Editorial

Treatment of large-vessel vasculitis: where do we stand?

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Giant cell arteritis (GCA) and Takayasu arteritis (TA) are primary systemic vasculitides involving the aorta and its main branches (1). Glucocorticoids (GC) are still the mainstay of treatment of GCA and TA, but a sizeable number of patients relapse upon tapering of the GC dose or after discontinuation of GC therapy (2). In addition, GC are fraught with a wide array of adverse events that impart a significant morbidity risk. In a population-based study of 120 patients with GCA, 86% of patients incurred side effects attributable to GC, including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastro-intestinal haemorrhage, posterior subcapsular cataract, and hypertension (3). Therefore, despite the resounding success of GC in rapidly getting disease activity under control and in preventing disease-related complications, alternative or adjunctive treatments have eagerly been sought.

The majority of non-steroidal medications tried in vasculitis have first been tested in the benchmark inflammatory disorder of rheumatoid arthritis (RA). Unfortunately, none of the drugs proposed so far to treat GCA and TA has conclusively been demonstrated to have major efficacy as adjunctive therapy, let alone proved able to replace GC, unlike what has happened in RA.

Azathioprine (at a daily dosage of 150 mg) showed some steroid-sparing action in a small randomised controlled trial (RCT) involving 31 patients with GCA, polymyalgia rheumatica, or both. However, a significant (modest) difference in the mean prednisolone dose was noted between the azathioprine and the placebo arm only at week 52 (4). In an open-label trial containing 15 patients with active TA, azathioprine (2 mg/kg/day) together with prednisolone completely resolved clinical symptoms without progression of lesions at 1-year follow-up angiography (5). However, no RCT has formally investigated the efficacy of azathioprine in TA.

The efficacy of methotrexate in GCA has been investigated by three RCT, which have produced somehow conflicting results (6-8). A meta-analysis based on these RCT subsequently concluded that adjunctive methotrexate at a mean dose of 11 mg weekly reduced the risk of a first relapse by 35% and of a second relapse by 51% (9). Cumulative GC dose was lower by 842 mg within 48 weeks in the methotrexate-treated group; nevertheless, the incidence of GC-related side effects was similar in both groups. The efficacy of methotrexate (10-15 mg/week) as add-on therapy has also been reported in a series of five patients with PMR associated with large-vessel GCA requiring a mean prednisone dose of 13.1 mg/day (10). Combined treatment of GC and MTX resulted in improvement of clinical features and laboratory parameters, while mean daily prednisone requirement decreased from 13.1 to 7.9 mg. There are no RCT on methotrexate in TA, but an open study on 18 GC-resistant patients showed that add-on methotrexate therapy was able to maintain remission in about half of cases (11). Uncontrolled observations also suggests some efficacy for cyclophosphamide in active TA and GCA (12, 13) and mofetil mycophenolate (14, 15) in active TA, but the limited data available do not allow to arrive at definite conclusions regarding the magnitude of the benefit conferred by these drugs.

The advent of biological agents has opened up new possibilities in the treatment of various inflammatory disorders. However, even the "wonder weapons" TNF-α blocking agents, which have shown such remarkable efficacy in RA, have proved somehow blunt when turned against GCA and TA. In a RCT on 44 GCA patients that had achieved remission with GC,

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the TNF-α inhibitor infliximab was no better than placebo in maintaining remission and increasing the length of time to first relapse upon tapering of the GC dose (16). On a brighter note, in an open study infliximab was able to induce longstanding remission in 3 out of 4 GCA patients who had suffered relapses upon tapering the prednisone dose to 7.5–12.5 mg/day (17). A subsequent RCT involving 17 GCA patients who required prednisone doses of 10 mg daily or greater to maintain disease control tested the efficacy of etanercept 25 mg twice weekly against placebo (18). Etanercept allowed to discontinue prednisone therapy more frequently than placebo (although the difference did not reach statistical significance), while etanercept-treated patients had a significantly lower cumulative prednisone dose after 12 months of treatment. Taken together, this data suggests that TNF-α inhibitors may have a role in relapsing, but not in newly diagnosed GCA. Similarly, two open studies have demonstrated some efficacy of TNF-α blockade in refractory/relapsing TA. In one study, 10 out of 15 patients with relapsing TA achieved a complete, GC-free remission following institution of anti-TNF-α therapy that was sustained for 1–3 years (19), while in the other study TNF-α blockade led to GC-free remission in 15 out of 25 patients with refractory TA (20).

Recently, the recognition of the key role played by the proinflammatory cytokine interleukin-6 (IL-6) in large-vessel vasculitis has paved the way to pilot studies aimed at investigate the efficacy of the IL-6 receptor inhibitor tocilizumab. More specifically, IL-6 has been shown to be expressed in aortic tissue from patients with TA (21), while raised serum IL-6 levels have been reported in active GCA patients in correlation with disease activity (22). IL-6 is also known to induce the production of acute-phase reactants and to cause constitutional manifestations, both of which are characteristic features of large-vessel vasculitis (23). In 2008, Nishimoto *et al*. first reported on the effect of tocilizumab therapy in a patient with TA refractory to multiple immunosuppressants and requiring daily prednisone at a dose of 30 mg/day (24). Tocilizumab (4 mg/kg/weekly with a tapering scheme) rapidly improved clinical manifestations and laboratory parameters, while signs of vascular ischaemia were partially reverted. Another study published this year showed efficacy of tocilizumab (8 mg/kg/month) in seven patients with large-vessel vasculitis (5 with GCA and 2 with TA) (25). Of these seven patients, three were newly diagnosed, and four had a relapsing course when the prednisone dose was tapered below 7.5 mg/day. All patients achieved a rapid and complete clinical response and normalization of the acute phase proteins, while the prednisone dosage could be reduced within 12 weeks to a mean of 2.5 mg/day.

We have treated so far four patients with large-vessel vasculitis (2 with TA and 2 with GCA) with tocilizumab (8 mg/kg/month for six months). Two patients were treatment-naïve, while two had relapsing disease upon tapering of the GC dose. All our patients treated with tocilizumab showed a resolution of their clinical manifestations and normalisation of inflammatory markers, while vascular inflammation as assessed by ^{18F}-Fluorodeoxyglucose positron emission/computerised tomography significatly improved in all cases (manuscript submitted). This data suggests that tocilizumab could be a promising approach to treat both treatment-naïve and relapsing patients with large-vessel vasculitis.

What are the future prospects of therapy of large-vessel vasculitis? There is clearly a need to demonstrate in a more rigorous fashion the effectiveness of tocilizumab in a formal RCT. In addition, a RCT is also needed to investigate whether TNF-α inhibitors might be useful in relapsing large-vessel vasculitis, as uncontrolled studies seem to hint. There are open questions regarding the use of methotrexate: might methotrexate prove more effective when given at higher doses (20–25 mg/week) (26)? Should methotrexate be used earlier on in the disease course? The role of aspirin in GCA also warrants further studies. Two retrospective studies have suggested that aspirin might be useful to prevent ischaemic complications in GCA (27, 28), but this assumption has been challenged by other data (29, 30). A prospective, RCT is thus required to establish whether aspirin should be part of the management of GCA patients, particularly of those who are at risk of developing ischaemic complications.

Advances in the understanding of the pathogenesis of vasculitis are continually being made, and they will inevitably help to identify key molecules or cell subsets that play a role in triggering and/or maintaining disease activity. The demonstration of the dual role of Th17 and of Th1 cells in the pathogenesis of GCA is especially important, since GC can effectively suppress Th17, but not Th1 cells (31). This makes Th1 cells an attractive therapeutic target that could be well amenable to specific treatment. Finally, last but not least, more studies on revascularisation procedures are needed to define which are the best interventions to repair aneurysms and treat occlusions once these complications have occurred. Much progress has been made since GC were first introduced in the treatment of large-vessel vasculitis, but much also remains to be done to reach the goal of managing safely and effectively patients with this challenging disorder. Both inroads into the pathogenesis and a better understanding of the efficacy and safety profiles of existing drugs will help to provide better patients' care.

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