A Contemporary Take on How to Treat Giant Cell Arteritis in 2025

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INTRODUCTION

Giant cell arteritis (GCA) is the most frequent primary systemic vasculitis in adults, involving medium-to-large-sized vessels. It occurs almost exclusively in individuals over the age of 50 years, with the highest incidence in those in their 70s. Clinical manifestations of GCA vary widely and are partly determined by whether the patient primarily has cranial (e.g., temporal arteritis) and/or large vessel involvement (e.g., aortitis).[1,2] Treatment goals are to alleviate patient symptoms, prevent acute (e.g., vision loss) and late (e.g., aortic thoracic aneurysms) complications, and reduce the risk of relapses while minimising treatment-related toxicities. However, the ideal strategy for both treatment and disease monitoring remains a topic of intense research and significant debate. This feature focuses on the contemporary management of GCA, highlighting recent advancements and remaining knowledge gaps.

GLUCOCORTICOIDS

Glucocorticoids (GC) have been widely used since their discovery in the 1940s and remain the cornerstone of treatment for GCA based on observational data and considerable clinical experience.[1] For active GCA, the recommended starting dose of oral GCs is around 1 mg/kg/day of prednisone (typically ranging between 40–60 mg).[2-4] Early introduction of high-dose GCs is critical to prevent cranial ischaemic complications and results in swift symptomatic improvement, usually within 48 hours. The role of initial high-dose intravenous GCs (e.g., methylprednisolone 0.25–1 g/day for 3–5 days) remains controversial but is often used in patients presenting with cranial ischaemic complications (e.g., vision loss or stroke). High-dose GCs can typically be tapered after 2–4 weeks, provided the patient is improving. The dosage is then gradually decreased to the lowest effective level to prevent relapses and minimise side effects. Comparative data regarding the optimal tapering regimen and duration of therapy

are scarce. Clinicians typically aim for a prednisone dose of approximately 15–20 mg after 3 months and 0–5 mg by 12 months. GCs are generally continued for an average of 18 months when used as monotherapy in order to improve the chances of remission and reduce relapse risk.[2-4] Relapses are common when GCs are tapered and/or shortly after their discontinuation, and prolonged use of GCs often leads to treatment-related toxicities.

TOCILIZUMAB

IL-6 is a pro-inflammatory cytokine and acute-phase protein that plays a vital role in GCA, with elevated levels observed in histopathologic specimens of temporal arteries. Increased serum concentrations are thought to reflect disease activity. Tocilizumab (TCZ), a monoclonal IL-6 receptor antibody, has proven effective in treating GCA.

In a Phase II RCT, intravenous TCZ showed higher rates of complete remission and relapse-free survival compared to placebo.[5] The GiACTA trial, a subsequent Phase III RCT of 251 patients with new-onset or relapsing GCA, compared subcutaneous TCZ combined with a 26-week prednisone taper schedule with prednisone monotherapy. At Week 52, sustained remission was achieved in 56% of patients treated with weekly TCZ and 53% with biweekly TCZ, compared to 18% of those treated with prednisone monotherapy.[6] This pivotal trial confirmed that TCZ decreased the risk of relapse and provided a significant GC-sparing effect, leading to its FDA approval for GCA in 2017. There is a growing consensus that, in the absence of contraindications, a new diagnosis of GCA should be treated with first-line TCZ and rapidly tapered GC.[4] Otherwise, early introduction of TCZ should be considered in patients with relapsing disease, large vessel involvement (linked to prolonged course and higher relapse risk), or those at greater risk of GC toxicities.[2-4]

However, in the GiACTA extension study, only 42% of patients treated for 1 year with weekly TCZ maintained a complete remission 2 years after stopping therapy.[7] This further demonstrated the persistent nature of GCA and showed that over 50% of patients relapse after discontinuing TCZ. While the ideal duration of therapy is unknown, TCZ is commonly administered for at least 1 year, with many patients receiving a longer course of therapy to prevent relapses. The optimal approach to stopping TCZ remains controversial. Some experts consider bridging with methotrexate, while others simply stop TCZ after 1–2 years, and then closely monitor patients off therapy, possibly reducing the dosage frequency (e.g., weekly to every-other-week), as tested in the MAGICA study.[8]

To date, no prospective comparative trials have examined the optimal GC tapering regimen in patients treated with TCZ. In the GUSTO study, which assessed the efficacy of shorter GC protocols, 18 patients received 3 days of intravenous methylprednisolone followed by TCZ monotherapy, which was given as a single intravenous dose, followed by weekly subcutaneous injections for 52 weeks. Within 24 weeks, 78% of patients achieved remission. At Week 52, 72% had not relapsed, although one patient was affected by anterior ischaemic optic neuropathy.[9] In another study, 30 patients received an 8-week GC taper alongside weekly TCZ.[10] All patients entered remission within a month, with 77% remaining in remission without GC at Week 52. While these findings are promising, more studies are required to assess the safety and efficacy of this approach.

METHOTREXATE

Three older RCTs, conducted before the TCZ era, assessed the use of methotrexate in GCA. A meta-analysis of these trials combining data from 161 patients suggested a modest reduction in relapse rates and cumulative GC use.[11] Of note, the methotrexate doses in these studies (7.5–15 mg/week) were less than those traditionally used in other systemic vasculitides. Although methotrexate has somewhat fallen out of favour in the initial management of GCA since the approval of TCZ, more evidence is needed; however, it could remain an alternative when TCZ is not tolerated or

available. The ongoing METOGiA trial will compare higher dosing of subcutaneous methotrexate (0.3 mg/kg/week up to 20 mg/week) with weekly TCZ to prevent relapses in GCA.[12] The METEORITICS trial will assess the efficacy of methotrexate maintenance therapy in patients who have previously received GCs and at least 6 months of TCZ. Other conventional immunosuppressants, such as leflunomide or azathioprine, and the alkylating agent cyclophosphamide, have limited evidence supporting their use in GCA.[13,14]

JAK/STAT SIGNALLING PATHWAY

The inhibition of the JAK/STAT signalling pathway in GCA aims to downregulate the effects of inflammatory cytokines (IL-6, IL-12, IL-23, and interferon-γ), thus reducing T cell activity. The recently published SELECT-GCA trial, a Phase III RCT, examined the role of the JAK inhibitor upadacitinib in 428 patients with relapsing or newly diagnosed GCA. Patients were randomised to oral upadacitinib (7.5 mg or 15 mg/day) plus a 26-week GC taper, or placebo plus a 52-week GC taper. At Week 52, the 15 mg/day dose significantly improved sustained remission rate (46% versus 29%) and conferred a substantial steroid-sparing effect, without unexpected safety signals.[15] In light of these data, upadacitinib was approved in Europe for GCA in early 2025. Its position in the treatment algorithm, relative to other GC-sparing agents like TCZ, has yet to be determined, but will likely depend on patients' comorbidities and preferences. Although there are ongoing concerns about a potentially increased risk of cardiovascular and thromboembolic adverse events with JAK inhibitors, this signal was not found in the SELECT-GCA trial. In the authors' view, TCZ may be preferred for patients with cardiovascular risk factors, established cardiovascular disease, or prior thrombotic events, while upadacitinib could be favoured for those who prefer oral therapy over subcutaneous treatment.

OTHER INVESTIGATIONAL DRUGS

Other biological therapies are being explored in GCA, and while some have shown promising results, additional research is needed. Mavrilimumab is a monoclonal antibody that blocks the granulocyte macrophage colony-stimulating factor (GM-CSF) receptor. In a small RCT involving 42 patients with GCA, mavrilimumab improved time-to-flare and sustained remission compared to placebo when combined with a 26-week GC tapering schedule.[16]

Given the detection of activated CD4+ T cells in temporal artery infiltrates, and the upregulation of T helper Type 1 and T helper Type 17 pathways in GCA, a trial of abatacept, a T cell costimulation blocker, was proposed. In this RCT, 49 patients were given GC and intravenous abatacept for 3 months, and then randomised to continue abatacept or switch to placebo. Relapse-free survival after 1 year was achieved in 48% in the abatacept group compared to 31% in the placebo group, which reached borderline statistical significance.[17] A larger trial on abatacept, the ABAGART study, is currently underway.[18]

T cells producing IL-17 and interferon-γ are detected in the arterial tissue of patients with GCA. In a Phase II RCT, 52 patients with GCA were randomised to either secukinumab, a monoclonal antibody targeting IL-17A, or placebo, with a 26-week GC taper. Bayesian analysis showed that 70% of patients achieved sustained remission through 28 weeks with secukinumab, compared to 20% with placebo.[19]

Ustekinumab targets the T helper Type 1 and T helper Type 17 pathways implicated in GCA by inhibiting IL-12 and IL-23. However, a clinical trial investigating ustekinumab in GCA was terminated prematurely due to high relapse rates.[20]

MONITORING AND RELAPSE MANAGEMENT

Disease monitoring involves tracking clinical signs of GCA, treatment-related toxicities, and inflammatory markers like C-reactive protein (CRP), sometimes alongside

imaging. Notably, an increased CRP level without accompanying clinical symptoms or worsening imaging should not automatically lead to an increase in GC dose. Close monitoring is essential, and investigation into other potential causes of elevated CRP (e.g., infection) should be pursued. Of note, TCZ suppresses acute phase reactants, preventing the use of CRP as a reliable biomarker of disease activity in patients treated with IL-6 receptor antagonists.

Periodic imaging studies (e.g., CT angiogram) should be performed in large vessel disease to detect the progression of structural damage, but the optimal interval for imaging remains unknown. The use of PET/CT and colour Doppler ultrasonography of the temporal arteries to monitor disease activity remains an evolving area of research and is beyond the scope of this feature.[21] Defining a relapse also remains a topic of significant debate, particularly with the increasing use of imaging techniques (PET/CT, ultrasound, MRI, and CT angiograms). The proper use of imaging for follow-up is unclear, especially in patients who are asymptomatic. As a rule of thumb, relapse is often considered in the presence of two signs of disease activity, either by clinical presentation, inflammatory markers, or imaging.

For example, the authors do not systematically intensify immunosuppression in patients who are asymptomatic with persistent vascular uptake on PET/CT, especially when inflammatory markers are normal.

Severe relapses (e.g., visual symptoms) are typically treated by reintroducing high-dose GC. In contrast, minor relapses (e.g., polymyalgia rheumatica) can generally be managed by increasing the daily prednisone dose by 5–10 mg or to the last effective dose. In the event of a relapse, introducing a GC-sparing agent should be considered if one has not already been initiated.[2-4]

CONCLUSION

The management of GCA has made significant strides with the introduction of TCZ. Nevertheless, relapses and GC-related toxicity continue to pose considerable challenges. While emerging immunomodulatory agents such as JAK inhibitors show promise, further research is essential to refine treatment plans based on individual patient characteristics and improve quality of life for patients with GCA.

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