Treating giant cell arteritis

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Giant cell arteritis (GCA) remains a rheumatology emergency. Critical ischaemia of the temporal arteries can lead to anterior ischaemic optic neuropathy and irreversible sight loss. This is a significant cause of morbidity among these patients, not least due to subsequent loss of independence and depression. If the symptoms of GCA are recognised promptly and treated appropriately, then the incidence of this catastrophic event could be reduced.

There is increasing evidence regarding the efficacy and positive outcomes of ‘Fast Track Pathways’. This is a process whereby patients are offered rapid access to specialist clinical assessment, with the goal of providing a secure diagnosis in as many patients as possible. Glucocorticoid (GC) therapy can then be continued or importantly stopped if inappropriate. Evidence from current services of this type has shown significant reduction in morbidity. For example, at Southend Hospital, the incidence of sight loss has been reduced from 37% to 9%.1 Similar results have been replicated in other centres.

Presentation and classification

In clinical practice, it is clear there are subgroups within GCA. Recognition of these subgroups is important to determine additional investigations and management. It is no longer sufficient to label this simply as a ‘headache’ disease. Some patients may have isolated cranial GCA, presenting with headaches and ischaemic symptoms such as jaw or tongue claudication and uniocular visual disturbance. However many are found to have more extensive large vessel involvement, termed large vessel giant cell arteritis (LV-GCA). With the advent of improved imaging techniques, the estimated prevalence of this group is greater than previously recognised; 12–37% depending on the modality used.2

A clinical suspicion of LV-GCA can be prompted by patients presenting with more predominant constitutional symptoms, including unintentional weight loss, and night sweats and fevers, or in patients who have already developed symptoms of vascular compromise such as limb claudication secondary to stenotic disease. In reality, there is a significant degree of symptom overlap between cranial GCA, LV-GCA and polymyalgia rheumatica (PMR), and it may be more accurate to think of them as a spectrum of disease rather than discrete conditions.3

Another clinically significant method of classification is ‘response to treatment’. Figure 1 divides patients into four groups: remission; relapse; refractory disease; and adverse effects or intolerance.4 It is these latter three groups, outlined in the red box, for which there is currently an unmet need for effective disease modifying and glucocorticoid-sparing treatment. Observational cohort studies report flares in 34–62% of GCA patients, with only 15–20% achieving sustained remission with GC alone.3
Investigations

Advances in vascular ultrasound (US) have transformed the management of GCA in recent years. EULAR now recommends it as the first-line investigation in acute GCA if there is appropriate equipment and expertise available. Vascular US forms a significant part of ‘Fast Track Pathway’ clinics, as it potentially offers a ‘one-stop shop’ for investigation and treatment. Vascular US can detect characteristic sonographic findings, which allows for a diagnosis of GCA without the need to progress to temporal artery biopsy (TAB). Specifically the ‘Halo’ sign is indicative of an acutely inflamed vessel wall. This is seen as a homogenous, hypo-echoic wall thickening, which should be appreciable in both the longitudinal and transverse planes, and does not disappear on compression with the ultrasound probe.

Vascular US has multiple advantages. Visualising the entire length of the temporal arteries bilaterally can give increased sensitivity compared with TAB, as it minimises the problem of skip lesions. Furthermore, it is widely available and well tolerated by patients. There is also reasonable evidence to suggest that additional ultrasound of the axillary and subclavian arteries assessing intima-medial complex thickness would be a useful screening tool for LV-GCA. At the axillary artery, an intima-medial complex >1.0mm is considered abnormal. US changes in acute GCA typically start to diminish after initiation of glucocorticoid treatment; however observed changes at the axillary arteries can persist for months. The role of vascular US in monitoring and follow-up is yet to be determined. Further studies on the persistence of sonographic findings and effect of glucocorticoids are required.
Cross-sectional imaging may be useful for assessing disease extent in LV-GCA, as well as monitoring vascular complications. However, there is currently no consensus on the best modality. This is a decision that is influenced by practical constraints as well as clinical considerations. 18F-FDG PET-CT, MRI and CT have all been utilised. High-resolution MRI has comparable sensitivity and specificity to TAB in detecting GCA, as well as identifying cranial vessel involvement other than the temporal artery. However, these facilities are not widely available. 18F-FDG PET-CT attributes the FDG signal to a precise anatomic location, and is therefore useful in establishing disease extent and severity.

It is particularly useful in situations where there is ongoing concern of LV-GCA despite prior negative tests, or to exclude differential diagnoses such as infection or malignancy. Although it should be interpreted with caution because FDG signal is attenuated by glucocorticoid use and increased with vascular re-modelling and atherosclerosis. This could lead to under- and over-diagnosis of active inflammation, respectively.

**Treatment options in GCA**

Initial treatment of new onset GCA remains high-dose glucocorticoids, at a dose of either 1mg/kg, or a dose equivalent to 40mg prednisolone for uncomplicated disease and 60mg prednisolone for those with ischaemic and sight-threatening presentations. Methyprednisolone pulses may be required initially for those with severe visual complications. Yet the traditional view that this will provide a complete response in all patients is not borne out in clinical practice. From the GiACTA trial baseline data, 17% of the overall cohort was classified as having disease refractory to glucocorticoids. In PMR, a related condition, some groups of patients also respond less well to glucocorticoids, with only 45–55% having a complete response, 25–27% with a partial response and 15% with no response respectively. GCA patients typically exceed a cumulative dose of 5000mg prednisolone over several years.

In a large UK retrospective study the average cumulative prednisolone use over the first two years from diagnosis was 8600mg; however, 33.4% received over 10,000mg and 3.3% more than 25,000mg. It is estimated that for every 1000mg cumulative increase in GC dose, the adverse event hazard ratio increases by 3%. Unfortunately, this does not treat the underlying inflammation and contributes to a higher incidence of steroid related side effects, estimated to affect 85% of patients with LV-GCA. These side effects include diabetes, glaucoma, cataracts, hypertension, heart failure, osteoporosis, mood disturbance and increased susceptibility to infection, but this is not by any means an exhaustive list.

GCA cohorts are particularly vulnerable due to their older age and higher prevalence of comorbidities. EULAR taskforce recommendations suggest the risk of harm is low for the patients at long-term dosages of ≤5mg prednisone equivalent per day, whereas at dosages of >10mg/day, the risk of harm is elevated. Between 5 and 10mg, the risk of harm is dependent on additional patient-specific factors. Not only are patients with relapsing and refractory GCA at higher risk of adverse effects secondary to toxic levels of glucocorticoids, but by definition the disease is sub-optimally controlled. This can lead directly to vascular damage such as aneurysms, dissection, rupture and stenotic disease. As such, the clinical and economic burden of these sub-groups is amplified.
There remains a large unmet need for effective glucocorticoid-sparing agents. Currently there is no good evidence for cDMARDs in GCA. One meta-analysis based on three small randomised-controlled trials (RCTs) suggested a role for methotrexate. However its addition did not help to significantly reduce cumulative glucocorticoid dose or morbidity and mortality. There are case series recommending the use of leflunomide and mycofenolate mofetil, but these are yet to be tested in an RCT setting. Trials of biologic agents in GCA have had varying success. To date, no role has been found for use of anti-TNF agents, with infliximab, etanercept and adalimumab showing inefficacy.

Tocilizumab, an IL-6 receptor blocker, now has a good evidence base. IL-6-driven inflammation has been implicated in GCA since first described by Dasgupta and Panayi in 1990; however, it was not until recently that an agent utilising this pathway was available in GCA. In the Phase III trial, GiACTA, 119 newly diagnosed and 132 relapsing patients were randomised to receive either weekly or fortnightly subcutaneous tocilizumab with a 26-week prednisone GC taper, versus the placebo arms with a 26- and 52-week prednisone taper alone. Sustained prednisone-free remission was achieved in 56% and 53% of the weekly and fortnightly tocilizumab groups, respectively, compared with only 14% and 18% in the 26-week and 52-week placebo arms, respectively.

Importantly, the cumulative prednisone dose was significantly lower in the treatment arm. Based on these results, tocilizumab has now been licensed for use by the US FDA and NICE in the UK. However, even in GiACTA, there were patients who did not achieve remission on tocilizumab, and it is not certain about its long-term impact on vascular damage. Other trials using biologics such as abatacept are currently ongoing, and we await the results. Ultimately there is still more work to be done in finding alternative treatments.

Conclusions
Introduction of ‘Fast Track Pathways’ can offer a prompt and secure diagnosis, reducing morbidity in patients with GCA and minimising inappropriate glucocorticoid use in those who do not. Vascular US is a promising and rapidly developing area in GCA and LV-GCA diagnosis, potentially avoiding the need for further invasive investigations such as TAB.

There is a large unmet need beyond glucocorticoids in GCA and LVGCA. There are some new promising treatments, including biologic therapies such as tocilizumab, but this will not be suitable for every patient. Further robust RCTs of other glucocorticoid-sparing agents are required.

References

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