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Our approach to the diagnosis and treatment of polymyalgia rheumatica and giant cell (temporal) arteritis

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ABSTRACT We believe there is a strong case for formalised collaborative care between GPs and rheumatologists in the management of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), which can be difficult conditions to diagnose and manage. Our rapid access diagnostic care pathways allow early referral of patients who appear to have PMR or GCA, before glucocorticoids are prescribed. Using set referral criteria, we identify patients with PMR who can follow our slow-reduction glucocorticoid regimen without recurrence or exacerbation in about 80% of cases, a much lower relapse rate than that reported using more rapid reduction regimens. We have a low threshold for performing a temporal artery biopsy in GCA and where possible defer treatment until this is done. Using this approach, we can establish a secure diagnosis in the vast majority of patients and refer them back to primary care for our standardised treatment regimens.

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INTRODUCTION AND OVERVIEW

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two common,[1] sometimes overlapping inflammatory conditions of unknown cause that affect patients over the age of 50.[2] Both are treated with glucocorticoids. In PMR there are no clear-cut pathological findings, although several investigators promote arthritis, bursitis or a subclinical vasculitis as the underlying cause.[3] Giant cell arteritis is a medium-vessel vasculitis where complications of visual loss in one or both eyes or stroke are preventable if patients are diagnosed and treated early.[4]

The diagnosis of PMR is often missed and conversely, many patients diagnosed and treated for PMR in primary care do not have the condition.[5] A structured approach to diagnosis and a patient's immediate response to 15 mg prednisolone daily can be used to identify those who can follow a slow-reduction glucocorticoid regimen without recurrence or exacerbation in about 80% of cases, a much lower relapse rate than that reported using the more rapid reduction regimen proposed by the British Society of Rheumatology (BSR).[6,7] However, there are no clinical trials showing the best glucocorticoid dosing regimen – a lack that should be addressed.

A definitive pathological diagnosis may be made in GCA using a temporal artery biopsy (TAB). However access to TAB may be limited or available only after treatment has started, so (as with PMR) the diagnosis has to be made on clinical grounds. We treat GCA with high-dose glucocorticoids (60 mg prednisolone daily) reducing over six months to 15 mg daily then following the same regimen as for PMR. Our experience is that patients without the benefit of TAB often face a dilemma later in the course of their management when the diagnosis becomes uncertain or the adverse effects of glucocorticoids become substantial, and the potential for identifying alternative conditions is seriously hampered by the earlier treatment decision. Our practice favours a low threshold for TAB, and we have recently established a pathway to facilitate this.

In this article, we will explain the rationale for our approach to these conditions, including our rapid-access PMR clinic, our structured GCA diagnostic pathway, and our treatment regimen.

DIAGNOSIS OF POLYMYALGIA RHEUMATICA

Although traditionally a disease diagnosed and managed in primary care, our experience is that GPs have difficulty with the diagnosis of PMR. A review of 13

consecutive patients referred to hospital with PMR found that half the patients probably did not have it.[5] A study of the GP records of 47 PMR patients from six widely distributed practices found that 25% showed only a gradual improvement on treatment, suggesting that PMR was not the underlying diagnosis; 38% were eventually referred to hospital for help with management.[9] In other centres, change of diagnosis on follow up has been reported in up to a quarter of patients.[10,11]

This is perhaps not surprising, as there is no single diagnostic test and no universally agreed set of diagnostic criteria for PMR.[12,13] In clinical practice diagnosis relies on a combination of non-specific symptoms including aching and stiffness in the shoulder girdle, a raised acute phase response (APR), exclusion of a wide differential diagnosis and a classical response to glucocorticoids.[2]

We believed we could improve this situation with more formalised collaboration between primary and secondary care. In 2008 we started a weekly rapid-access PMR clinic. Our referral criteria include bilateral shoulder pain and stiffness which is abrupt in onset (reaching a peak within two weeks) and worse in the morning, plus a raised APR (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] or plasma viscosity). Once on glucocorticoids, the true diagnosis can be hard to establish, so we ask GPs not to prescribe prednisolone before referral and we support them in doing this by aiming to see patients within 2–3 weeks (normal referral time 8–10 weeks).

The recent British Society of Rheumatology (BSR) guidelines for the management of PMR provide a pragmatic structure for diagnosis, which largely mirrors our approach in clinic.[6] However, in most areas the strength of available evidence is weak, so this guidance cannot be regarded as absolute and we would question the advice regarding the presence of peripheral joint involvement in PMR, the existence of PMR without a raised APR, and the diagnostic importance of glucocorticoid responsiveness.

Those who diagnose PMR in patients with peripheral arthritis argue that the arthritis is different from late onset seronegative rheumatoid arthritis (RA) because it involves fewer joints, is more glucocorticoid-responsive and does not recur on eventual cessation of glucocorticoids.[14–17] However, patients with PMR and arthritis appear to have more severe disease[18] with a more protracted course of glucocorticoid therapy and need for additional treatments such as intra-articular glucocorticoids or disease-modifying anti-rheumatoid drugs than pure PMR patients.[15] The inclusion of patients with this mixed picture in pure PMR cohorts obscures the clinical interpretation of study results, as these patients respond differently and are more likely to require ongoing secondary care input. We do not diagnose these patients with PMR. In support of our approach, there was little international expert agreement for the presence of peripheral signs in PMR during development of the recent European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for PMR.[19]

We consider a raised APR essential for diagnosis and it is included in all published diagnostic or classification criteria.[19–23] A combination of both ESR and CRP provides the highest sensitivity and specificity for diagnosis. For example, in a prospective follow-up study of PMR patients, only one patient in 177 (0.56%) reported had both a normal CRP and a normal ESR at diagnosis (defined as ESR <30 mm/h and CRP <0.5 mg/dL).[24] It is unfortunate that the clinical features and response to treatment of this patient were not described. Up to 22.5% of PMR patients may have a normal ESR at the time of diagnosis, depending on the study and the definition of a normal ESR,[24,25] so we routinely measure both CRP and plasma viscosity in order to assess the APR. Plasma viscosity is a better measure as it can increase in parallel with the ESR, but unlike ESR is not influenced by age, sex, haematocrit, or time to analysis.

Rapid and significant responsiveness to glucocorticoid treatment is a key feature of PMR; it is included in two sets of PMR diagnostic criteria.[21,23] We routinely use a glucocorticoid 'sandwich' test as part of our assessment of patients when we are not certain of the diagnosis (20–90% likelihood of PMR). We explain to the patient that the pattern of any changes that occur in their symptoms (if indeed there are any changes) will help us make a diagnosis and ask them to keep a daily record of their symptoms. We prescribe 100 mg ascorbic acid daily for one week, followed by 15 mg prednisolone daily for one week, and finally another week of ascorbic acid. Marked relief (more than 80% improvement) of myalgic symptoms within 48 hours of starting the glucocorticoid followed by relapse in a similar period of time is strong supportive evidence of PMR.[26] A lesser response prompts us to look for alternative diagnoses (Figure 1).

We have found that using this standard approach, the diagnosis of pure PMR can be confirmed or refuted within two visits to the PMR clinic in 95% of cases. At the first visit, the diagnosis is clear-cut (>90% likelihood PMR) in about one-third of patients, who can be commenced on our standard treatment regime and discharged back to their GP. About one-third do not have PMR (<20% likelihood) and may need further investigation in the general rheumatology clinic. The remaining third may have PMR (likelihood 20–90%) and for these patients we perform a glucocorticoid sandwich test, which clarifies the diagnosis either way in most cases. In all, about 45% of our referred patients do not have PMR[27] and do not therefore receive PMR treatment unnecessarily (Figure 2).

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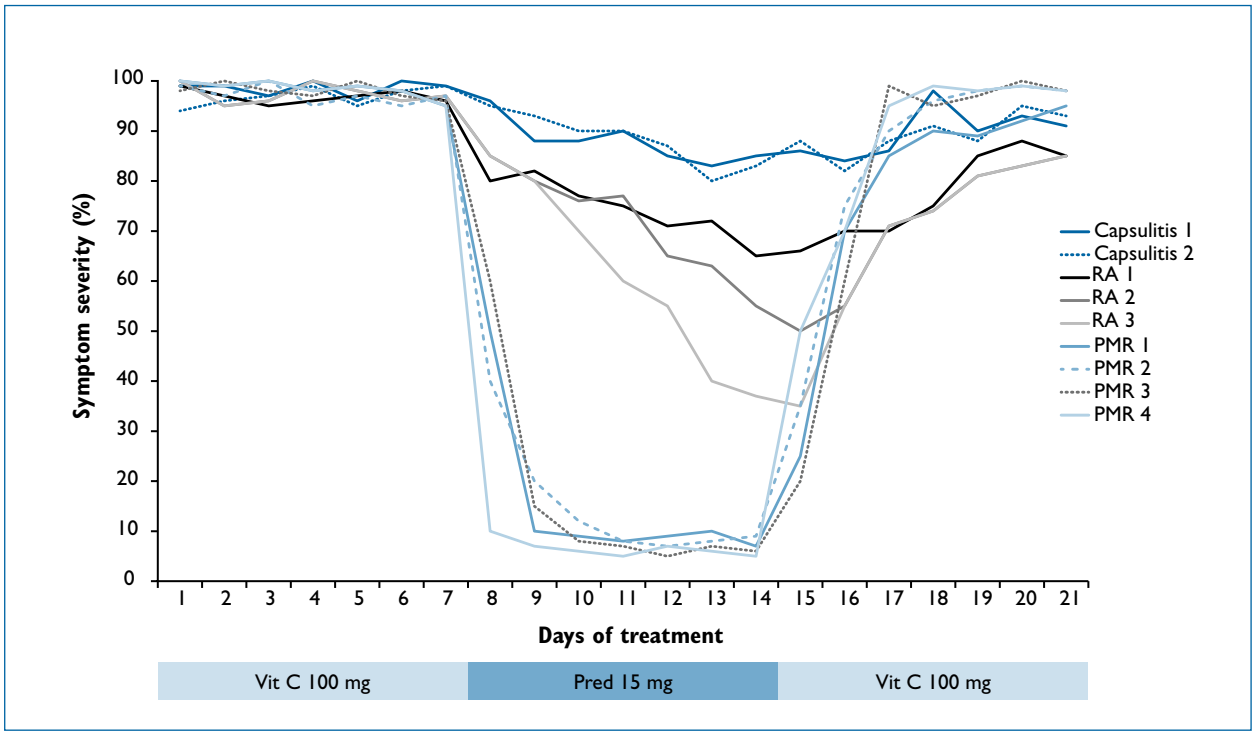

FIGURE 1 Diagrammatic illustrative responses representing patients with shoulder capsulitis, rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR).

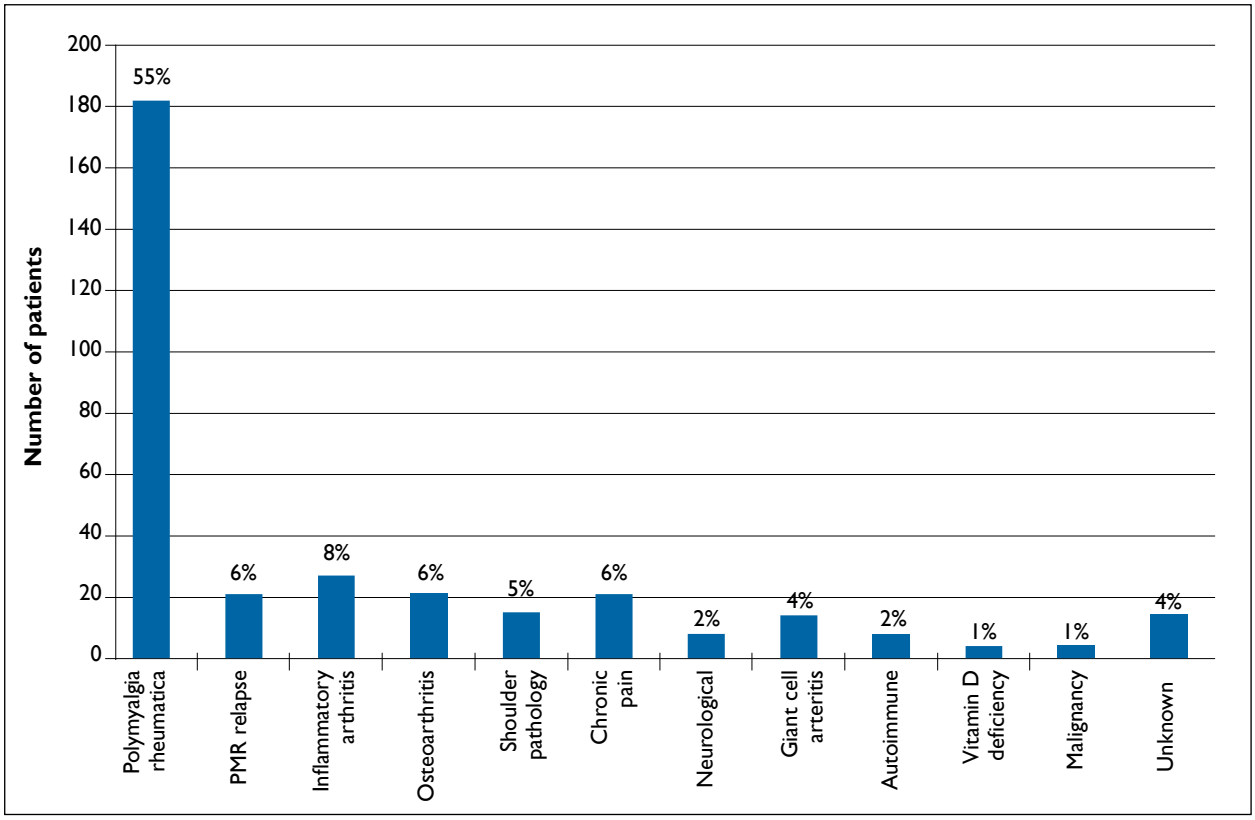

FIGURE 2 Diagnosis at the Bristol Royal Infirmary Rapid Access PMR Clinic.

EDUCATION

The published diagnostic and classification criteria for PMR provide a useful guide, but we do not routinely apply them to our patients to make a diagnosis (Table 1). These criteria were developed by rheumatologists from a population of their patients referred to secondary care and the sensitivities and specificities of each set of criteria only apply to the population in which they were developed. The gold standard for diagnosis remains expert opinion, so if the assessor's internalised definition is aligned with one set of criteria, then that set of criteria will perform well in their cohort. Broadly, in our population of patients published criteria are either sensitive, but tend to over-diagnose,[19,20] or specific, but miss an unacceptable percentage of patients.[21–23]

TREATMENT OF POLYMYALGIA RHEUMATICA

Glucocorticoids remain the mainstay of treatment in PMR[3] and attempts to find a glucocorticoid-sparing agent in PMR have been disappointing.[28–31] No clinical trials have been conducted to allow an adequate definition of the best treatment regimen, where the ideal balance is set between inducing and maintaining remission and avoiding adverse treatment effects. A systematic review of PMR therapy concluded that a starting dose of prednisolone 15 mg daily will control disease activity in most patients,[32] a view unchallenged by more recent studies.[33] Evidence from published cohorts of patients suggests that the dose should then be slowly reduced and that stopping PMR treatment is feasible from two years onwards.[34–38] Rate of steroid tapering at more than 1 mg/month is a clear predictor of relapse.[14,39] Higher relapse rates seem associated with too high a dose of glucocorticoids initially and/or with too rapid a reduction in treatment thereafter.[8,36,40–44] Some controlled trials of treatment have shown disappointing results because of a similar rapid reduction in dose.[45,46]

The drive to keep glucocorticoid dose to a minimum is the fear of side-effects, particularly cardiovascular and fracture risk. These depend on the daily and cumulative dose, the potency of glucocorticoid prescribed, as well as duration of exposure, but there is increasing evidence that they may also depend upon the underlying pathology of the disease being treated.[47] In common with other chronic inflammatory disorders, PMR may already have an increased risk of complications such as cardiovascular disease[48] and bone loss. In treating such patients with appropriate doses of glucocorticoids and reducing their inflammatory burden, there may be an overall net benefit. Two substantial cohorts of patients with PMR showed that treatment with glucocorticoids was not associated with an increased risk of cardiovascular diseases[49] or all adverse events[50] when compared to treatment with non-steroidal anti-inflammatory drugs (NSAIDs). In one of these studies, a trend for a protective effect was seen and there was no significant association between cumulative glucocorticoid dose and any cardiovascular, peripheral vascular or cerebrovascular event.[49] A recent cohort study supports these findings.[51] Several studies of PMR have shown a clear association between the cumulative dose of glucocorticoid and the rate of other glucocorticoid complications, particularly fragility fractures,[35,45,50,52] but at the time, the use of osteoporosis prophylaxis was not routine practice. We now know that bisphosphonates are effective at preventing glucocorticoid-induced bone loss.[53]

Our patient-centred approach has taught us that our patients fear relapse.[54] Based on this, and the evidence outlined above, we favour a regime that minimises the risk of relapse (Table 2).

TABLE 2 Our polymyalgia rheumatica treatment regimen over 104 weeks

15 mg daily for six weeks, then
12.5 mg daily for six weeks, then
10 mg daily for one year, then
Reduce daily dose by 1 mg/per month thereafter

Our treatment regimen has a significantly lower rate of relapse at two years (20%; manuscript in preparation) compared to a published cohort[44] which used a more rapid dose reduction regime in line with current BSR recommendations[6] but had 60% relapse at two years. Our cumulative dose of prednisolone is necessarily higher at 6.2 g vs 3.2 g. However, when dose increases due to relapse are taken into consideration, the dose regimens are more closely aligned at 6.4 g vs 4.2 g.

TABLE 3 The American College of Rheumatology giant cell arteritis classification criteria[56]

Based on the presence of three or more of the following:
1. Age >50
2. New onset localised headache
3. Temporal artery tenderness or decreased pulsation
4. Erythrocyte sedimentation rate (ESR) >50 mm/h
5. Abnormal temporal artery biopsy

DIAGNOSIS OF GIANT CELL ARTERITIS

Like PMR, diagnosis of GCA can be a challenge. History, physical examination and lab results provide useful information, but they are neither highly sensitive nor specific for GCA.[55] As there are no agreed diagnostic criteria for GCA, the 1990 ACR classification criteria for GCA,[56] developed to differentiate different forms of vasculitis, are often used for diagnosis, where they function poorly (Table 3). In the clinical setting, their positive predictive value may be as low as 29%,[57] and while common clinical findings have low positive predictive value for histological diagnosis, clinical findings with good prediction occur only rarely (Table 4).[58]

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TABLE 1 Diagnostic and classification criteria for polymyalgia rheumatica

Feature	Published criteria				
	Bird (1979)[20]	**Hazleman (1981)[21]**	**Hunder (1982)[22]**	**Healy (1984)[23]**	**Dasgupta (2012)[19]**
Age onset (years)	>65	>65	>50	>50	>50*
Limb girdle involvement	Bilateral shoulder pain/ stiffness	Shoulder or pelvic girdle pain	Bilateral aching or tenderness in at least 2/3 of: neck or torso, shoulders or proximal arms, hip or proximal thighs	Pain in at least 2/3 specific areas: neck, shoulders, pelvic girdle	Bilateral shoulder ache* Hip pain or limited range of motion: 1 point
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	ESR>40	ESR>30 or CRP>6	ESR>40	ESR>40	Raised ESR and/or CRP*
Morning stiffness (minutes)	>60	>60	–	>60	>45: 2 points
Other symptoms	Bilateral upper arm tenderness	Absence of muscle disease	–	–	Absence of other joint pain: 1 point
Absence of rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA)	–	Absence of RF	–	–	Absence of RF or ACPA: 2 points
Onset duration	<2 weeks	–	–	–	–
Disease duration	–	>2 weeks	>1 month	>1 month	–
Constitutional symptoms	Weight loss, depression	–	–	–	–
Differential diagnosis	–	–	Excluded other diagnoses except GCA	Diagnosis of exclusion	–
Response to glucocorticoids	–	Rapid response to prednisolone	–	Rapid response to prednisolone ≤20mg	–
Number of criteria for polymyalgia rheumatica (PMR)	≥3	All	All	All	*Required criteria, plus ≥4 points

TABLE 4 Clinical features associated with a positive biopsy[58]

Clinical features	Positive predictive value	Proportion of patients with this feature
New headache	46%	49%
Scalp tenderness	61%	18%
Jaw claudication	78%	17%
Double vision	65%	10%
Jaw claudication + scalp tenderness + new headache	90%	6%
Jaw claudication + double vision or decreased vision	100%	0.7%

The recent BSR/British Health Professionals in Rheumatology (BHPR) guidelines for the management of GCA provide a useful structure for diagnosis. However, in most areas the strength of available evidence is weak, so the guidance cannot be regarded as absolute and we would question the balance of their advice regarding GCA with a normal APR, the role of temporal artery ultrasound (TAUS) and the need to treat with glucocorticoids before TAB.[7]

Although in GCA there is the possibility of a definitive pathological diagnosis in the form of a superficial TAB, in many cases it is negative because of prior glucocorticoid treatment, segmental inflammation or suboptimal biopsy.[55,59] In clinical practice, patients are often treated without biopsy, either because of difficulty obtaining a timely TAB, practical considerations (such as anticoagulation or inability to lie still for the procedure) or because the clinician feels biopsy would not change management (due to a high clinical probability of the diagnosis). Our experience is that patients without the benefit of TAB often face a dilemma later in the course of their management if the diagnosis becomes uncertain or the adverse effects of glucocorticoids become substantial, and the potential for identifying alternative conditions is seriously hampered by the earlier treatment decision. Our practice therefore favours a low threshold for TAB.

In response to these challenges, we have recently set up a structured GCA diagnostic pathway. We aim to see all referred patients before treatment, within one working day of referral. Each patient is then considered for two guaranteed TAB slots per week, agreed with our ophthalmology and vascular surgery colleagues.

The BSR and EULAR recommend immediate initiation of high-dose glucocorticoids pre-TAB, in an attempt to minimise visual loss. However, the evidence for this approach is weak (level of evidence 3, strength of recommendation C)[7,60] and there is conflicting data that starting glucocorticoids pre-TAB affects the TAB yield.[58,61–63] We do not know the relative risks of deferring glucocorticoids until TAB result is known compared to those of unnecessarily treating patients who do not have GCA with high-dose glucocorticoids. It has been suggested that the absence of clinical features such as visual disturbance or jaw claudication can be used to estimate those at lower risk of a positive TAB in whom glucocorticoids can be deferred until after TAB (Table 4),[58,64] but as our patients wait a maximum of four days for TAB, we do not start glucocorticoids until after TAB unless ophthalmic symptoms have occurred.

TREATMENT OF GIANT CELL ARTERITIS

Glucocorticoids are the mainstay of treatment in GCA[7,60] and as with PMR, attempts to find a glucocorticoid sparing agent have so far been disappointing.[65–67] The available evidence suggests that initial doses of 40–60 mg are needed, then about two or three times the total PMR cumulative dose will be required for perhaps six months longer (Table 5).[14,35–37] The same pitfalls are seen as in PMR trials, namely the use of too high a dose of glucocorticoids initially, with too rapid a reduction in treatment thereafter.[36,41] This then leads to high rates of relapse which affects the glucocorticoid tapering rate, duration of treatment and cumulative dose.

TABLE 5 Our giant cell arteritis treatment regimen over 124 weeks

- 60 mg daily for four weeks, or until remission induction, then
- 50 mg daily for four weeks, then
- 40 mg daily for four weeks, then
- 30 mg daily for four weeks, then
- 20 mg daily for four weeks, then
- As per PMR regimen for 104 weeks

The potential for glucocorticoid-related adverse effects is much more clear-cut in GCA than in PMR, presumably as much larger initial and cumulative doses are used,[35,36,41,68] which highlights the importance of confirming the initial diagnosis with TAB.

SUMMARY AND A LOOK TO THE FUTURE

We believe there is a strong case for formalised collaborative care between GPs and rheumatologists in the management of PMR and GCA. Our rapid access diagnostic care pathways allow early referral of patients who appear to have PMR or GCA before glucocorticoids are prescribed. We are able to establish a secure diagnosis in the vast majority of patients and discharge back to GP care. They then supervise our standard treatment regimens with a low level of relapse and we are ready to quickly review any patients who deviate from the expected course.

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Published guidelines for the diagnosis and management of PMR and GCA are hampered by a paucity of good quality research in this area.[6,7] For example, randomised controlled trials of different treatment regimens for PMR and GCA are needed, where the balance between disease control and the side-effect burden of the treatment can be properly assessed. There is also a need to make a formal assessment of the relative risk of blindness due to deferring glucocorticoids until after TAB vs the side-effects of high-dose glucocorticoids in patients who do not have GCA. However, promising treatment breakthroughs such as the use of glucocorticoid chronotherapy in PMR[69] and anti-IL6 therapy in GCA[70–73] raise the possibility that we will be able to control these conditions on much lower doses of glucocorticoids and thus minimise the side-effect burden.

The role of TAUS looks very promising in the diagnosis of GCA, where an inflamed temporal artery is seen as a dark, hypoechoic circumferential wall thickening or 'halo sign'. Compared to TAB, TAUS is a cost-effective, easy to access, non-invasive investigation, almost without complication. There have been three meta-analyses demonstrating the usefulness of the halo sign in the diagnosis of GCA[74–76] which suggest that provided technical quality criteria are fulfilled, the halo sign's sensitivity and specificity are comparable to those of autoantibodies such as rheumatoid factor and dsDNA. When the pre-test probability of GCA is low, negative TAUS practically excludes the disease.[74] Specificity of bilateral halo sign approaches 100%.[76] In other centres in the UK and across the world, TAUS is being used increasingly to aid clinicians with the diagnosis of GCA and to reduce the need to proceed to TAB, as there is no evidence to suggest GCA patients should be treated differently according to biopsy findings. Although it is operator-dependent and widespread routine use is in its infancy in the UK, this is no reason not to try to develop local expertise. We have therefore incorporated TAUS into our assessment of potential GCA patients. All our patients are scanned within 24 hours of their clinical assessment by our vascular studies technicians. In the long term, based on the experience of others, we anticipate we will be able to use TAUS to reduce the requirement for TAB and/or improve diagnostic yield through directed TAB.

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