

Immunosuppressive treatment for giant cell arteritis: where do we stand?

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Giant cell arteritis (GCA) is the most common vasculitis in individuals aged 50 or over, with an estimated lifetime risk of 0.5% in men and 1% of women in the US (1). Glucocorticoids (GC) remain to date the mainstay of therapy for GCA. However, while GC act swiftly and effectively control both symptoms and ischaemic complications of GCA including visual loss, their flip side is the high rate of adverse effects (2), to which elderly subjects are particularly prone. There is thus a recognised, unmet need to develop therapeutic strategies to reduce as much as possible exposure to GC while retaining full clinical efficacy.

Recently, Yates *et al.* (3) published the results of a meta-analysis on the efficacy and safety of steroid-sparing agents in GCA. Inclusion criteria for the studies analysed were a diagnosis of GCA supported by a positive temporal artery biopsy (TAB) or the 1990 American College of Rheumatology (ACR) criteria and a randomised design with at least 20 participants. Their findings showed a marginal decrease in the frequency of relapses using either GC pulses at onset or methotrexate (MTX) as adjunctive treatment to GC. Patients treated with GC pulses (but not those receiving MTX) had a greater risk of infections. No definite recommendations could be made regarding the other agents investigated (hydroxychloroquine, infliximab, adalimumab and dapsone) because of negative results or methodology issues. In line with their own findings, Yates *et al.* noted elsewhere that “no steroid-sparing agents have been found to be more effective [than GC] (4).

The meta-analysis by Yates *et al.* follows on to the previous meta-analysis by Mahr *et al.* (5), which also showed a moderate beneficial effect for MTX in reducing the risk of relapses in patients with GCA treated with GC. Meta-

analyses of randomised controlled trials are considered the gold standard for guiding treatment, and the concordant findings of Yates’ (3) and Mahr’s (5) meta-analyses would appear to support the use of MTX as steroid-sparing agent in GCA. However, it is equally important to recognise that published evidence does require some interpretation in order to translate its findings into clinical practice.

Both meta-analyses of MTX in GCA are based on three RCT in which MTX was used as adjunctive treatment induction rather than in patients with relapsing disease (6-8). All these studies aimed to assess whether add-on MTX (used at ~similar doses, yielding a median of 11 mg/week across the three studies) could reduce the frequency of relapses when the GC dose was tapered. Because patients were randomly recruited and relapses were broadly defined in a similar manner across the studies, one would have expected similar results. However, only one of these trials showed a significant benefit for MTX in decreasing relapse rates and the cumulative GC dose (8), while the two others did not. One of the two trials that did not show a steroid-sparing effect for MTX enrolled only a limited number of patients, hence a type II error cannot be ruled out (7). On the other hand, in the trial by Hoffman *et al.* that also produced negative results alternate-day GC were allowed after the first three months of treatment (6). Because alternate-day GC have been mapped to high relapse rates, one might speculate that the MTX was unable to compensate for the insufficient GC coverage provided, which does not rule out a steroid-sparing effect for MTX when GC are given continuously. Taken together, these results suggest that MTX probably has some steroid-sparing effects in GCA, although – to use Yates’ words (4) – it is

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certainly no more effective than GC. In addition, the steroid-sparing properties of MTX failed to translate in a decrease in the incidence of GC-related adverse events. Therefore, despite the positive findings of Yates' (3) and Mahr's (5) meta-analyses, the rationale for using MTX as initial, add-on treatment in GCA remains questionable. It remains to be established whether higher doses of MTX (up to 20 mg/week) may be more effective and, perhaps even more importantly, whether MTX might be more effective in the subset of patients who suffer frequent relapses (9). On this line, it is worth noting that in RCT adjunctive TNF- α blockade provided no benefit over and above that of placebo in reducing relapse rates in patients with new-onset GCA (10), whereas it did prove able to reduce the cumulative GC dose in patients with relapsing GCA (11).

Lastly, among the biological agents, tocilizumab (TCZ) appears to hold promise in patients with GCA. So far, over thirty patients with GCA have been treated with the IL-6 receptor antagonist TCZ, about half of whom had cranial manifestations and half large-vessel involvement (12-14). A partial or complete response was achieved in over 90% of treated patients. Most patients had refractory disease and had already received GC and often other immunosuppressive agents, while in six patients TCZ was used as monotherapy. However, the number of patients with

ischaemic manifestations was small, while the results of controlled studies using IL-6 inhibitors are still pending.

We agree with Yates *et al.* that no medication has yet been demonstrated capable of replacing GC for the treatment of GCA (4). On the other hand, immunosuppressive agents might well have a role in the management of relapsing disease. So, while GC remain the cornerstone of treatment, adjunctive immunosuppressive therapy may be justified in those patients who have frequent relapses despite continuous GC therapy, particularly if they are at risk of, or have developed serious GC-related adverse events. Future studies will be able to tell whether steroid-free regimens could ever become part of our therapeutic armamentarium for GCA.

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