



BSR and BHPR guidelines for the management of polymyalgia rheumatica

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Key words: Guidelines, Polymyalgia rheumatica, Diagnosis, Treatment, Corticosteroid.

Why do we need guidelines for PMR?

PMR is one of the most common inflammatory rheumatic diseases of the elderly and represents one of the commonest indications for long-term corticosteroid therapy in the community [1–3]. It is also a rheumatic disease subject to wide variations of clinical practice and it may be managed in primary or secondary care by general practitioners, rheumatologists and non-rheumatologists [4].

What health benefits are expected from these guidelines?

These guidelines are designed to ensure better management of patients with PMR by:

- a safer and more accurate diagnosis;

- outlining an approach to the diagnosis of patients presenting with polymyalgic symptoms;
- ensuring earlier specialist referral of appropriate cases;
- ensuring appropriate corticosteroid dosage at diagnosis and gradual corticosteroid taper; and
- ensuring early bone protection to reduce the common morbidity of osteoporotic fractures.

Can there be problems with the diagnosis in PMR?

Many features of PMR predispose the unwary clinician to diagnostic error [5]. The proximal pain and stiffness syndrome—the main symptoms of PMR—can occur in many other illnesses [6]. A third of the patients have systemic symptoms, such as fever, anorexia and weight loss. A considerable number may have distal musculoskeletal manifestations such as peripheral arthritis, distal swelling with pitting oedema and carpal tunnel syndrome [7]. PMR is also associated with GCA in 10% of the cases and up to 50% of the cases of GCA may have polymyalgic symptoms at presentation [8]. An acute-phase response can occur in other settings such as other rheumatological conditions, neoplasia and infection [9].

Many clinicians and two empirically developed diagnostic criteria use a response to corticosteroids as the main defining feature of this condition [10]. This may encourage diagnostic error since corticosteroids are potent anti-inflammatory agents that can mask symptoms

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Submitted 26 May 2009; revised version accepted 13 August 2009.

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from a host of serious conditions ranging from OA, rotator cuff problems, RA, cancer and infection, especially if used in high doses and for protracted lengths of time. Studies have shown a revision of the initial diagnosis on follow-up in several cases [10].

Who is the target audience for these guidelines?

These guidelines are directed at the diagnosis and management of PMR in primary and secondary care (including rheumatologists and non-rheumatologists).

Clinical situations covered by these guidelines

These guidelines apply to the clinical evaluation and investigation of patients with new symptoms of proximal bilateral shoulder or hip pain allowing accurate diagnosis of PMR. It also outlines the subsequent management (treatment, monitoring and referral) of patients with PMR. These guidelines do not cover the management of GCA, which is published separately.

What are the objectives of this guideline?

- (1) To outline a safe and specific diagnostic process for PMR.
- (2) To specify a minimum data set that should be recorded for diagnosis of PMR.
- (3) To outline a diagnostic algorithm and clues in the presentation that will help differentiate from other mimicking conditions.
- (4) To specify referral guidelines for the general practitioner.
- (5) To provide advice on management of PMR.
- (6) To specify the goals of treatment including clinical and patient-based outcomes.
- (7) To provide advice on monitoring for disease activity and complications of disease and the treatment.
- (8) To specify audit standards for the optimal management of PMR: diagnostic accuracy, initial corticosteroid dose and taper, relapses and use of bone protection.
- (9) To identify areas for future research.

What are the areas that the present guidelines do not cover?

GCA, RA, other CTDs and other inflammatory muscle diseases.

How have the patients' views been incorporated in the guidelines?

Patient representatives have been present at all the guideline group meetings. Each version of the guideline has been circulated to the representatives for comment.

In particular, the new ARC patient education booklet has been re-formatted entirely under their leadership.

What is the evidence to support these guidelines?

Please see the literature review in Appendix 1.

How will these guidelines be piloted?

These guidelines will be piloted by the members of the Guidelines group among the adjacent rheumatology and primary care community in the Midlands, South London and Essex. All results will be incorporated into future revisions of the document.

How often will these guidelines be reviewed?

These guidelines will be reviewed every 3 years or more frequently when new evidence is published.

How will these guidelines be publicized and implemented?

The guidelines will be published on the BSR website and sent to all BSR members and Primary Care Trusts. The guidelines will also be sent to the Royal College of General Practitioners and to the *BMJ Clinical Evidence*. A programme of education and training will be developed for relevant primary and secondary care staff. The quick reference guide (see Appendix 2) will be sent to all GP practices.

Cost implications and conflicts of interest

Cost implications are outside the scope of these guidelines and there has been no funding associated with their development; therefore, there is no conflict of interest to disclose. These guidelines have been developed with complete editorial independence.

Key recommendations

- Use core inclusion and exclusion criteria items and minimum data set as a first step in a step-wise process to diagnose PMR.
- Commence low-dose corticosteroids with gradual corticosteroid taper.
- Systematic assessment of the corticosteroid response—whether it is rapid, complete and sustained.
- Early referral to a specialist for atypical cases and treatment dilemmas.
- Vigilant monitoring of proximal pain, morning stiffness, disability, osteoporotic risk factors and for any other symptoms that may suggest an alternative diagnosis.

- Prevention of osteoporotic complications.
- Polymyalgic disease relapse should be treated with re-escalation of corticosteroid therapy. Development of GCA symptoms require 40–60 mg prednisolone. Adjunctive DMARD therapy should be considered after the second relapse.

Guidelines

(1) We recommend that a safe, stepped diagnostic process is adopted for the evaluation of PMR [5, 10–12] (Level of evidence 3, Strength of recommendation C).

The International PMR Classification Criteria Group endorsed by ACR and the European League Against Rheumatism has agreed an approach (supported by a wider survey) for the polymyalgic syndrome that sees the diagnosis of PMR as a stepped process.

The following criteria have been proposed and these are being validated in a prospective case–control study [11]. The steps for diagnosis of a patient presenting with the polymyalgic syndrome are as follows:

(i) Evaluate for inclusion criteria

Core (essential):

- Age >50 years, duration >2 weeks
- Bilateral shoulder or pelvic girdle aching, or both
- Morning stiffness duration of >45 min
- Evidence of an acute-phase response (e.g. raised ESR, CRP)

PMR has been diagnosed with normal acute-phase response, but the group felt that this required further investigation in the prospective study. Patients with suspected PMR and normal inflammatory markers should be referred to secondary care.

(ii) Evaluate for exclusion criteria (see algorithm)

Core (absolute contraindication to corticosteroids):

- Active infection and cancer
- Active GCA (see part iii)

Others (these decrease likelihood of PMR and should be excluded):

- Rheumatic diseases: RA, inflammatory arthropathies, SLE, other CTDs and inflammatory myopathies
- Drug-induced myalgia, e.g. statins
- Pain syndromes, e.g. fibromyalgia
- Endocrine, e.g. thyroid
- Neurological, e.g. Parkinson's disease

Co-existing conditions that should be noted as a cause of persistent pain are OA, degenerative and other peri-articular conditions of the shoulder, neck and hips.

(iii) Patients should be assessed for evidence of GCA, as it requires urgent institution of high-dose steroid (see separate guidelines)

- Abrupt-onset headache (usually temporal) and temporal tenderness
- Visual disturbance, including diplopia
- Jaw or tongue claudication
- Prominence, beading or diminished pulse on examination of the temporal artery
- Upper cranial nerve palsies
- Limb claudication or other evidence of large vessel involvement

(iv) Evaluate a standardized response to corticosteroids. Oral prednisolone 15 mg/day (the consensus group suggested this with >90% agreement). Most reported trials have used doses between 10 and 20 mg [11–14].

Response is defined as a patient-reported global improvement of 70% within a week of commencing corticosteroids and normalization of inflammatory markers within 4 weeks (consensus group >75% agreement).

A lesser response should encourage the search for an alternative condition because steroids are potent anti-inflammatory agents that mask symptoms from a host of serious conditions including OA, rotator cuff problems, RA, cancer and infection.

Urgent institution of steroid therapy is not necessary in PMR with no features of GCA, but rather, it is preferable to have a full assessment of the patient prior to steroid therapy. However, if the patient does present with symptoms suspicious of GCA, then urgent institution of high-dose steroid therapy is needed (see Guidelines for Management of GCA).

(v) Confirmation of the diagnosis on follow-up. Follow-up visits should include the search for mimicking conditions such as other rheumatological diseases (e.g. RA) [12] in the following:

- Symptoms and signs (e.g. persistent synovitis)
- Pertinent laboratory abnormalities (e.g. haemoglobin, ESR, biochemistry, auto-antibodies)
- Other investigations (e.g. erosions on radiographs)
- Poor response to corticosteroids or inability to reduce the dose should prompt a careful review and revision of diagnosis if necessary

(2) We recommend the following documentation of the basis for the diagnosis of PMR in the patient's medical record (Grade C).

Clinical features. The core inclusions and exclusions should be documented in patient records.

Laboratory investigations. Minimum data set required before commencement of corticosteroid therapy should be recorded:

- Full blood count
- ESR and/or CRP and/or plasma viscosity
- Urea and electrolytes
- Liver function tests
- Bone profile: calcium, alkaline phosphatase
- Protein electrophoresis (also consider Bence Jones Protein)
- Thyroid stimulating hormone

- Creatine kinase
- Rheumatoid factor (anti-nuclear antibody and anti-CCP antibody may also be considered)
- Chest radiograph (in some cases, e.g. prominent systemic symptoms)
- Dipstick urinalysis

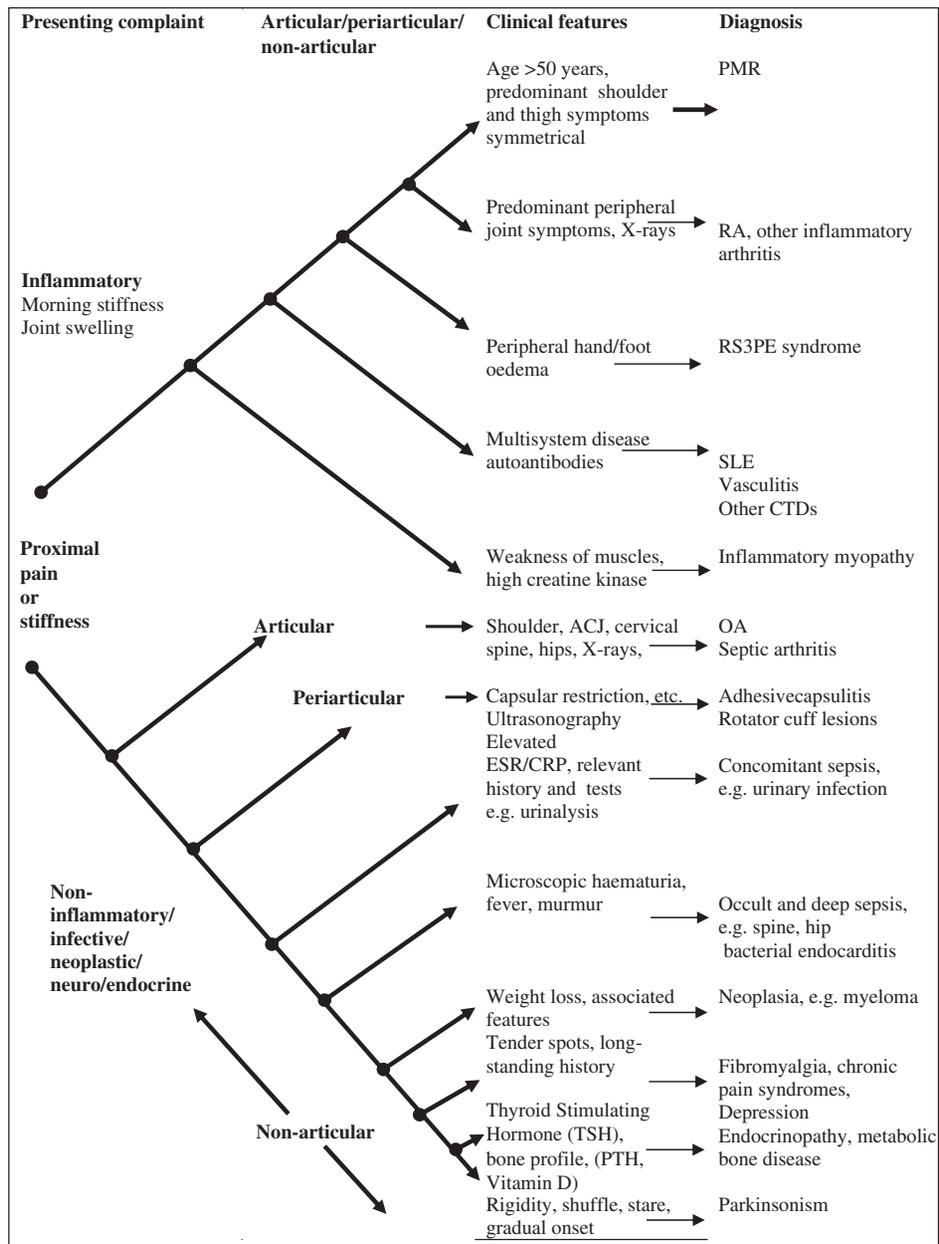
(3) We recommend the following approach for the evaluation of proximal pain and stiffness [5] (Fig. 1).

(4) We recommend early specialist referral from primary care in the following circumstances (Level of evidence 3, Strength of recommendation C).

Patients with atypical features or features that increase likelihood of a non-PMR diagnosis such as:

- Younger patient <60 years
- Chronic onset (>2 weeks)
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- 'Red flag' features: prominent systemic features, weight loss, night pain, neurological signs
- Peripheral arthritis or other features of CTD or muscle disease
- Normal acute phase response (APR) or very high APR

Fig. 1 Approach to the evaluation of proximal pain and stiffness. ACJ: acromio-clavicular joint.



Treatment dilemmas such as:

- Incomplete or non-response to corticosteroids
- Ill-sustained response to corticosteroids
- Unable to reduce corticosteroids
- Contraindications to corticosteroid therapy
- The need for prolonged corticosteroid therapy (>2 years)

However, patients who have no atypical features, who have a complete sustained response to low-dose corticosteroids, and who have no adverse events can be managed by a general practitioner.

(5) We recommend the initiation of low-dose corticosteroid therapy with a gradual taper in patients with straightforward PMR [10–14] (Level of evidence 2, Strength of recommendation B).

Evidence for an ideal steroid regimen suitable for all patients with PMR is lacking. The suggested dosage regimen given below is based on the consensus decision of the working group. Additionally, as in other rheumatic diseases, patients with PMR show heterogeneity in their clinical and laboratory features, response to treatment, disease course and relapse rate. Therefore, flexibility is needed to tailor treatment to the individual patient, for the initial dose of corticosteroids, the tapering regimen and the duration of therapy. Therefore, the actual regimen required by an individual patient may differ to what is suggested subsequently. In the absence of features of GCA, there is little indication for urgent corticosteroid prescription before the clinical evaluation is completed.

We suggest the following regimen:

- Daily prednisolone 15 mg for 3 weeks
- Then 12.5 mg for 3 weeks
- Then 10 mg for 4–6 weeks
- Followed by reduction by 1 mg every 4–8 weeks or alternate day reductions (e.g. 10/7.5 mg alternate days, etc.)

Some patients may benefit from a more gradual corticosteroid taper, or a period of treatment at a stable dose, such as 5 mg prednisolone for 3 months. The dose may also need adjustment, due to disease severity, comorbid factors (e.g. diabetes, cardiorespiratory or renal disease), fracture risk, patient wishes and adverse events.

Intramuscular methylprednisolone (i.m. depomedrone) may be used in milder cases and may reduce the risk of corticosteroid-related complications [15]. Initial dose is 120 mg i.m. repeated at 3–4 weekly intervals. The dose is then reduced by 20 mg every 2–3 months and given monthly (Grade A). Avoid NSAIDs, especially in the very elderly and in those with renal impairment.

Usually 1–2 years of steroid treatment is needed [4]. The need for ongoing therapy after 2 years of treatment should prompt the consideration of an alternative diagnosis, and referral for specialist evaluation.

(6) We recommend the use of immediate bone protection to prevent the complications of

osteoporosis in someone treated with corticosteroids for PMR (Grade A–).

Individuals at high risk of fracture, for example, those aged ≥ 65 years and those with a prior fragility fracture should be advised to commence a bisphosphonate with calcium and vitamin D supplementation when starting corticosteroid therapy. These patients do not require measurement of BMD prior to commencement of bone protection (Grade A).

Other individuals should have an adequate intake of calcium and vitamin D (Grade C). We recommend co-prescription of calcium and vitamin D supplements when starting corticosteroid therapy. Measurement of BMD to assess fracture risk is recommended in these individuals as well. A bone-sparing agent may be indicated if T-score is -1.5 or lower.

Those at the risk of higher cumulative corticosteroid dose due to higher dosing should also be advised to commence bisphosphonates at the time of starting corticosteroids. Please see the Royal College of Physicians' guidelines on glucocorticoid-induced osteoporosis [22] for details.

(7) We recommend vigilant monitoring of patients for response to treatment and disease activity (Grade B).

Patients should have early (1–3 weeks) review after commencement of corticosteroids to assess the response to treatment, for any complications of disease and therapy and to evaluate the possibility of an alternative diagnosis.

When assessing for the response to treatment, it is important to distinguish between symptoms due to inflammation and those due to co-existing degenerative problems. Relevant symptoms of PMR: proximal pain or stiffness, fatigue, disability related to morning stiffness and proximal involvement (e.g. problems rising, dressing and undressing, reaching, etc.)

Early rapid improvement in symptoms is typical of PMR:

- $\geq 70\%$ patient global response in 1 week—likely to be PMR
- If $<70\%$ response—consider increased dose up to 20 mg prednisolone
- If still $<70\%$ response—reconsider diagnosis and specialist referral

Complications of disease, including symptoms of GCA such as headaches, jaw claudication should be elicited. Patients should be assessed for corticosteroid-related adverse events: weight gain, diabetes, osteoporosis, hypertension and lipid dysregulation.

Many studies have shown high rates of corticosteroid-related complications in PMR-treated patients [16]. Most studies agree that PMR requires 1–3 years of steroid treatment [17]. Hence, the minimum effective dose of corticosteroids should be used and alternative causes of persistent pain should be sought. High initial dosing and rapid tapering has been shown to be associated with longer duration of therapy [18].

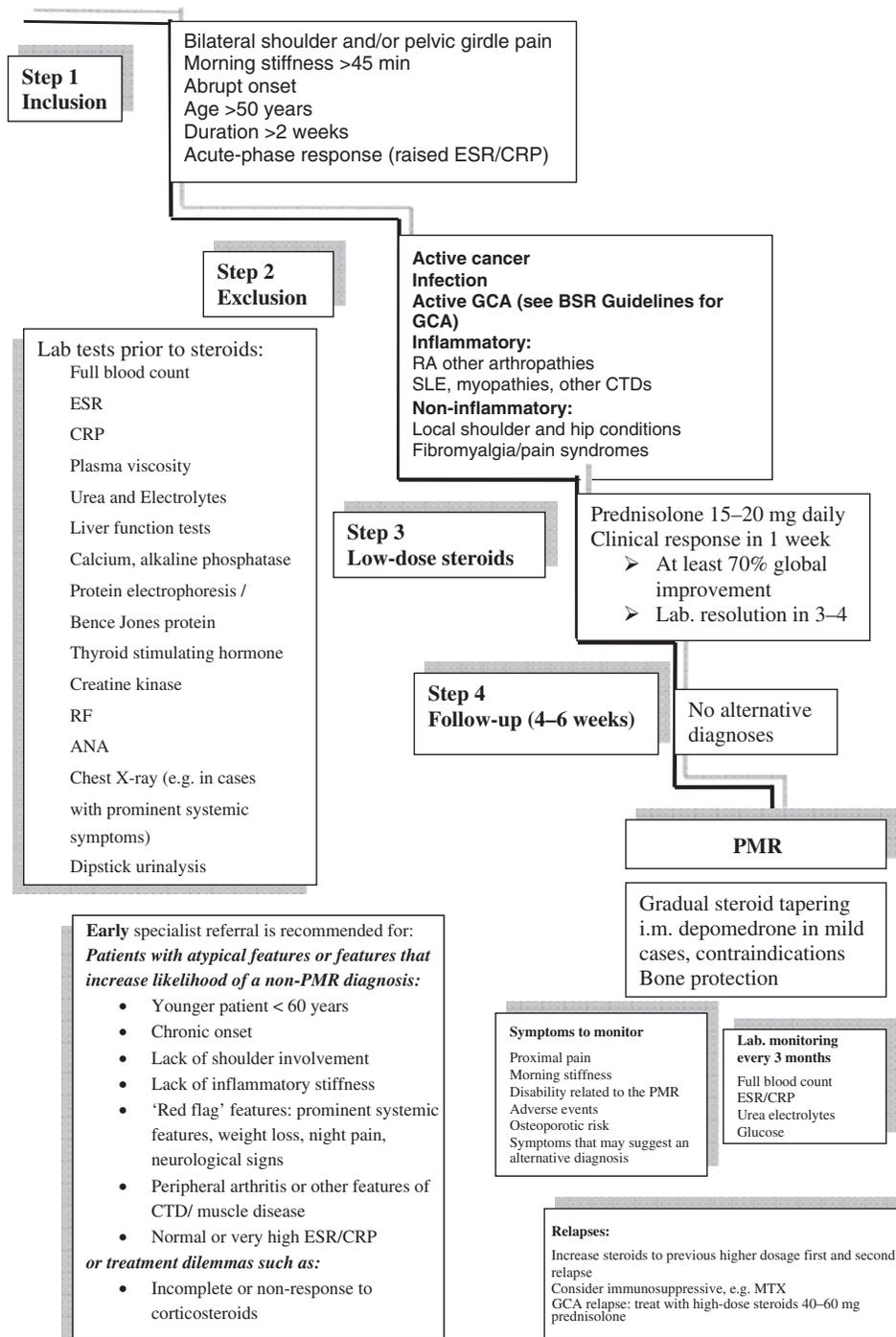
Patients should be assessed for other symptoms that may suggest an alternative diagnosis. Atypical and severe cases as well as those with poor corticosteroid response should be assessed for early re-evaluation and referral.

Laboratory monitoring. Full blood count, ESR (plasma viscosity)/CRP, urea and electrolytes, glucose.

Frequency of follow-up. This should be at Weeks 0, 1–3 and 6 and Months 3, 6, 9 and 12 (with extra visits for relapses and adverse events) in the first year.

Duration of treatment. Although the suggested treatment duration is for 1–2 years, some patients with PMR will require small doses of corticosteroids beyond 2 years. Flexibility in the approach is necessary given the

Fig. 2 Approach to the evaluation of proximal pain and stiffness. ACJ: acromio-clavicular joint.



heterogeneous nature of the disease. Provided that the patient is asymptomatic in terms of their original symptoms, corticosteroids may continue to be tapered at the rate advised above and then stopped.

(8) We recommend the following approach to relapse of disease.

Relapse is defined as recurrence of symptoms of PMR or onset of GCA symptoms, e.g. headaches, jaw claudication, visual symptoms, usually with rise in ESR/CRP [23]. An isolated raised ESR or CRP does not necessarily indicate relapse or the need for continued steroid therapy, which may require further investigation and referral. Also, persistent pain may arise from co-existing degenerative conditions, such as OA and rotator cuff tears, rather than ongoing inflammatory disease.

Treatment of relapse

Clinical features of GCA relapse. Treat as GCA (usually with oral prednisolone 40–60 mg/day) (see GCA guideline) (Grade B).

Clinical features of PMR relapse:

First and second relapses: increase prednisolone to previous higher dose, monitor for response (Grade B). Single i.m. injection of depot methylprednisolone 120 mg can also be given (as in treatment of RA flare).

Further relapses: consider introducing DMARDs [after two relapses (Grade B–C)].

There is a lack of adequate evidence regarding most DMARDs although one study of MTX concluded that it was effective [24]. All previous studies of MTX, AZA and other DMARDs have had very small sample sizes, high drop-out rates, and poorly designed and inconsistent results. However, such DMARD use has been shown to be effective on a case-by-case basis—especially where further investigations (e.g. PET scan) have shown arteritic pathology.

The approach to diagnosis and management of PMR is summarized in Fig. 2.

Patient education

The new ARC booklet on PMR has been re-formatted according to the guidelines group recommendations. The booklet was developed in conjunction with patient representatives on the working group. Further patient information and support is available from local patient groups, under the auspices of the umbrella organization PMRGCA-UK.

Audit standards

● *Measures of process and adherence to guidelines*

Minimum data set recorded prior to corticosteroid therapy:

- (v) clinical features, e.g. symmetrical proximal pain and stiffness or important exclusions;
- (vi) investigations, as specified in guidelines.

● *Initial corticosteroid dose and taper*

- *Monitoring frequency*
- *Bone protection:*
 - Co-prescription of calcium and vitamin D
 - Bisphosphonates
 - DXA as required
- *Patient education provided*

Areas for future audit and research

It is recommended that the future audits should contain outcome measures such as disease relapse, persistent disease activity such as proximal pain and morning stiffness and ESR/CRP, current corticosteroid dosage, adverse events and complications of therapy and quality of life.

Future research needs to address the following:

- Corticosteroid dosage and route, and tapering regimens
- Novel corticosteroid preparations and other alternative agents
- The best approach to adjuvant therapy including the use of newer therapies (e.g. leflunomide and biologics) as adjuvant therapy
- The role of ultrasound and other imaging modalities in the evaluation of PMR

Other unanswered questions are:

- (v) Can patients present with proximal pain and stiffness and respond to corticosteroids even though we do not think they have PMR?
- (vi) Can a patient have PMR even if they do not respond to corticosteroids at a specified dosage?

Disclosure statement: The authors have declared no conflicts of interest.

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Appendix 1

Literature review

Search strategy

To obtain all the relevant literature, a sensitive search with appropriate search strings (for treatment in PMR) was undertaken in the most common medical databases:

- The Cochrane database of randomized controlled trials (RCTs) (up to January 2005)
- MEDLINE (through OVID; 1966 to January 2007)
- CINAHL (through OVID; 1982 to January 2007)
- EMBASE (through OVID; 1980 to January 2007)

Reference lists of retrieved articles were examined and experts in the field of PMR research were contacted for additional references. Searching through journals by hand for relevant papers was not carried out.

Common methodological problems

- (1) Dearth of studies conducted within primary care.
- (2) Studies commonly not powerful enough to measure differences in clinically important outcomes with high precision.
- (3) Diversity of measurement instruments—very few validated.
- (4) Problems with internal validity—absence of strict randomization and blind assessment of observer-rated outcomes. There were very few RCTs.
- (5) Inadequate information on content and quality of intervention. Quality checks and protocol adherence hardly ever mentioned.
- (6) Few studies report patient data before steroid intervention. Multiple diagnostic entry criteria used with blurred distinction between isolated PMR and GCA with polymyalgia.
- (7) Few studies of long-term outcome.

Results of literature review

Initial corticosteroid dose in PMR. There are no RCTs. There are several observational studies. The initial dose favoured is ~15mg daily prednisolone. Lower doses (particularly <10mg) associated with higher incidence of relapse and higher doses (particularly >20mg) with higher incidence of adverse events. Several studies describe differences in corticosteroid requirement in individual patients. One study observes that low maintenance dose is related to low initial dose. Another study finds higher initial dose and rapid

steroid tapering were significant predictors of frequency of relapse.

Disease course, duration of treatment, adverse events.

Observational studies recommend that corticosteroid doses are reduced gradually to prevent relapse of symptoms, with studies reporting around half the patients having relapses and median duration of steroid treatment ~2–3 years. Three categories of disease course have been proposed: a short duration of treatment following a rapid response to corticosteroids and without significant relapse; a rapid response to corticosteroids requiring extended treatment to control disease flares; and an incomplete resolution of symptoms requiring increased doses of corticosteroids and extended treatment to control disease flares.

The benefits from treatment with corticosteroids need to be balanced with the increased risk of adverse outcomes such as diabetes and fractures [16]. In the UK, one study reported corticosteroid-related side effects in a third (two-thirds if weight gain is included) of the patients.

DMARDs in PMR

There are very few RCTs of corticosteroid sparing DMARDs in PMR. Of the five reported studies with MTX in PMR, only two showed benefit (one RCT with 76 patients and one open randomized study).

Three are limitations with small numbers, large number of drop outs, corticosteroid taper schedule, dose of MTX used, lack of documented benefit vs corticosteroids alone in the first 6 months.

There are two studies on AZA (one in English and one in non-English). One is an RCT with 31 patients showing beneficial effects of MTX with reduced corticosteroid doses in 12 months.

There is one RCT on tenidap, few on deflazacort. However, these agents are rarely used in clinical practice and may not be relevant. A small open study with infliximab suggests that it should probably be reserved for patients with refractory disease. A Phase 2 study of infliximab in GCA was withdrawn because of lack of efficacy.

Appendix 2

Quick Reference Guide

(1) Establish diagnosis of PMR in a step-wise manner (Grade C).

Include: Patients presenting *age* > 50 years, *duration* > 2 weeks, *bilateral* shoulder and/or pelvic girdle aching, *morning stiffness* duration of >45 minutes, evidence of an acute-phase response e.g. raised erythrocyte sedimentation rate or C-reactive protein.

Exclude: active cancer, infection, RA and other inflammatory diseases, thyroid, local shoulder and hip conditions, statin-related myalgia/myopathy.

(2) Investigate: full blood count, urea and electrolytes, liver function tests, CRP, ESR, RF, creatine kinase, TSH, protein electrophoresis and urinalysis. May need chest radiograph, ANA (Grade C).

(3) Commence low-dose corticosteroids with gradual taper (Grade B). Daily prednisolone 15 mg (3 weeks), 12.5 mg (3 weeks), 10 mg (4–6 weeks), followed by reduction by 1 mg (every 4–8 weeks) or alternate day reductions, e.g. 10/7.5 mg on alternate days, etc.

In milder cases and relative contraindications to steroid therapy consider i.m. depomedrone 120 mg every 3 weeks for four injections and thereafter gradual tapering doses given monthly (Grade A).

The dose may need adjustment and stabilization for disease severity, comorbid factors, fracture risk, patient wishes and adverse events.

(4) Evaluate the corticosteroid response (Grade C).

- More than or equal to 70% patient global response in 1 week—likely to be PMR.
- If <70% response—consider increased dose up to 20 mg prednisolone.
- If still <70% response—reconsider diagnosis and specialist referral.

(5) Follow-up evaluation—to ensure corticosteroid response is complete and sustained with no other features of alternative diagnosis.

Early referral to a specialist for patients with atypical features, features that increase likelihood of a non-PMR diagnosis and treatment dilemmas (Grade B).

(6) Immediate bone protection—co-prescribe calcium, vitamin D supplementation with commencement of corticosteroids.

Individuals at high risk, for example, those aged ≥ 65 years and those with a prior fragility fracture, should be advised to commence bisphosphonates (Grade A).

Those at the risk of higher cumulative steroid dose due to higher dosing should also be advised to commence bisphosphonates.

DXA scan for BMD determination may be needed in patients not commenced on bisphosphonates at the start, i.e. in patients aged <65 years, without fragility fractures.

(7) On-going monitoring of: Symptoms (Grade B).

- Proximal pain
- Morning stiffness
- Disability related to the PMR
- Adverse events
- Osteoporotic risk factors
- Other symptoms that may suggest an alternative diagnosis

Lab. monitoring (Grade B)

- FBC
- ESR/CRP

- U&E
- Glucose

Relapses (Grades A–B)

- Increase steroids to previous higher dosage at first and second relapse.
- Consider additional immunosuppression, e.g. MTX at third relapse.
- GCA relapse: treat with high-dose steroids 40–60 mg prednisolone.
- Consider alternative diagnosis in patients with partial or no response to steroids.