Editorial

Tocilizumab for giant cell arteritis: what is optimal?

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Giant cell arteritis (GCA) is a systemic vasculitis of unknown aetiology seen mostly in white individuals over age 50 years (1, 2). GCA involves large and medium-sized arteries, primarily the aorta and its main branches; vascular damage from this disease may result in blindness, ischaemic stroke and aortic aneurysm (1, 2). The clinical presentation of GCA is heterogenous with a spectrum of phenotypes ranging from cranial-predominant to large-vessel disease (3). While temporal artery biopsy has historically been the gold standard diagnostic test for GCA, the use of non-invasive imaging has taken centre stage in the evaluation of these patients (4). Imaging of the cranial arteries as well as the aorta and its major branches can provide information regarding vascular inflammation and luminal changes (4). Indeed, a population based study confirmed the increased use of imaging as a diagnostic modality for GCA in recent decades (5).

It has become apparent from imaging and histopathology data that GCA is a chronic vasculopathy and despite glucocorticoid therapy, 44% of temporal artery biopsies had evidence of vascular inflammation 12 months into the disease course (6). Moreover, patients often require prolonged immunosuppression due to high rates of relapse during follow-up, resulting in significant glucocorticoid toxicity (7). The use of tocilizumab for the treatment of GCA has ushered in a new era in the management of this disease (8). The 2021 American College of Rheumatology/Vasculitis Foundation (ACR/VF) guidelines and 2018 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations both endorse the use of this biologic, albeit with slight variation (9, 10). While the ACR/VF guideline recommends starting tocilizumab for all patients with newly diagnosed GCA, EULAR recommends starting tocilizumab in those with, or at risk of, glucocorticoid-related adverse events or in patients who have relapsing disease (9, 10).

The use of tocilizumab has been largely guided by results of the phase 3 Giant Cell Arteritis Actemra (GiACTA) trial showing superior remission outcomes and glucocorticoid sparing in patients treated with a 26-week prednisone taper combined with tocilizumab for one year compared to those treated with prednisone monotherapy (8). Subsequently, the two-year-long open-label extension phase of the GiACTA trial revealed that the relapse rate following abrupt discontinuation of tocilizumab is unacceptably high. Indeed, more than 50% of those achieving remission on tocilizumab later relapsed when this biologic was stopped (11); similar findings were reported from an earlier phase 2 trial of tocilizumab (12).

Therefore, although the efficacy of tocilizumab as induction therapy for GCA has been clearly demonstrated (8), clinicians are left with several unanswered questions. First and foremost, the optimal duration of treatment and dosing schedule beyond 12 months remains unclear. Additionally, risk factors for relapse after tocilizumab discontinuation are largely unknown.

In this regard, in this issue, Calderón-Goercke *et al.* from Spain reported the real-world outcomes of the largest GCA cohort to date, comprised of 471 patients, of whom 231 were in prolonged remission after a median 12 months of tocilizumab therapy (13). Patients in remission were then treated with either optimised (by decreasing the dose or increasing the interval) or non-optimised (by continuing the standard dose) tocilizumab regimens for approximately two years. At the end of the study, investigators found similarly high remission rates between these two groups, while relapse rates were low and not

significantly different (about 6% and 10% respectively). Importantly, the rate of serious infections was lower in the optimised group and as expected, cost savings were also observed with this regimen. Although this was an observational and retrospective study, it replicates what is often done in clinical practice and provides valuable insight regarding use of tocilizumab beyond 12 months. Indeed, the findings of the Calderón-Goercke study suggest that for patients in remission after 12 months of treatment, a tocilizumab dose reduction appears to maintain most patients in remission, is safe and cost effective. However, the reported treatment discontinuation rate was low (less than 20%) and longer term outcomes remain to be determined (13).

The real-world efficacy of tocilizumab was also confirmed in a cohort of 114 patients from the USA (14). Investigators demonstrated a reduction in GCA relapse rate and glucocorticoid sparing with use of tocilizumab. About one-third of patients in this cohort also underwent tocilizumab dose reduction during the maintenance phase. Among patients later discontinuing tocilizumab, the relapse rate was high (>50%) and no predictors of relapse could be identified. Specifically, duration of tocilizumab treatment was not predictive of subsequent risk of relapse suggesting that some patients remain at risk of relapse despite prolonged therapy (14, unpublished data).

Additional data on the use of a tocilizumab optimisation approach comes from a recent open-label, prospective study of 23 patients with GCA treated with tocilizumab 162 mg once weekly for one year followed by every other week dosing for an additional year (15). During the second year of the trial, relapse rate was also low at 9%, again suggesting that a reduced dose regimen is a reasonable maintenance option following the initial 12-month treatment phase. After 2 years of treatment, around one in four patients relapsed in the 6 months after stopping tocilizumab; risk factors for relapse were also not identified in this trial (15).

One of the most serious and feared complications of GCA is vision loss and the use of accelerated glucocorticoid tapering regimens in combination with tocilizumab has raised theoretical concerns regarding possible visual complications. However, data regarding visual outcomes of patients treated with tocilizumab are reassuring (16, 17). The few reported cases of vision loss in tocilizumab-treated patients occurred early in the disease course during induction of therapy rather than during the maintenance treatment phase (16). Moreover, in the studies utilising a tapering dose of tocilizumab, no new cases of vision loss were reported (13, 15). On the other hand, a treatment course of tocilizumab with only a 3-day regimen of glucocorticoids may be inadequate. In the open-label GCA treatment with ultra-short glucocorticoid and tocilizumab (GUSTO) trial that enrolled 18 patients with newly diagnosed GCA, time to remission was longer than expected (mean time of 11 weeks), 3 participants did not respond and one developed anterior ischaemic optic neuropathy (18).

Despite the fact that large-vessel involvement in GCA is increasingly recognised, none of the tocilizumab clinical trials incorporated radiographic findings as a primary or secondary outcome measure (19). Studies have shown improved 18F- fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) activity and magnetic resonance angiography signals among patients with GCA who received tocilizumab; however, complete resolution in radiographic findings was not observed in a substantial proportion of patients (12, 20, 21). The role of FDG-PET in predicting the risk of subsequent relapse remains controversial (22). In a prospective study by Grayson *et al*. 39 patients with large-vessel vasculitis underwent an FDG-PET scan while in clinical remission; those with a PET vascular activity (PETVAS) score of 20 or more were more likely to relapse than those with a PETVAS score of less than 20 (23). However, a recent retrospective study with a larger sample size could not show an association between the PETVAS score and the subsequent risk of relapse (24). Therefore, it remains unclear whether imaging studies could guide the clinician on when to reduce or discontinue treatment with tocilizumab.

Undoubtedly, there is an unmet need for a reliable and specific biomarker of disease activity in GCA, especially since traditional markers of inflammation are less useful in tocilizumab-treated patients. Similarly, a better understanding of the risk factors for GCA relapse after treatment discontinuation would be essential in determining the duration of treatment. Although female patients and patients with large-vessel GCA were found to have a higher risk of relapse, there is no data to guide optimal length of treatment in these patient subgroups (25-28).

In conclusion, further research is needed to determine the optimal use of tocilizumab beyond 12 months for patients with GCA. Factors such as sex differences in response to treatment, presence of large-vessel involvement and subclinical disease activity (as detected by imaging) should be considered in the efficacy analysis of future studies (29). Both the landmark prospective trials and the growing body of evidence from observational studies should be taken into account when formulating a treatment plan for GCA (30). While further studies are eagerly awaited, the duration and dosing schedule of tocilizumab therapy must be individualised and tailored to patient characteristics and preference with shared decision-making being an integral aspect of patient management.

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