

Do we need treatment with tumour necrosis factor blockers for giant cell arteritis?

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For many years glucocorticoids (GCs) have been known to effectively suppress the clinical manifestations of giant cell arteritis (GCA), and prevent its ischaemic complications. GCs are still the treatment of choice for this disease. It is recommended that GC therapy be commenced as soon as the diagnosis of GCA is established. An initial dose of 40–60 mg/daily of prednisone (or equivalent) as a single or divided dose is generally found to be adequate in the vast majority of the cases.^{1,2} Higher-dose pulse GC therapy has been advocated by some for patients with recent or pending visual disturbances, but an observational study and a randomised controlled trial (RCT) failed to demonstrate superiority of pulse over oral GC therapy in preventing ischaemic complications.^{3,4}

The initial dose of GCs is usually given for 2 to 4 weeks until all reversible signs and symptoms have resolved and acute phase reactants are back to normal. Subsequently, the dose can be gradually reduced every 1–2 weeks by a maximum of 10% of the total daily dose. Because of the variability of the course of GCA, no fixed rules have been established regarding treatment duration. Most patients are treated for 1–2 years, but some with a prolonged or relapsing course may require low doses of GCs for several years.^{5–7} Clinical flares usually occur when the prednisone (or equivalent) dose is reduced to approximately 5–10 mg/daily.^{7–9} The benefit conferred by GCs needs to be balanced against the common and well recognised complications related to long-term GC use. In a population-based study of 120 patients with GCA, 86% of patients had adverse events including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastrointestinal bleeding, and

cataract.⁷ Adverse events were related to the age of patients and higher cumulative dose of GCs.

GCA-related cranial ischaemic complications, including vision loss and the less common cerebrovascular accidents cause irreversible damage. They are early manifestations of the disease but occur in less than 20% of patients.^{10–14} The risk of visual loss after initiating GC treatment is very low. In one study, Kaplan–Meier analysis showed that at 5 years the probability of new loss of vision after GC therapy was 1%;¹¹ in a second study visual loss occurred after therapy onset only in 1 (3.8%) of the 26 patients who developed this complication.¹⁰ Aortic aneurysm, aortic dissection, and large artery stenosis are late vascular complications of GCA that occur years after the onset of the disease, even after the completion of GC therapy. Furthermore, potentially catastrophic thoracic aneurysm and dissection occurs only in 7.6% and 1% of patients, respectively.¹⁵

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The prevention of vascular complications is the primary goal of treatment of GCA. However, the rarity of the development of ischaemic complications once GC therapy has been instituted and the late occurrence of other large vessel manifestations has made their prevention impractical as primary outcome in RCTs. Furthermore, much of the total morbidity of GCA is not related to the disease itself, but to the impact of long-term GC therapy in a population of elderly patients. Therefore, most treatment studies in which other drugs have been added to GCs have been aimed at early reduction of steroids while maintaining the suppression of GCA for the duration of time the disease evolves through its natural course to become inactive.

In previous investigations, a number of steroid-sparing drugs have been

evaluated.^{1,2} Only methotrexate (MTX), azathioprine and the tumour necrosis factor (TNF)-blocker infliximab have been tested in RCTs.^{8,9,16–19}

The three RCTs that have assessed the efficacy of MTX in recent-onset GCA arrived at different conclusions^{8,9,16} and have been the subject of a recent formal meta-analysis.¹⁷ This analysis suggested that adjunctive MTX treatment in dosages of 7.5–15 mg/week for GCA reduced the risk of a first relapse by 35% and of a second relapse by 51%. In addition, MTX reduced the cumulative exposure to GCs. However, the superiority of the treatment effect of MTX over placebo fully appeared only after a latency period of 24–36 weeks and there was no between-group difference in the occurrence of adverse events. Higher doses of MTX (20–25 mg/week) have not been adequately studied.

The benefit observed in the azathioprine treated patients appeared to be unimpressive and of late onset.¹⁸ Furthermore, this study was limited by the low number of patients enrolled and by the fact that patient population included patients with polymyalgia rheumatica (PMR) and GCA.

Finally, a recently published RCT showed that adding infliximab to GCs provided no measurable benefit in the management of newly diagnosed GCA.¹⁹ A second study with a similar trial design found no statistically significant benefit of TNF α blockade with infliximab in newly diagnosed PMR, which is a condition closely related to GCA.²⁰ Thus, to date GCs remain the only clearly dependable drug in GCA.

The study by Martinez-Taboada *et al* in this issue (*see page 625*) tested the hypothesis that TNF inhibition with etanercept could reduce GC exposure in patients with GCA with refractory disease requiring a stable dose of prednisone ≥ 10 mg/day for maintaining clinical remission and with at least one GC-related side-effect.²¹ The investigators randomly assigned 17 patients with GCA treated with prednisone ≥ 10 mg/day to receive etanercept 25 mg twice weekly or placebo. Eight patients were randomly assigned to receive etanercept and nine to placebo. The duration of the double-blind placebo controlled trial was 12 months. Subsequently the experimental medication was stopped and the patients were followed an additional 3 months. The primary outcome measure was the proportion of patients no longer taking prednisone at 12 months. Secondary outcomes were the cumulative

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prednisone dose, the number of disease flare-ups, the number of new GC-related side effects or worsening of previous side effects. To justify the relative small sample size, the authors designed their study to detect a large effect of etanercept (a fourfold increase of the percentage of patients no longer taking prednisone in the etanercept group). The results showed that patients in the etanercept group were more successful in discontinuing prednisone therapy (although the difference was not significant) and they required a significant lower cumulative prednisone dose ($p = 0.03$) after 12 months of treatment. In addition, only one patient treated with etanercept discontinued the study due to lack of efficacy compared to six patients in the placebo group. By contrast, there were no differences in the number and type of adverse events. Although the minimum defined sample size was not achieved in the study, these findings may not be only explained by chance. Although not definitive, the findings suggest that TNF α blockade with etanercept suppresses disease activity in refractory GCA.

Can the results of this study be reconciled with the two previous RCTs that showed no effect of anti-TNF α therapy with infliximab in GCA and PMR?

The three trials were designed in a similar fashion to detect a large effect of anti-TNF α drugs and they were adequately planned and conducted.^{19–21}

The major differences between the infliximab and etanercept trials are related to the respective study populations. In the two infliximab trials the subjects enrolled were patients with newly diagnosed disease,^{19, 20} while in the etanercept trial they were patients with refractory GCA (still treated with a median dose of 15 mg/day of prednisone after 10 months, median duration, of GC therapy).²¹ The efficacy of TNF blockers in patients with relapsing disease has a possible pathophysiological rationale. In fact, an elegant study by Hernandez-Rodriguez and colleagues has shown that high TNF α production was associated in GCA with longer steroid requirements and relapsing disease.²²

It is possible that TNF-blocking agents might be mainly effective in patients with GCA and PMR with relative GC-resistant disease, while their efficacy is less clear in patients with non-relapsing disease in whom TNF has a more limited pathophysiological role.²³ The short follow-up period and the small sample size of the two infliximab trials raise the possibility that these studies might have been unable

to capture the treatment effect in patients with relapsing disease who represent the 30–50% of newly-diagnosed patients.^{1, 5–7} Furthermore, three open pilot studies support the results of the study of Martinez-Taboada and colleagues.^{24–26} These studies reported that TNF blockade with infliximab or etanercept was effective in reducing GCs requirements in patients with longstanding, relapsing GCA and PMR.

If TNF blockers do have a place in the treatment of relapsing GCA, when should they be started and how long should they be given? Unfortunately, at the present time no consistently reliable predictors of relapsing disease in GCA have been found. There is some evidence that interleukin 6 (IL6) may be more sensitive than erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as disease-related acute phase reactant and therefore be a better predictor of disease flare, however currently this test is not readily available in most laboratories.^{27–29} Anti-TNF drugs are very expensive and potentially toxic. Furthermore, the clinical significance of the lower cumulative GC dose observed by Martinez-Taboada *et al* in patients with GCA treated with etanercept is unclear, because they did not observe less GC-steroid related morbidity.²¹ Therefore, at least at the present time, anti-TNF therapy might be considered in patients with longstanding GC-resistant GCA who are at risk of GC-related adverse events but few others. Although Martinez-Taboada *et al* observed no relapses in patients with GCA after stopping etanercept for 3 months at the end of their study, it would be helpful to know if the effect is more persistent. A larger trial with longer follow-up is needed to determine if TNF blockers are able not only to reduce the cumulative GC dosage but also to decrease GC-associated morbidity.

Although the trial by Martinez-Taboada *et al* suggests that TNF α inhibitors are helpful in a subset of patients with GCA who have longstanding, recalcitrant disease, there is need of new effective treatments for all with GCA and PMR. There is evidence that cytokines different from TNF, such as IL6, may play a major role in the pathophysiology of GCA and PMR. Increased production of IL6 is typically found in patients with GCA, and GC rapidly reduces levels of IL6. IL6 seems to be a sensitive indicator of disease activity in GCA and PMR, in particular patients with persistently elevated levels are at higher risk of developing relapse/

recurrence.^{27–29} Therefore, IL6 inhibition with tocilizumab (humanised monoclonal anti-IL6 receptor antibody) may be a logical target for future RCTs.³⁰ Other possible therapeutical agents include rituximab, an anti-CD20 monoclonal antibody,³¹ and abatacept, a recombinant fusion protein that modulates CD28-mediated T cell co-stimulation.³²

Another avenue to explore is the development of a more effective way to use GCs. A smaller RCT showed that intravenous pulse methylprednisolone (15 mg/kg/day for 3 days) given at onset of therapy allowed more rapid tapering of the GC dose over the ensuing weeks and resulted in a higher frequency of discontinuation of oral GC therapy, whereas a larger trial with lower pulse doses did not show an additional benefit over oral GCs.^{3, 33} Additional investigations are needed on the use of pulse GC at the onset of treatment for GCA to confirm whether this regimen may reduce GC toxicity. Treatment with alternate-day GC administration has also been proposed to reduce the risk of GC-related adverse reactions, but in a RCT it has been shown to be associated with a higher rate of treatment failure (70% vs 20%), and is thus not recommended.³⁴ Initial treatment with low-dose (10–40 mg/day) prednisone has also been proposed to reduce the risk of GC-related adverse events, however it has been tried in too few patients to allow confident conclusions to be reached.^{35, 36} Therefore, multi-centre RCTs need to be organised to define the minimal effective starting GC dosage. Measures to prevent GC-induced osteoporosis should be considered in all patients.³⁷

Finally, the continuous advancements in understanding the molecular mechanisms involved in the pathogenesis of GCA and PMR, together with the availability of new treatments that can specifically inhibit single molecules or pathways, will provide the development of new therapeutic approaches.

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