.

Evidence for TCZ in TAK

Clinical trial. TCZ was evaluated in a randomised, double-blind, placebo-controlled, phase 3 study, TAKT (5). In this trial, 36 patients with active, relapsing TAK, age >12 years, were randomised to subcutaneous TCZ 162 mg weekly (n=18) or placebo (n=18) (5). All patients were on glucocorticoids which were tapered by 10% per week to a minimum of 0.1 mg/kg/day (5). The primary endpoint of time to relapse in the intent-to-treat analysis was similar in both groups (5).

In a per-protocol analysis (17 patients placebo arm, 16 patients TCZ arm), the primary endpoint favoured TCZ (5). The estimated relapse-free rate at 24 weeks was 51% in the placebo arm compared to 23% in the TCZ arm suggesting benefit of TCZ (5). In a subsequent open-label extension of the study, 29 patients received TCZ for 96 weeks with ability to lower prednisone dose to <0.1 mg/kg/day in 46% (16). Eighteen relapses occurred in 14 patients (16). Finally, when evaluating imaging findings in 28 patients with at least one dose of TCZ, improvement or stability was noted in 57% with partial progression (worsening in a previously affected artery) in 11% (17). However, new lesions occurred in 9 patients (29%), 6 of whom experienced relapses during treatment with TCZ (17).

Other studies. Efficacy of TCZ has also been reported in an open-label trial and several observational studies (18-23).

In an open-label trial, TCZ in treatment-naive patients with TAK (TOCITAKA), 13 patients were treated with intravenous TCZ 8 mg/kg/month for 7 months and prednisone 0.7 mg/kg (18). All patients underwent imaging at baseline and month 6 (18). The primary endpoint of discontinuation of glucocorticoids after treatment was met in 54% (18). Sustained remission at 6 months on prednisone <10 mg was observed in 85% (18). However, 45% of patients in remission relapsed at 12 months after discontinuation of therapy (18). Details are not provided about imaging outcomes apart from a statement that "no significant vascular complications or interventions were noted during follow-up" (18).

A prospective study from China compared patients with TAK on TCZ (n=9) to patients on cyclophosphamide (n=15) (23). Only 2 patients in the TCZ group had received other adjunctive therapy (methotrexate and leflunomide in 1 each) and 1 patient in the cyclophosphamide group had received TCZ (23). The investigators observed improvement in disease activity in both groups at month 6 (23). There was no significant change in imaging in either group (23). A greater reduction in erythrocyte sedimentation rate, c-reactive protein, and matrix metalloproteinase 9 was noted in the TCZ group (23).

In a multicentre observational study from Japan (ACT-Bridge), 120 patients with TAK (47% newly diagnosed) without TCZ exposure in the past 6 months were enrolled as part of a phase 4 study and received TCZ 162 mg weekly for 52 weeks (21). Thirty eight percent were also on other immunosuppressive therapy; only 8% had previously been on any biologic therapy (21). Relapses were observed in 24 patients (20%) including imaging abnormalities in 50% of those who relapsed, though it is not clear if all patients underwent routine imaging (21). At last observation, relapse free survival while on prednisone equivalent <10 mg was 83% (21).

In a retrospective study of 19 patients with TAK treated with TCZ, positron emission tomography (PET) was available prior to treatment in 16 patients and after treatment in 15 patients (24). Fluorodeoxyglucose uptake decreased after treatment with TCZ in 12 patients who also had clinical improvement, adding evidence that TCZ improves vascular inflammation in TAK (24).

Retrospective studies have also reported efficacy of TCZ (19, 20, 22, 25). In a multicentre cohort of 46 patients treated with TCZ (7 without exposure to other immunosuppressive therapies and 20% with prior biologic therapy), improvement in disease activity and glucocorticoid sparing effect was observed with relapse free survival of 81% at 12 months (19). In another retrospective study of 54 patients treated with TCZ, 12 patients (22%) with previous biologic therapy, clinical remission was observed in 75% at 1 year with a glucocorticoid sparing effect (20). TCZ was used as monotherapy in 42% of these patients (20). An observational study from China included 37 patients with TAK with refractory or severe disease treated with intravenous TCZ; 18 patients received concurrent non-biologic immunosuppression (25). No details were provided regarding prior treatment exposures including biologic therapies. The authors report complete response (no new or worsening symptoms, no new or worsening vascular signs/symptoms and prednisone ≤15 mg) of 70% at month 6 (25). Imaging was assessed every 6 months with progression in 15% at month 6, though it is unclear if this represents worsening of previously noted lesions or new lesions (25). Among 23 patients with complete response at month 6, treatment was discontinued in 14 patients with relapse in 43% (25). Another international retrospective study of 109 patients (68% with prior biologic exposure) treated with subcutaneous or intravenous TCZ for at least 3 months, reported that a complete response (defined by NIH Kerr criteria <2 with prednisone dose <7.5 mg) was achieved in 69% at month 6 (22). Fifty percent were also on other adjunctive immunosuppressive therapy (22). A higher relapse rate was noted in patients on subcutaneous TCZ (cumulative incidence at month 12 of 31% *vs*. 14% for the intravenous group) (22). However, doses of TCZ used are not provided and it is unclear if that may have accounted for this finding (18). The authors propose adherence with subcutaneous formulation may be an explanation (22). Finally, a meta-analysis of 19 studies included 466 patients with TAK treated with TCZ; 417 patients had previously been on non-biologic adjunctive immunosuppression and 194 patients on previous TNFi (26). Glucocorticoid sparing was noted in 76%, remission in 79% and imaging progression in 16% (26). However, there was high heterogeneity (I^2 85–94% for the different analysis) and only 4 of the included studies had available imaging outcomes which limit interpretation of this meta-analysis (26).

TCZ or TNFi

Several studies have evaluated TNFi and TCZ use in TAK with reports of similar efficacy (27-30). In a large observational cohort of 209 patients with TAK, (84%) had failed or not tolerated conventional immunosuppression and were treated with TNFi (132 patients) or TCZ (77 patients) (28). Complete response (NIH score <2, prednisone <10 mg/day) was reported in 66% on TNFi and 70% on TCZ at month 6 (28). Likewise, in a retrospective cohort of 111 patients with TAK from Turkey (109 who had been on conventional immunosuppression), first line biologic agents included TNFi in 88 patients and TCZ in 23 patients (27). There were no differences between the two groups with respect to remission or ability to taper glucocorticoids (27). The patients all underwent routine imaging as part of their follow-up and while not statistically significant, radiographic progression (new lesions, progression in luminal vascular lesions or FDG uptake on PET) was observed in 9 patients (39%) on TCZ and 17 patients (19%) on TNFi (27).

Two meta-analyses have been published evaluating TCZ *versus* TNFi (29, 30). The first included 517 patients from 29 observational studies and 2 randomised-controlled trials and found similar efficacy for TNFi (65% remission rate) and TCZ (70% remission rate) though there was high heterogeneity (I^2 49–69%) (30). There was a statistically significant difference between relapses on TNFi (28%) *versus* TCZ (17%, p=0.017) but the authors suggest variations in duration of treatment and follow-up, study design, disease severity, glucocorticoid regimens and prior exposure to other biological agents as potential confounding factors (30). Another meta-analysis included 35 studies (1 randomised clinical trial, 11 controlled and 21 uncontrolled studies) with 1082 patients with TAK treated with TCZ, TNFi or conventional immunosuppression (29). When comparing TCZ to TNFi (6 studies), there were no differences in outcomes including partial response to therapy (no significant heterogeneity, I^2 0%) or radiographic stability (moderate heterogeneity with I^2 53%) (29).

A recent open label study compared the TNFi adalimumab 40 mg subcutaneously every 2 weeks (n=21) to TCZ 8 mg/kg intravenously every 4 weeks (n=19) in patients with active TAK (31). All patients received glucocorticoids and background immunosuppression with methotrexate 15 mg weekly. The primary end point was efficacy at 6 months (31). Efficacy was defined as a prednisone dose of ≤15 mg per day at 6 months or ≤10 mg per day at months 9 and 12 without new or worsening systemic symptoms, vascular symptoms or vascular lesions. The primary endpoint was achieved in 86% in the adalimumab group versus 53% in the TCZ group (p 0.02) though at month 9, there was no differences in efficacy between the 2 groups (62% adalimumab, 42% TCZ). Relapse rates and ability to reach prednisone dose ≤10 mg at 12 months was similar. However, there were differences in the baseline characteristics between the two treatment arms (even though not statistically significant). This includes a longer disease duration in the group treated with TCZ (38 months *vs*. 24 months for the ADA group) (31). Additionally, 40% in the ADA group had previously received treatment with CYC compared to only 6% in the TCZ group (31). The small number of patients limits the generalisability of these results and future randomised controlled trials are needed to address whether TNFi are superior or equivalent to TCZ.

Areas of uncertainty

One of the challenges with TCZ is the inability to rely on acute phase reactants, particularly the C-reactive protein which normalises while on this medication. This can further limit disease activity assessment, which is already difficult in TAK and often relies on a number of variables including clinical assessment, acute phase reactants and imaging. Additionally, there are reports of radiographic progression while on treatment despite improvement on clinical assessment (32, 33). The data to date are primarily retrospective with heterogeneity in the populations studied (new *vs*. relapsing or refractory), and variability in terms of previous exposure to immunosuppressive or biologic therapies, concurrent use of other adjunctive immunosuppression, imaging used and definitions of remission. All of these need to be considered when interpreting the studies or making a clinical decision regarding use of TCZ.

Summary and future directions

Based on the data thus far, TCZ appears to be an efficacious option in the treatment of TAK. At present, there is insufficient information to make any definitive recommendation favouring one agent as the first line biologic therapy over another. We recommend the clinician's decision take into account patient preferences, comorbidities, plans for pregnancy in women and other factors. It is imperative that all patients with TAK should be followed closely with comprehensive clinical and laboratory assessments as well as regular imaging studies. It is evident from data thus far that routine imaging is important in the assessment of patients on TCZ, including those who appear to be in clinical remission. In patients who fail TNFi or have intolerance, switching to a different TNFi or to TCZ may be reasonable. Several other treatments are currently being explored in TAK and will likely offer new alternatives. To enable better clinical decision making, future clinical trials need to include standardised outcome measures and definitions for disease activity, standardised imaging and assessment of vascular damage as part of the study, patient reported outcomes and randomised clinical trials with head-to-head comparison studies. The recent trend of multicentre clinical trials in this rare disease will allow rigorous evidence-based data to guide treatment decisions that will better control disease activity, minimise vascular damage, allow glucocorticoid sparing and, most importantly, improve quality of life for our patients.

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