Review

Development of an evidence-based regimen of prednisolone to treat giant cell arteritis – the Norwich regimen

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Abstract

We have reviewed the literature to form a bespoke regimen for daily oral prednisolone (DP) in GCA. Initial DP in clinical trials is 40–60 mg daily, but relapse rates are 67–92%. Cumulative prednisolone (CP) of 3.2 and 3.9 g (at 6 months) resulted in a relapse rate of 83 and 67%, respectively; and 3 and 3.9 g (at 12 months) resulted in 92 and 82% relapse, respectively. CP was 6.2–7.1 g in the first year. Mean DP was 18.8 mg at 3 months and 6.6–7.4 mg at 12 months. The duration of treatment with prednisolone for GCA was 22–26 months. The CP to achieve discontinuation was 6.5–12.1 g. Using these data, the Norwich regimen starts DP at 1 mg/kg/day of lean body mass, discontinuing over 100 weeks. For the average UK woman, initial DP is 45 mg daily, reaching 21 mg daily by 12 weeks and 6 mg daily by 52 weeks. The CP for the average UK woman would be 6.5 g at 52 weeks and 7.4 g to discontinuation.

Key words: giant cell arteritis, prednisolone, relapse, treatment

Key messages

- The Norwich regimen is a bespoke regimen of daily oral prednisolone for managing GCA.
- Daily oral prednisolone dose may be ~20 mg by 12 weeks and 5–7.5 mg by 52 weeks.
- Over 100 weeks, prednisolone can be discontinued with a cumulative dose of 164 mg/kg.

Introduction

GCA is the most common vasculitis in those over the age of 50 years, with an annual incidence of ~200/million [1]. GCA was first described in 1890 by Sir Jonathan Hutchinson [2]. Initial treatments included injection of procaine hydrochloride [3], i.v. histamine [4], aureomycin [5] and even surgical excision of the perceived culprit artery [6]. Before the discovery and use of cortisone, there was a high incidence of visual loss. In 1950, Bruce reviewed 84 cases and reported visual involvement in 34; 22 (26%) had blindness, 13 cases (15%) of which were bilateral [7]. Loss of vision has catastrophic consequences on the quality of life of an individual. Typically, in GCA, this happens without warning and is irreversible. One can go from being completely independent to being completely dependent for all activities of daily living if the diagnosis is missed or the treatment inadequate. Anecdotal success at reversal of visual involvement with anticoagulation [8] has not been verified statistically [9]. The use of adrenal cortex hormones for managing the inflammatory burden of this disease was first reported formally in 1957 [10], and since then CSs have been the only evidence-based treatments until the steroid-sparing effect of MTX was demonstrated in a meta-analysis [11], and tocilizumab was shown to have disease-modifying properties and steroid-sparing effects [12]. Prednisolone or prednisone has become the CS of choice for the long-term management of this condition. No single dose or regimen for their use has been validated. It is probably fair to say...
that there are numerous different regimens in use, with little scientific basis. We have formulated a regimen that has become the standard for the management of GCA across all hospital departments in the Norfolk and Norwich University Hospital. In this review, we discuss the evidence examined to form the regimen.

The role of i.v. methylprednisolone

Intravenous methylprednisolone (MP) has been used since the 1990s at presentation, in an effort to preserve vision [13]. Reports of improvement after i.v. MP, from loss of light perception to baseline visual acuity, were extremely encouraging [14]. However, there were contrary reports about this strategy on the basis of anecdotal worsening of vision despite the use of i.v. MP [15]. Foroozan et al. [16] treated 32 consecutive biopsy-proven GCA patients with anterior ischaemic optic neuropathy or central retinal artery occlusion with 1 g i.v. MP for 3 days. There was some recovery in 13% of eyes, but all were left with significant constriction of the visual field [16]. Likewise, Danesh-Meyer et al. [17] treated 34 consecutive patients and reported continuing deterioration in 27% of eyes in spite of the high dose of i.v. MP. They found that irrespective of high-dose CSs, there remained a risk of visual deterioration in the first 6 days [17]. The only randomized controlled trial of i.v. MP vs placebo excluded patients with visual involvement, and none of the patients in the trial developed new vascular complications [18]. In our centre, we do not regularly give i.v. MP to patients with visual involvement but would consider it on a case-by-case basis. Considering the small risk of high-impact complications, such as gastric erosions, sepsis, other infections, anaphylaxis and cardiac arrest, reported after i.v. MP [19–21], this is a decision that requires careful consideration in all individuals. Current EULAR recommendations state that pulsed i.v. MP may be of benefit to some patients who present early after the onset of visual symptoms [22]. The current British recommendations state that pulsed i.v. MP should be considered in evolving visual loss or amaurosis fugax [23]. Practically, we administer i.v. MP for patients who present with central or branch retinal artery occlusion or anterior ischaemic optic neuropathy. Patients with diabetes mellitus, a history of avascular necrosis, acid-peptic disease, previous history of pancreatitis, psychiatric disorders, epilepsy, recent myocardial infarction (in the previous 12 months), congestive heart failure or a past history of thromboembolism are considered to have relative contraindications to i.v. MP.

The starting dose of prednisolone

There is no agreement on the starting dose of oral prednisolone, only that high-dose CSs must be commenced as soon as the suspicion of GCA is raised [22]. The often-quoted starting dose of oral prednisolone is 60 mg daily. This anachronism is based on the first clinical trial published in 1957, in which the starting dose of cortisone was 300 mg daily [10], which is equivalent to prednisolone 60 mg daily. Clinical trials have used several different doses in different ways. The starting dose has varied from prednisolone 20 mg daily [24, 25] to 60 mg daily [12, 26–31]. Some studies have reported using a weight-based starting dose of 0.7 mg/kg/day [32, 33]. The current European recommendations suggest 1 mg/kg/day to a maximum of 60 mg daily [22]. Universally, every author has commented that their patients entered remission as defined by amelioration of clinical signs and normalization of inflammatory markers. Myles et al. [24] commented that prednisolone 20 mg daily was sufficient to avoid visual complications. Proven et al. [31] published their experience from the Mayo Clinic, and although the median starting dose was 60 mg daily, the lower end of the range was 10 mg daily. It could be inferred that the practice of giving higher doses of prednisolone is either a historical aberration or it has value in preventing future relapses. Evidence for the latter is discussed later.

In an ideal world, we would want to provide a tailored CS regimen to individuals to fine-tune the risk of relapse vs the risk of adverse effects of prednisolone. We could consider various factors that might alter this risk–benefit ratio: cranial vs extra-cranial disease, sex, body size, co-morbidities, inflammatory markers etc. However, as it happens, even when we are left to our own devices and treat our patients depending on the changing clinical scenario, we do not treat cranial and extra-cranial disease any differently [34]. De Boysson et al. [34] performed a retrospective review of 80 patients (40 with cranial GCA and 40 with further involvement of extracranial large arteries). There was no difference between the two groups in the initial median dose of prednisone or overall duration of prednisolone therapy [34].

The pharmacokinetics of prednisolone is complicated in humans. After single high doses, the pharmacokinetics is predictable, with plasma protein-bound drug showing dose-dependent clearance and volume of distribution. But after repeated high doses, the drug is increasingly unbound and the pharmacokinetics not linear. Rohatagi et al. [35] concluded, in a study comparing prednisolone and MP, that it was difficult to determine a dose needed to obtain a desired concentration of prednisolone in comparison with MP. However, the more predictable pharmacokinetics of MP would suggest that clearance is ~40% less in obese subjects, needing a lower dose. Therefore, Dunn et al. [36] advise that MP should be administered on the basis of ideal body weight rather than actual body weight. When starting doses are calculated to actual body weight, should we keep changing the dose to varying body weights? Weight gain is a common effect of high-dose prednisolone. Continuing weight-based adjustments are not practical because the fat content of the body composition is likely to continue fluctuating. But there is evidence that lean body mass (LBM) does not fluctuate, at least peripherally [37]. Formulae for LBM use gender, height and weight as variables. The LBM is defined as the weight of the body without the fat content. Universally accepted formulae for this are unaffected by
race and ethnicity. The LBM for men = \[0.32810 \times \text{weight (in kg)} + 0.33929 \times \text{height (in cm)} - 29.5336\]; and for women = \[0.29569 \times \text{weight (in kg)} + 0.41813 \times \text{height (in cm)} - 43.2933\] [38]. In our centre, we decided that using LBM for tailoring prednisolone starting doses was at least modestly evidence based rather than the one size fits all of 40–60 mg daily.

**Prednisolone tapering**

If the initial dose of prednisolone represents the remission induction plan, the subsequent taper forms the plan to maintain remission. To begin with, we looked at the design of the prednisolone regimens of several clinical trials (Fig. 1a) and plotted the mean and 95% CIs (Fig. 1b). From the clinical trials, we selected the prednisolone regimen that was used without another steroid-sparing agent or i.v. MP. Next, we overlaid the relapse rates from these clinical trials to give us an idea of the efficacy of the regimens. Fig. 2a highlights the prednisolone regimen of the control arm from Mazlumzadeh et al. [18]. Of the 13 patients treated with this regimen, 12 suffered relapses (92% relapse rate). The relapse rate was calculated to be 190/100 person-years. Stone et al. [12] had four arms in their trial; two of them were placebo arms and one of those arms used a 52-week prednisolone taper (Fig. 2b) [12]. Of the 51 patients

**Fig. 1** Prednisolone regimens in clinical trials

(a) Individual regimens from RCT of GCA

(b) Mean regimen from GCA RCTs with 95% confidence intervals

(a) Prednisolone reduction regimens from 10 individual clinical trials. (b) Mean and 95% CIs of the prednisolone dose from 10 clinical trials.
enrolled in that arm, 42 relapsed (82% relapse rate). In between those two extremes fall the control arm regimens of Jover et al. [27] (15/18 individuals relapsed), Seror et al. [33] (26/35 individuals relapsed), Villiger et al. [39] (8/10 relapsed) and Langford et al. [29] (14/21 relapsed).

These data make it apparent that prednisolone regimens from clinical trials cannot be used for routine clinical practice because they have an impractically high relapse rate. They are usually designed to demonstrate treatment effect of the experimental drug. Therefore, is there anything we can learn from them? Clinical trials have multiple stake-holders, and the authors represent the leaders in their fields. The agreed regimens for the above clinical trials represent the distillation of the efforts of several academic clinicians. Although the high relapse rates make them ineffective for clinical use, they do give us an idea of how prednisolone might be tapered over time. Having plotted the mean and CIs (Fig. 1b), we tested statistical models that gave the best statistical fit (Table 1). The best information that we could derive from the 10 regimens was that, in the view of the experts, the reduction should be logarithmic.

One of the justifications for giving a larger than necessary initial dose of prednisolone is that it might result in longer remission maintenance. We tested this

**Fig. 2** Relapse rates in two clinical trials superimposed on regimens from 10 clinical trials

(a) Hatched area highlights the regimen used by Mazlumzadeh et al. [18] in the placebo arm of the trial. This regimen had a 92% relapse rate. (b) Hatched area highlights the regimen used by Stone et al. [12] in the 52-week placebo arm of the trial. This regimen had 82% relapse rate.
hypothesis indirectly by looking at the relapse rates and the cumulative doses of prednisolone used in the above clinical trials. Relapse rates have been reported for prednisolone regimens used in six clinical trials (Fig. 3). Statistical analysis of these data is not possible. But if we divide the six regimens into two groups, those lasting for <6 months or those lasting >6 months, then visually the relapse rate appears to be an inverse function of the cumulative prednisolone dose.

If our goal is drug-free sustained relapse, then pragmatic cohort studies give us some idea of what the stepping stones for prednisolone taper could be. Similar to the starting dose, it seems that the presence of extra-cranial disease does not affect the decision of the clinician about prednisolone dosing. Muratore et al. [40] published their experience in 332 patients (212 with cranial GCA and 120 with extra-cranial involvement). The mean daily dose of prednisolone was the same for both groups [40]. This study also helps us to make the point that clinical regimens produce lower relapse rates compared with clinical trials. The relapse rates were 49/100 and 30/100 person-years in patients with extra-cranial disease and cranial GCA, respectively. We may not require statistics to demonstrate that these numbers are probably superior to the only clinical trial (Mazlumzadeh et al. [18]), which reported a relapse rate of 190/100 person-years in the control arm. Ly et al. [41] reported outcomes in 395 patients in an inception cohort. The mean (S.D.) daily dose of prednisolone was 18.8 (6) mg at 3 months and 7.4 (3.9) mg at 12 months. Likewise, the 12 month mean prednisolone dose was reported to be 7.38 mg by Kyle and Hazleman [42] and 6.6 mg by Myklebust and Gran [43]. The aim to reach 20 mg by the end of 3 months and 7 mg by the end of 12 months would therefore seem reasonable. There are further clues to the amount of prednisolone use necessary in the first year. Chandran et al. [44] published 60 years of Mayo Clinic experience but divided their cohort into two 30-year groups because of changes in practice. One hundred and eighty-four patients treated between 1980 and 2009 needed a mean (S.D.) of 6.2 (2.7) g prednisolone in the first year [44]. One hundred and fifty-seven patients treated in Regio Emilia needed 7.1 (2.5) g mean (S.D.) prednisolone in the first year [45]. When compared with the cumulative dose achieved from the clinical trial regimens (Fig. 3), these data from cohort studies inform us that far more prednisolone is necessary in clinical practice.

### Duration of treatment

Autoimmune rheumatic diseases are not known for their ability to be cured. But long-term remission is a real possibility for almost all of them now. However, drug-free sustained remission is possible in very few conditions. We think GCA is one of them. From the original description, Hutchinson remarked, ‘The old gentleman lived, I believe, several years after this without any other manifestation of arterial disease’ [2]. Robertson remarked, in 1947, ‘The disease often lasts up to a year; it seems to be self-

| Model       | Equation              | $R^2$ |
|-------------|-----------------------|-------|
| Exponential | $y = 16.475e^{-0.005x}$ | 0.81  |
| Linear      | $y = -0.0358x + 19.112$ | 0.45  |
| Logarithmic | $y = -10.24\ln(x) + 63.441$ | 0.87  |
| Polynomial  | $y = 0.0002x^2 - 0.1525x + 32.744$ | 0.77  |

**Table 1** The equations of the statistical models for reduction of prednisolone and the coefficient of determination

![Fig. 3](https://academic.oup.com/rheumap/article-abstract/3/1/rkz001/5305663/5305663) Cumulative prednisolone dose (in grams) for six different prednisolone regimens and reported relapse rates in percentages.
limiting and is rarely fatal’ [46] This was an opinion shared by a number of early academics who had the opportunity to observe the natural history of the disease. Thus, is there a need to continue treating GCA beyond the first year, or at all? Early on, it is imperative to treat the urgent risk of ischaemic vascular complications. There is evidence that GCA might continue to smoulder in the larger vessels [47]. There is need to treat this subclinical disease to avoid long-term vascular complications. Prednisolone at a dose of <7 mg daily (having aimed for this in the first year) also starts functioning as a glucocorticoid supplement.

The data for discontinuation of prednisolone is reasonably consistent. Koorey et al. [48] from Australia and Proven et al. [31] from Minnesota, USA have both reported 22 months to discontinuation of prednisolone in 35 and 87 patients, respectively. The French experience concurs with this data. Ly et al. [41] reported the mean time to discontinuation for 395 patients was 26 months. In other cohorts, Fernandez-Herlihy et al. [49] (n = 29), Andersson et al. [50] (n = 90) and DelecourGuiet et al. [51] (n = 78) reported the time to discontinuation as 6 years, 5.8 years and 31 months, respectively [49–51]. There is a wide spread in this data, but three studies from different parts of the world came remarkably close to the 2-year mark for discontinuation of prednisolone. It would also be reasonable to surmise that if we reached 7 mg daily at the end of the first year, we could consider discontinuation at the end of the second year.

There are some data that guide us to the overall cumulative dose of prednisolone necessary to achieve discontinuation. Proven et al. [31] from the USA used a median cumulative dose of 6.5 g. Restuccia et al. [45] from Italy used twice as much, at a mean dose of 12.1 g. Chandran et al. [44] did not report on cumulative steroid use to discontinuation, but by the end of the second year they had used a mean of 8.4 g of prednisolone. It is interesting that Chandran et al. [44] and Proven et al. [31] have published from the same centre but at different time points. The second paper comments about the need to use higher doses of prednisolone to achieve the same results, but they cannot explain the reasons for this change. The true dose to achieve discontinuation is probably between 6.5 and 12 g.

### The Norwich regimen

Using the information from the data discussed so far, we ended up with an evidence base to formulate a regimen:

- The starting dose needed to be between 20 and 60 mg daily but should be tailored to the individual. LBM was a very reasonable measurement to base the dose on.
- The taper should be logarithmic rather than linear. We should aim to reach ~20 mg daily by the end of 3 months and ~7 mg daily by the end of 12 months.
- The cumulative dose of prednisolone in the first year should be ~6–7 g.
- The length of prednisolone treatment should be ~2 years, and the cumulative dose of prednisolone to discontinuation may be 6–12 g.

Using the above information, we created the following regimen:

- Starting prednisolone dose of 1 mg/kg/day of LBM, thus achieving a tailored regimen.
- The taper was calculated as dose = LBM × (1 − log_{10} W), where W is the number of weeks of being on prednisolone. We used 100 as the base for ease of calculation and to ensure that the dose of prednisolone reduces to 0 mg at 100 weeks.
- Change in dose was made every 4 weeks only. In 25 steps, the regimen would be finished.
- The prednisolone dose was rounded to the nearest 5 mg for doses >20 mg daily.
- All patients receive 164.64 mg/kg LBM over the 100 weeks.
- Each individual receives a printed copy of the regimen at diagnosis so that dose changes do not need medical supervision (Supplementary material, available at Rheumatology Advances in Practice online).
- Patients have open access to medical advice and urgent medical appointments supported so that a relapse can be diagnosed objectively in secondary care.

GCA is more common in women, and according to the Office of National Statistics, UK, the average UK woman is 161.2 cm tall and weighs 70.2 kg. Using our regimen:

- The start dose would be 45 mg daily.
- At 12 weeks, the regimen would reach 21 mg daily, and at 52 weeks the regimen would reach 6 mg daily.
- The cumulative prednisolone dose at the end of 1 year would be 6.5 g.
- At 100 weeks, the prednisolone would be discontinued after a cumulative dose of 7.4 g.

Using the data from a long-term epidemiological study in Norfolk [52], we know that at the extremes of the 95% CI, a heavy Norfolk man is 186.3 cm tall and weighs 114 kg, and a light Norfolk woman is 149.9 cm tall and weighs 45.7 kg. Using these data, their prednisolone dosing regimen is as in Fig. 4a. These data are for adults rather than the elderly, where the difference between the extremes may be less.

### Summary

We have formulated a prednisolone regimen that has become the recommended treatment for patients with GCA in our NHS Trust. This paper proposes that using a regimen based on LBM is preferable to one based on actual body weight, although this needs further validation. The Norwich regimen has been formulated using data from a wide variety of sources after an extensive literature review. Input was received from all the rheumatology consultants and an ophthalmologist to sense-check the statistical model. The regimen allows us to tailor the dose of prednisolone for individual patients and allows patients the autonomy of knowing when to
change the dose and what to change it to. The Norwich regimen therefore reduces the dependence that patients have on clinicians and, conversely, the need for clinicians to supervise every dose reduction. This reduces the need for hospital and primary care appointments. This does not mean that patients should not continue to be followed up to monitor disease and drug toxicity. We continue to see patients periodically to monitor their blood pressure, glycosylated haemoglobin and the symptoms of relapse until the patients successfully come off prednisolone. During this time, our patients also continue to have open access to our service for assessment of suspected relapse and side effects of prednisolone. We anticipate that the Norwich regimen will reduce the risk of relapses significantly, the outcomes of which will be published in the coming years. If the outcomes are favourable, this regimen could become the benchmark against which other regimens could be tested in clinical trials.

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**Supplementary data**

Supplementary data are available at *Rheumatology Advances in Practice* online.

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