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Giant Cell Arteritis: New concepts, treatments and the unmet need that remains.

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This is an exciting time for the management of giant cell arteritis (GCA). The National Institute for Health and Care Excellence (NICE) and NHS England have approved Tocilizumab (TCZ), an IL-6 receptor inhibitor, for use in GCA. However, it is restricted to refractory and relapsing disease, those who have not received TCZ previously, and for a maximum of one year (1). These stipulations highlight the importance of disease stratification based on severity, extent and damage.

The traditional view of GCA as a glucocorticoid (GC)-responsive disease is not accurate. Instead there is a spectrum of severity. Observational cohort studies report relapses in 34-62% of patients, with 15-20% achieving long-term sustained remission with GC alone (2). Patients can be separated into four sub-groups according to treatment response: remission, relapse, refractory disease and adverse effects or GC-intolerance (3). The last three groups exhibit the greatest unmet need for adjunctive therapy (Figure 1).

Representatives from the British Society for Rheumatology, Royal College of

Ophthalmology and the MRC TARGET consortium (a multi-speciality partnership for improving GCA outcomes) collaborated with NHS England to develop consensus definitions of 'relapsing' and 'refractory' disease. Otherwise, there is concern TCZ might be used inappropriately, causing issues with interpretation of post-marketing data. This is crucial since TCZ use will be reviewed again in 2-3 years. To mitigate this, a 'Multi-Disciplinary Team' approach has been advocated, whereby cases should be discussed at a regional level and potentially entered into a national or international registry.

Confirmation of GCA should be standard practice. EULAR guidelines recommend vascular ultrasound as the first diagnostic test given adequate expertise and equipment, and if not available temporal artery biopsy (4). Positive test results give reassurance regarding diagnostic accuracy, particularly if there are treatment complications or inadequate response. Fast-Track Pathways have proven an effective method of achieving rapid specialist assessment, reducing the incidence of complications such as sight-loss (5). Conversely, they also prevent unnecessary GC-therapy. It is important to recognise that ischaemic complications result predominantly from diagnostic delay rather than inherent disease severity (6). This delay is multifactorial, including older age of susceptible individuals, difficulty recognising non-cranial presentations and variable access to diagnostics.

'Refractory' disease has been defined as inability to induce remission in patients with a definitive GCA diagnosis despite optimal standard care. This especially applies to those with ischaemic signs or symptoms with a significant risk of end organ or vascular damage. 'Relapsing' disease is defined as a clear and evidenced recurrence of GCA symptoms or ischaemic complications, in those who previously responded to treatment. This can be with or without increased inflammatory markers for which no other cause has been identified (e.g. infection or neoplasia).

While NICE does not comment about GC side effects, patients should be considered 'refractory' when the maximum safe GC-dose for that individual is exceeded to control disease. GCA patients typically exceed a cumulative dose of 5000mg prednisolone over several years, with the adverse event hazard ratio rising by 3% for every 1000mg increase (7). Relapsing patients carry a higher cumulative GC-burden due to repeated dose increases. This contributes to a higher incidence of GC-related side effects, affecting up to 85% of GCA patients (2). These include diabetes, weight gain, glaucoma, cataracts, hypertension, heart failure, osteoporosis, neuropsychiatric effects and increased susceptibility to infection (7). GCA patients are particularly vulnerable because they are older and have a higher baseline prevalence of co-morbidities than the general population. EULAR taskforce recommendations suggest the risk of harm is low for long-term dosages ≤ 5 mg prednisone equivalent per day, increased for doses > 10 mg, and variable between 5-10mg, being dependent on patient-specific factors (8).

Another important concept is disease extent and vascular damage. With improvements in imaging such as ^{18}F FDG-PET-CT, MRI and CT angiography, the estimated prevalence of extra-cranial involvement is increasing, termed

large-vessel GCA (LV-GCA). LV-GCA may be less responsive to GC, so extensive vascular territory involvement, as in Takayasu arteritis, should be noted when considering suitability for adjunctive therapy for GCA. High aortic ¹⁸FDG uptake has been associated with increased likelihood of aortic dilatation (9). There is evidence that damage can progress even in seemingly stable disease (10). Therefore, those with refractory and relapsing LV-GCA may be at even greater risk of damage.

The unmet need for effective GC-sparing agents in GCA remains a significant problem. The phase III trial of TCZ (GiACTA), which formed the evidence base for its use, showed sustained GC-free remission in 56% and 53% of patients receiving weekly and fortnightly TCZ respectively, both with a 26-week GC-taper (11). This compared to 14% and 18% in the 26-week and 52-week GC-taper placebo-arms respectively. Until the extension data is available, use in England is limited to one year. Patients will subsequently require maintenance treatment if there is relapse on TCZ cessation (12). What form this should take is debated as there is currently no convincing evidence for conventional DMARDs in GCA. One meta-analysis of three randomised controlled trials (RCTs) suggested benefit from methotrexate. However there was no significant reduction in cumulative GC-dose, morbidity or mortality, and confidence in the effect size was low (2). There are promising case series of leflunomide and mycophenolate mofetil, but no reliable RCT data (2).

Disease activity assessment during TCZ therapy may be difficult due to suppression of the acute phase response. This may permit a potential disconnect between clinical remission and remission of vascular inflammation. Robust studies of different large vessel imaging modalities (e.g. ultrasound/cross sectional imaging) during the follow up of TCZ treated patients are therefore required.

We now have the opportunity to test the validity of these definitions in clinical practice. Stratifying patients according to disease severity, extent, damage and treatment response allows more appropriate targeting of therapies. However, it emphasises the remaining unmet need for resources to support timely assessment, imaging and treatments. Options are still limited, but it is hoped the wide approval of TCZ (within the UK, EU, Switzerland, USA) will be a catalyst for improving standards of care and robust trials of other cost-effective agents in GCA across the world..

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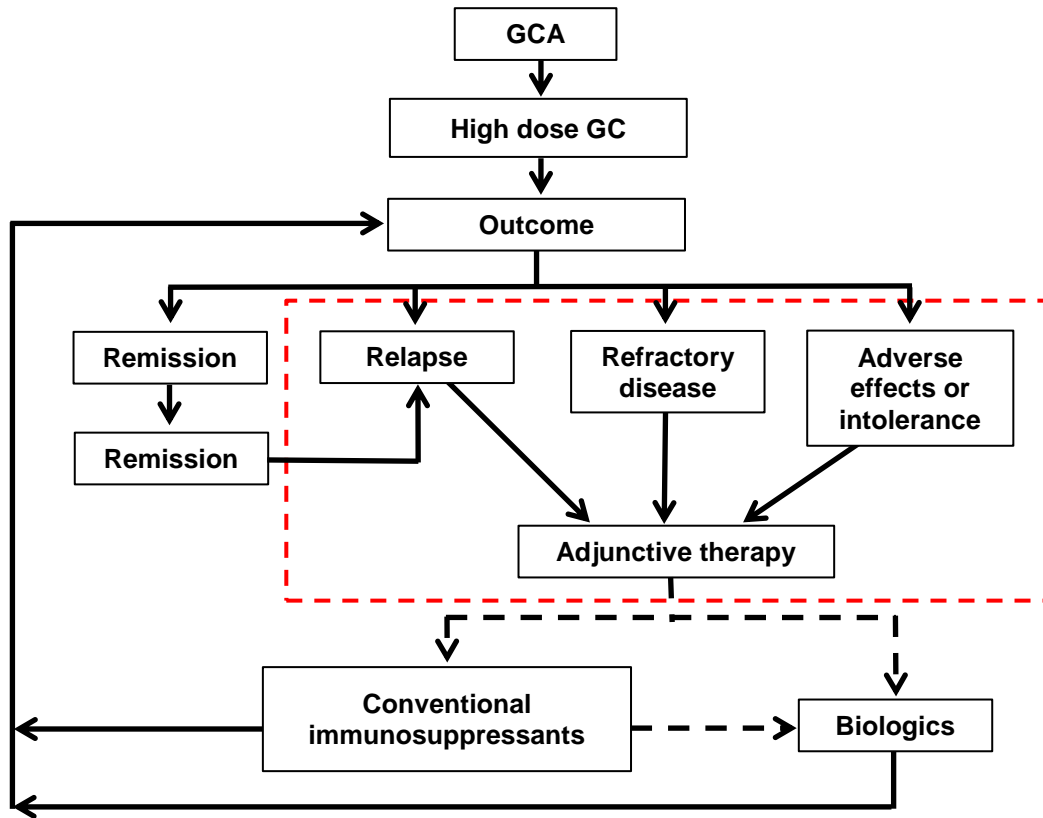


Figure 1. Adapted with permission from Kermani and Dasgupta; *Rheumatology (Oxford)* Oct 2017: Treatment algorithm for GCA, with the target group for TCZ highlighted in the red box.