Stratified glucocorticoid monotherapy is safe and effective for most cases of giant cell arteritis

Maira Karabayas1,2, Paula Dospinescu2, Marc Locherty2, Paul Moulindu3, Manvi Sobti3, Rosemary Hollick1,2, Cosimo De Bari1,2, Susan Robinson4, John Olson3, Neil Basu5

1 Aberdeen Centre for Arthritis & Musculoskeletal Health, University of Aberdeen, Aberdeen, UK
2 Rheumatology, NHS Grampian, Aberdeen, UK
3 Ophthalmology, NHS Grampian, Aberdeen, UK
4 Pathology NHS Grampian Aberdeen, UK
5 Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK

Correspondence to:
Maira Karabayas, Maira Karabayas
1 Mill of Forest House
Mill of Forest Road
Stonehaven
AB39 2LW
Scotland
Email: m.karabayas@nhs.net

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Key messages
- A stratified approach to glucocorticoid tapering is effective for most cases of GCA
- Glucocorticoid exposure can be aggressively, yet safely minimised in selected patients with GCA

Abstract

Objectives
High dose glucocorticoids anchor standard care in giant cell arteritis (GCA) but are associated with significant toxicity. We aimed to evaluate the safety and effectiveness of a stratified approach to glucocorticoid tapering. The strategy aggressively reduced glucocorticoid doses in those manifesting an adequate early response to treatment with view to minimising glucocorticoid complications.

Methods
A retrospective, population-based study of GCA was performed. All cases were confirmed by temporal artery biopsy between November 2010 and November 2015. Baseline and outcome data were extracted from secondary and primary care records at diagnosis and 1 year. The primary outcome was loss of vision. Secondary outcomes included remission and relapse rates as well as corticosteroid related complications.
Results
The cohort consisted of 73 patients (76% female; mean age 73.5, SD 7.6). At presentation reduction in visual acuity (VA) was recorded in n=17 (22.3%). Median CRP at diagnosis was 69.5mg/L (IQR 40.5-101mg/L) with median ESR 80mm/h (IQR 60-91mm/hr). At 1 year, remission was achieved in n=64 (87.7%) and n=10 (13.7%) relapsed. A single patient sustained visual loss following initiation of therapy. Median CRP at 1 year was 4mg/L (IQR 4-9.5mg/L) and mean Prednisolone dose was 5.4mg (0-15mg). Steroid related complications were observed in n=10(13.7%).

Conclusion
A stratified approach to corticosteroid tapering appeared safe and effective in GCA. It was associated with high rate of remission and promisingly low rates of relapse following 1 year follow up. This real-world data indicates glucocorticoid exposure can be safely minimised in some patients with GCA.

Introduction
Giant cell arteritis (GCA) is the commonest form of vasculitis in Caucasians. It predilects the cranial arteries with patients classically presenting with temporal headache, a spectrum of visual disturbance, jaw claudication and a degree of constitutional upset. The most catastrophic complication of the disease is loss of vision related to myo-intimal proliferation and subsequent vessel occlusion. This is typically unilateral but can be observed bilaterally and is often permanent. In historic cohorts, prior to the introduction of glucocorticoid therapy, visual complications were estimated in 35-60% of patients. However, more recent studies suggest that visual loss occurs in 13.2%-19.1% of glucocorticoid treated patients. Although the risk of visual loss significantly reduces once steroid therapy is initiated, in clinical practice the fear of inadequate therapy in relation to this complication may encourage excessive steroid use.

Historically, glucocorticoids (GC) have been the mainstay of treatment. A recent review identified a number of steroid regimens, although these have not yet been validated, and variability in steroid protocols in clinical practice remains an issue. Moreover, GC toxicity is an increasing concern with data attributing a significant proportion of morbidity to their adverse effects. A GCA cohort analysis showed a significant risk of adverse rates for every 1g increase in the cumulative GC dose (OR 1.17, 95% CI 1.06, 1.29).

Research initiatives are directed towards management strategies to reduce the overall burden of GC, without enhancing the risk of visual compromise. Evidence now supports an effective GC sparing role for modern biologics, although high financial cost limits their accessibility. In other forms of vasculitis, there is now data indicating that historical management protocols incorporate dispensable doses of GC. Aggressive tapering regimens appear to be equivalently effective but with preferable safety profiles. Similar evidence is lacking for GCA and was advocated as research priority in the 2009 EULAR large vessel vasculitis management recommendations.

Since 2010, our centre has employed an aggressive approach to GC taper with the view of minimising treatment related complications. However, in order to minimise the risk of visual compromise, patients slow to respond are stratified to receive a classical tapering regimen (figure 1). We have now conducted a retrospective study to examine the performance of this novel GC strategy.

Methods
We conducted a retrospective observational study on a population-based cohort of GCA in the North East of Scotland. Patients above the age of 50 with a positive temporal artery biopsy (TAB), as reported...
by the local pathology department, were included. No ethical approvals were required. The project was registered with local R&D.

All TABs carried out between November 2010 and November 2015 in the Grampian region of Scotland (population c550,000) were identified from a centralised pathology database. Electronic primary and secondary care records were interrogated to extract patient demographics and disease characteristics at time of diagnosis and outcomes at one year follow up. Individual primary care practices were contacted to determine an accurate Prednisolone dose at 1 year for each patient. Patient demographics included age, gender and smoking status. Baseline disease characteristics assessed included headache, visual disturbance, jaw claudication, constitutional upset and inflammatory markers at diagnosis. The primary outcome examined was loss of vision (defined as complete monocular visual loss) at 1 year. Secondary outcomes included rate of remission (defined as Prednisolone dose ≤ 7.5mg and complete resolution of symptoms), rate of relapse (defined as recurrence of symptoms requiring escalation of any immunosuppression) and corticosteroid related complications at 1 year.

In our region, all patients with suspected GCA are immediately started on Prednisolone 60mg in primary care and then fast-tracked to a central neuro-ophthalmology clinic. They are reviewed and clinically assessed within 2 days. TAB is undertaken at most within 2 weeks of diagnosis. All patients then follow the stratified steroid taper illustrated in figure 1. Patients are re-assessed between weeks 3-6 to determine adequate response (defined as complete resolution of symptoms and CRP <10 mg/L). When clinically appropriate, patients are discharged from the specialist clinic back to primary care with the recommended steroid taper as outlined above. All patients remain on 5mg until the anniversary of diagnosis. They further reduce by 1mg monthly until steroid cessation. In the event of any clinical concerns within primary care, patients are usually re-referred to the neuro-ophthalmology clinic.

The study was a clinical service evaluation and complied with local institutional governance.

**Results**

During the 5-year study period, a total of 329 TABs were performed. Of those, 246 were non-diagnostic and 83 were positive for GCA. Of the 83 positive cases, complete outcome data was available for 73.

Our final cohort consisted of 73 patients, 76% of which were female with a mean age at diagnosis of 73.5 (SD 7.6). At time of diagnosis, objective monocular reduction in visual acuity (VA) relating to GCA was recorded in n=17 (22.3%). More specifically, n=11 presented with anterior ischaemic optic neuropathy, n=3 with central retinal artery occlusion, n=2 with sixth nerve palsy and n=1 with posterior ischaemic optic neuropathy. However, n=39 (53.4%) reported subjective visual disturbance ranging from undifferentiated visual impairment (n=20) to blurry vision (n=10) and diplopia (n=8). Jaw claudication was reported in n=34 (46.6%) of the cohort, whilst n=37 (50.7%) described a degree of constitutional upset. On examination, n=20 (38.4%) reported temporal artery tenderness. All patients fulfilled ACR criteria 1990. At time of diagnosis, the median CRP was 69.5 mg/L (IQR 40.5-101 mg/L) and median ESR was 80mm/hr (IQR 60-91 mm/hr) (Table 1).

At 1 year, remission was achieved in n=64 (87.7%) of the cohort, whilst n=10 (13.7%) relapsed. The reported relapses were mainly in the form of headache and constitutional upset requiring temporary escalation in Prednisolone dose. A single patient sustained visual loss from initiation of therapy. The median CRP at 1 year was 4mg/L (IQR 4-9.5 mg/L), with a mean Prednisolone dose of 5.4mg (0-15mg).
and n=2 required additional immunosuppression. The mean discharge time from neuro-ophthalmology clinic was 18.3 weeks (SD 17 weeks) Steroid related complications were observed in n=15 (20.6%), cataract n=4, recurrent urinary tract infections n=3, thoracic wedge fracture n=2, avascular necrosis of femoral head n=1, pelvic fracture n=1, steroid induced diabetes n=1, steroid induced psychosis n=1, intra-abdominal sepsis requiring hospital admission n=1, osteoporosis n=1. Finally, the estimated cumulative Prednisolone dose for the aggressive steroid taper (group 1) was 2,997.5 mg, whilst the estimated cumulative dose for the slower group was 4,385mg. It was not possible to evaluate differences in outcomes between steroid regimens.

**Discussion**

In this single centre observational retrospective study of a service which employs an aggressive GC minimisation taper in early GC responders, visual loss was rare (1.4%), despite patients tapering to 20mg of prednisolone by 4 weeks. The majority of patients achieved disease remission (87.7%), whilst relapse was uncommon (13.7%).

Our low observed rates of visual loss align with those reported from another population-based cohort. Salvarani et al examined visual manifestations in Italian patients with biopsy proven GCA (n=136). They reported a single patient sustaining permanent visual loss 14 months from initiation of treatment\textsuperscript{14}. Aiello et al evidenced a 1% 5-year probability of developing new visual loss from initiation of therapy in an era where GC dosing was significantly higher\textsuperscript{2}.

Disease remission was achieved by 87.7% of the cohort. In general, existing literature indicates that only 15%–20% of patients achieve this disease state with GC monotherapy\textsuperscript{10}. Furthermore, our promisingly low rates of relapse (13.7%) also appear favourable in comparison to the extant literature, where typically rates between 34-74.5% have been reported\textsuperscript{15-16}. These discrepancies can be partly attributed to a few reasons. First, remission and relapse rates vary significantly within clinical trials and population-based cohort studies. These figures should be cautiously interpreted given the difficulty of adjusting for confounding factors such as disease duration, cumulative steroid use and follow up time. Second, there are significant variations in the definitions used for remission and relapse, which have only been recently standardised in the updated EULAR recommendations\textsuperscript{12}. Future studies will hopefully assess these newly homogenised outcomes in a more systematic manner to inform clinical practice. Third, our cohort consisted of patients presenting with cranial symptoms. It has been shown that cranial GCA is usually associated with a more monophasic disease course\textsuperscript{17}. That said, we did not routinely perform specialist imaging to confirm the presence or absence of extra-cranial artery involvement. Fourth, the majority of the literature is sourced from specialised centre sampling frames. More recent population level real world data evidence low relapse rates\textsuperscript{16}. Although this data aligns with our observations, it should be noted that this was a conference abstract publication with inherent limitations and potential methodical flaws that have not been peer reviewed. Finally, we speculate that our fast track service has enabled very early diagnosis, which allowed for the application of a stratified approach to glucocorticoid tapering, which in turn has conferred favourable long-term outcomes. Prognostic benefits of early therapy are certainly now established across other rheumatic disorders\textsuperscript{19}.

Adverse events relating to GC therapy at 1 year were prevalent. The estimated cumulative Prednisolone dose for the aggressive steroid taper (group 1) was 2,997.5 mg, a value which directly compares with the 26 week steroid placebo group (3,296mg) and significantly less than the 56 week steroid placebo group, in the GiACTA trial (3,818mg) and the group 2 steroid taper (4,385mg) which mirrors classical regimens\textsuperscript{11}. It is important to highlight that the values related to our cohort assume
full compliance with the taper protocol. Due to data capturing difficulties, we were not able to confirm this retrospectively for each individual patient to provide an accurate mean cumulative dose. Several other limitations should also be considered. Firstly, this study is retrospective designed and dependent on electronic records for data extraction. In our region, however, electronic records are centralised including laboratory, clinical and pathology records. In addition, a direct link between primary and secondary care made it feasible to capture a wide range of data. Incomplete data capture remained a challenge, it was for example not possible to confidently characterise group assignment. The mean discharge time from ophthalmology clinic to primary care was 18.3 weeks (SD 17 weeks) from time of diagnosis. Adherence to the standardised steroid taper was assumed in the absence of any referrals back to ophthalmology or rheumatology clinics or any relapses documented in primary care records. To account for that, we further contacted individual practices to obtain an accurate personalised Prednisolone dose at 1 year for all patients. Secondly, outcomes were only examined at one year and it is possible that we may have failed to capture later relapses. A longitudinal study cohort showed a mean time to first relapse 79+ 75 weeks (range 11-339), however 50% of these patients relapsed within the first year20.

Thirdly, in order to ensure our cohort consisted of patients with a true diagnosis of GCA, we elected to include only those with positive TAB. Due to the lack of TAB sensitivity, we may have missed cases. Our patient demographics align with epidemiological predictions predominantly affecting women (3.3:1) with a mean age at diagnosis of 73.5 (SD 7.6)21. A retrospective analysis examining the incidence of GCA in the United Kingdom between 1990 and 2001, suggested that the age standardised incidence ratio of GCA in Scotland is 67 (95% CI 54-82), a figure which directly compares to our cohort22. Taken together, we are likely to have captured a representative cohort. What transpires from this retrospective study is that having a centralised, fast track service allows the application of an aggressive stratified steroid taper to reduce cumulative steroid burden, whilst ensuring patient outcomes are optimal.

Although our study demonstrates reassuring outcomes, these findings are preliminary. Adopting this stratified steroid taper in different populations would be required to validate these observations further and correct for some of the limitations discussed. A larger prospective longitudinal study is desirable to more precisely quantify GC exposure and further characterise the morbidity relating to both disease and treatment. This would make it possible to differentiate and phenotypically characterise the two steroid taper groups, in an attempt to inform our future practice as the field finally moves towards to an era of personalised medicine.

**Conclusions**

In conclusion, in this retrospective observational study of a real-world population cohort in the North East of Scotland, a stratified approach to corticosteroid therapy, which leveraged initial treatment response as a method to triage patients towards aggressive steroid tapering, appears to be an effective model of GCA pathway. It was associated with high rates of remission and promisingly low rates of relapse at 1 year follow up. This real-world data suggests that glucocorticoid exposure could be safely reduced compared to classical regimens when integrated in fast track pathways with early specialist input.

**Figure legend**

**Figure 1: Steroid tapering protocol**
Baseline demographics and disease characteristics

|                          |         |
|--------------------------|---------|
| Mean age                 | 73.5 (SD 7.6) |
| Female                   | n=56 (76%) |
| ACR criteria 1990 fulfilled | n=73 (100%) |
| Headache                 | n=65 (89%) |
| Jaw claudication         | n=34 (46.6%) |
| Constitutional upset     | n=37 (50.7%) |
| Subjective visual impairment | n=39 (53.4%) |
| Objective reduction in VA | n=17 (22.3%) |
| Temporal artery tenderness | n=20 (38.4%) |
| Median CRP (mg/L)        | 69.5 (IQR 40.5-101) |
| Median ESR (mm/hr)       | 80 (IQR 60-91) |

Table 1: Patient demographics and baseline disease characteristics

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References

1) Soriano A, Muratore F, Pipitone N et al. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nautre Reviews Rheumatology. 2017; 13: 476-484. doi:10.1038/nrrheum.2017.98.

2) Aiello PD, Trautmann JC, McPhee TJ, et al. Visual prognosis in giant cell arteritis. Ophthalmology. 1993; 100: 550–5. doi:10.1016/s0161-6420(93)31608-8

3) Liozon E, Herrmann F, Ly K, Robert PY, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med 2001; 111: 211– 7. doi:10.1016/s0002-9343(01)00770-7

4) Nesher G, Berkun Y, Mates M, et al. Risk factors for cranial ischemic complications in giant cell arteritis. Medicine (Baltimore). 2004; 83(2): 114–22. doi: 10.1097/01.md.0000119761.27564.c9
5) Meskimen S, Cook TD and Blake RL Jr. Management of Giant Cell arteritis and Polymyalgia Rheumatica. Am Fam Physician. 2000;61(7):2061-2068

6) Mukhtyar C, Cate H, Graham C, et al. Development of an evidence-based regimen of prednisolone to treat giant cell arteritis - the Norwich regimen. Rheumatol Adv Pract. 2019;3(1):rkz001. doi: 10.1093/rap/rkz001

7) Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003; 49(5):703-8 doi: 10.1002/art.11388

8) Gale S, Wilson JC, Chia J, et al. Risk Associated with Cumulative Oral Glucocorticoid Use in Patients with Giant Cell Arteritis in Real-World Databases from the USA and UK. Rheumatol Ther. 2018 ;5(2):327–340. doi:10.1007/s40744-018-0112-8

9) Mukhtyar C, Guillemin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009; 68(3):318-23. doi: 10.1136/ard.2008.088351

10) Dejaco C, Brouwer E, Mason JC, et al. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol. 2017; 13(10) :578–592. doi: 10.1038/nrrheum.2017

11) Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017; 377(4): 317-328. doi: 10.1056/NEJMoa1613849

12) Hellmich B, Agueda A, Monti S, et al. Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2019. doi: 10.1136/annrheumdis-2019-215672

13) Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 Criteria for the classification of giant cell arteritis. Arthritis and Rheumatism. 1990; 33(8):1122-1128. doi:10.1002/art.1780330810

14) Salvarani C, Cimino L, Macchioni P, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Rheum. 2005; 53(2):293-7. doi: 10.1002/art.21075

15) Labarca C, Koster MJ, Crowson CS, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. Rheumatology (Oxford). 2015; 55(2):347–356. doi:10.1093/rheumatology/kev348

16) Restuccia G, Boiardi L, Cavazza A, et al. Flares in Biopsy-Proven Giant Cell Arteritis in Northern Italy: Characteristics and Predictors in a Long-Term Follow-Up Study. Medicine (Baltimore). 2016; 95(19):3524. doi:10.1097/MD.0000000000003524

17) Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford). 2015; 54(3):463-470. doi: 10.1093/rheumatology/keu329
18) Alibaz-Oner F, Balci M, Pamuk O, et al. SAT0526 Is relapse rate of giant cell arteritis in real-life experience lower than in the controlled trials? results of a retrospective, multi-centre cohort study. Annals of the Rheumatic Diseases. 2018; 77:1118-1119

19) Raza K, Buckley CE, Salmon M, Buckley CD. Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2006; 20 (5):849–863. doi:10.1016/j.berh.2006.05.005

20) Alba MA, Garcia-Martinez A, Prieto-Gonzalez S, et al. Relapses in patients with Giant cell arteritis. Prevalence, Characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine. 2014; 93(5) :194-201. doi: 10.1097/MD.0000000000000033.

21) Petri H, Nevitt A, Sarsour K, et al. Incidence of Giant Cell Arteritis and Characteristics of Patients: Data driven Analysis of Comorbidities. Arthritis Care & Research. 2015; 67(3): 390-395. doi: 10.1002/acr.22429

22) Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990–2001. Ann Rheum Dis. 2006; 65(8):19093-8. doi:10.1136/ard.2005.046912
### Group 1 – Adequate response

| Week | Prednisolone (mg) |
|------|-------------------|
| 1    | 60                |
| 2    | 45                |
| 3    | 30                |
| 4    | 20                |
| 5    | 15                |
| 6    | 12.5              |
| 7    | 10                |

- All patients are started on Prednisolone 60 mg at time of review by Ophthalmology
- Patients are re-reviewed at week 3-6 when clinical and biochemical response is assessed
- Patients are characterised as adequate or slow responders and follow the illustrated steroid tapering regime
- Adequate response is defined as CRP<10 and resolution of clinical symptoms at time of review

| Month | Prednisolone (mg) |
|-------|-------------------|
| 3     | 9                 |
| 4     | 8                 |
| 5     | 7                 |
| 6     | 6                 |
| 7     | 5                 |

### Group 2 – Slow response

| Week | Prednisolone (mg) |
|------|-------------------|
| 1    | 60                |
| 2    | 45                |
| 3    | 30                |
| 4    | 20                |

| Month | Prednisolone (mg) |
|-------|-------------------|
| 2     | 15                |
| 3     | 14                |
| 4     | 13                |
| 5     | 12                |
| 6     | 11                |
| 7     | 10                |
| 8     | 9                 |
| 9     | 8                 |
| 10    | 7                 |
| 11    | 6                 |
| 12    | 5                 |

**Figure 1: Steroid tapering protocol**