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Prescribing for polymyalgia rheumatica

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SUMMARY

Polymyalgia rheumatica is a common inflammatory condition but can be difficult to diagnose. Treatment is warranted in all cases to manage disabling symptoms.

Low–moderate doses of oral corticosteroids are highly effective. Once symptoms improve they can often be gradually reduced over months, but most patients require either prolonged or continuous treatment.

Despite their effectiveness, corticosteroids cause disproportionate damage in polymyalgia rheumatica compared to other rheumatic diseases. The therapeutic aim is to prescribe the minimum possible dose required for symptom control.

There is a lack of definitive evidence for steroid-sparing drugs in polymyalgia rheumatica. Methotrexate is typically used for relapsing disease. Leflunomide and tocilizumab are being investigated, but further research is needed.

Introduction

Polymyalgia rheumatica is the second most common autoimmune rheumatic disease after rheumatoid arthritis, with a lifetime risk of 2.4% for women, and 1.7% for men. It is the most common rheumatic disease in patients over 50 years old.[1]

Polymyalgia rheumatica and its treatment are often poorly understood by patients and healthcare professionals alike. The diagnosis can be difficult and there is a frequent dependence on corticosteroid therapy despite an increased propensity for long-term adverse effects.

Clinical features

The onset of polymyalgia rheumatica can be abrupt, often seemingly occurring overnight. There is bilateral shoulder girdle pain and prolonged early morning stiffness (typically >45 minutes, but often lasting several hours). The hips are involved in the vast majority of patients,[2] with neck, back or buttock pain also commonly reported. Distal manifestations are less frequent and may include a peripheral arthritis of the wrists and knees which is typically more sensitive than rheumatoid arthritis to prednisolone.[3]

It is possible to confuse polymyalgia rheumatica with other conditions including rheumatoid arthritis, spondyloarthritis, mechanical tendinopathies and fibromyalgia. To further complicate matters, elderly-onset rheumatoid arthritis may have an initial 'polymyalgic' presentation before overt arthritis emerges.

Diagnosis

The difficulty with diagnosis is accentuated by the absence of a gold standard investigation. Patients typically have a raised erythrocyte sedimentation rate or C-reactive protein, but infrequently the inflammatory markers are normal. Although interleukin-6 is typically elevated in untreated patients, no specific biomarker exists. Alternative diagnoses such as myositis, infection, malignancy and endocrinopathies should be excluded (Box).[2,4]

A rapid resolution of symptoms in response to prednisolone 15 mg daily was previously thought to represent a diagnostic surrogate for polymyalgia rheumatica. However, a small proportion of patients do not respond to three weeks of this therapy[5] so it cannot be used to make the diagnosis. Classification criteria therefore combine clinical features and serology with the optional incorporation of ultrasound (Table 1).[6] Ultrasound may show bursitis or tenosynovitis. In practice, the diagnosis is a clinical one and may require specialist involvement.

Giant cell arteritis

The most feared complication of polymyalgia rheumatica is giant cell arteritis. These conditions are closely related, and 16–21% of patients with polymyalgia rheumatica either have or will go on to develop giant cell arteritis.[7] All patients with polymyalgia rheumatica should be educated about this complication and the need to seek urgent medical attention if they develop suggestive symptoms. Giant cell arteritis may present with

headache, localised scalp tenderness, jaw claudication and, more concerningly, sudden visual loss or stroke. A small rise in erythrocyte sedimentation rate does not exclude giant cell arteritis.[7] Giant cell arteritis requires high-dose corticosteroids, which should never be delayed while a diagnostic temporal artery biopsy is obtained.

Extracranial giant cell arteritis is under-recognised and most commonly presents with constitutional features and persistently elevated inflammatory markers. Untreated it can eventually lead to formation of aortic aneurysms or stenoses of other large arteries.[8] Imaging is being increasingly used to detect extracranial giant cell arteritis. CT angiography or magnetic resonance angiography may be useful. Nuclear medicine studies such as positron emission tomography (PET) with fluorodeoxyglucose (FDG) have been used.[9] Although cost and radiation limit its use in routine practice, PET can identify important differential diagnoses such as infection and malignancy, and characteristic features of polymyalgia rheumatica may also be seen.[10]

Corticosteroids

Typically, untreated disease is markedly disabling due to the combination of pain, extensive stiffness and accompanying constitutional features. Corticosteroid therapy is therefore indicated and can result in a dramatic improvement for many patients. However, there is no evidence to suggest that it alters the likelihood of developing giant cell arteritis.

Prednisolone 15 mg daily is highly effective in most patients, although a few may need up to 25 mg daily.[11–13] Moderate-dose corticosteroids have been the first-line treatment for over 50 years, but were introduced before the widespread use of placebo-controlled trials to confirm effectiveness.[12]

After several weeks of treatment, approximately one-third of patients are able to gradually reduce their prednisolone over many months and can eventually stop.[14] Different weaning protocols have been devised, although the ideal approach remains controversial and individual tailoring may be necessary.

The British Society of Rheumatology has proposed a regimen[15] which is globally accepted[2] and reflected in local guidelines.[16] This recommends prednisolone 15 mg daily for three weeks, then tapering to 12.5 mg daily for an additional three weeks, 10 mg daily for 4–6 weeks and then a reduction of 1 mg daily every 4–8 weeks thereafter. Disease relapse, defined by a recurrence of symptoms accompanied by a rise in inflammatory markers, warrants an escalation of prednisolone to the last effective dose before recommencing the weaning schedule from that dose.

Box **Important differential diagnoses of polymyalgia rheumatica**

Inflammatory musculoskeletal diseases:

- rheumatoid arthritis
- spondyloarthritis
- ANCA-associated vasculitis and other connective tissue disorders
- inflammatory myositis
- crystal arthropathies

Non-inflammatory musculoskeletal disorders:

- osteoarthritis
- mechanical tendinopathies including rotator cuff syndrome
- pain syndromes including fibromyalgia
- other myopathies including drug-induced myopathies

Endocrinopathies:

- thyroid and parathyroid disease
- vitamin D deficiency

Infection

Cancer including paraneoplastic syndromes

Parkinson's disease

ANCA antineutrophil cytoplasmic antibody

Table 1 **Scoring algorithm for classifying polymyalgia rheumatica**

Required criteria: age 50 years or older, bilateral shoulder aching and abnormal C-reactive protein or erythrocyte sedimentation rate*

Criteria	Points without ultrasound (0–6)	Points with ultrasound (0–8)
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of rheumatoid factor or anticitrullinated protein antibody	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis, or biceps tenosynovitis, or glenohumeral synovitis (either posterior or axillary), and at least one hip with synovitis or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

* A patient is categorised as having polymyalgia rheumatica if the total score without ultrasound is 4 points, or is 5 or more points with ultrasound.

Source: Reference 6

The British weaning schedule is more rapid than most others, but involves at least 46 weeks of prednisolone therapy. This is a much longer period of exposure compared to most other inflammatory diseases. In practice the majority of patients will need corticosteroids for at least two years and a large proportion will require ongoing low-dose prednisolone to control their symptoms.[17] There are currently few data to help predict which patients will require ongoing therapy. Extended exposure to prednisolone is inevitable for these patients.

Adverse effects

Corticosteroids cause dose-dependent adverse effects. While the doses of prednisolone used in polymyalgia rheumatica might be lower than what was historically considered acceptable in many inflammatory conditions, they still confer a burden of morbidity.

The damage from prolonged use of low–moderate doses of corticosteroids is multimodal and has been better appreciated in recent years with more sophisticated investigative methods (Table 2).[18-20] Screening for these complications and treating them is important in mitigating their impact, although prevention is preferable.

In polymyalgia rheumatica the morbidity from similar doses of corticosteroids is both greater and occurs more frequently than in other rheumatic diseases.[21] It is not clear why, and this area warrants further research as it may have therapeutic implications. The cumulative effect, however, is that up to 81% of patients develop adverse events in the first year.[5] Furthermore polymyalgia rheumatica is a disease of older people who are at risk of complications as a consequence of these adverse events.

Uncontrolled inflammation itself can also cause problems, therefore corticosteroid therapy in polymyalgia rheumatica is a balance. Aim to achieve the minimum total exposure to prednisolone while maintaining control of the disease.[4]

Steroid-sparing drugs

There is great impetus to develop treatment alternatives to corticosteroids. However, there is currently no alternative drug in polymyalgia rheumatica which is supported by good evidence and is affordable. Steroid-sparing drugs, such as methotrexate, are therefore not currently recommended to be started soon after diagnosis, as is the case in rheumatoid arthritis. The decision to commence a steroid-sparing drug is a personalised one based on perceived ongoing need for prednisolone. It is not possible to predict who will benefit. One approach is to consider a steroid-sparing drug in patients who flare at least twice while following the British weaning schedule[15] or who develop overt inflammatory arthritis.

Methotrexate is currently recommended by both international[4] and local guidelines[16] as the first-line steroid-sparing drug to consider in polymyalgia rheumatica. These recommendations acknowledge that the evidence to support this advice is of poor quality. Leflunomide might have promise,[22,23] and it is currently the subject of a trial in Europe, but there may be problems with individualising the dosing.[24] Both of these drugs are used in rheumatoid arthritis, but there is no role for most other antirheumatic drugs in polymyalgia rheumatica.[4] This emphasises the fact that polymyalgia rheumatica is not merely an extension of rheumatoid arthritis. The use of either leflunomide or methotrexate in polymyalgia rheumatica is off label so specialist oversight is recommended.

Tocilizumab, an interleukin-6 receptor antagonist, has become of increasing interest as interleukin-6 is elevated in polymyalgia rheumatica.[25] The drug has also had recent success in treating giant cell arteritis,[26] but there are important immunological differences between the two diseases[27] so the results are not necessarily transferrable. Dedicated studies in polymyalgia rheumatica are therefore required. Two phase II trials have supported the use of tocilizumab[28,29] and a phase III trial is currently underway.[30] Even if this trial is successful, the cost of tocilizumab is likely to be prohibitive for routine use, and there is a risk of serious infection, myelosuppression, hypertension and dyslipidaemia.[31]

Conclusion

Polymyalgia rheumatica can be hard to diagnose and to treat optimally. While corticosteroids are effective and necessary to prevent disease-related morbidity, they have a burden of morbidity themselves and no steroid-sparing drug has yet emerged as ideal for routine use. Close clinical monitoring is important to detect the evolution of giant cell arteritis and to minimise and manage the adverse effects of therapy.

More research is required into the mechanisms behind corticosteroid-related damage in polymyalgia rheumatica. There is also a need to find ways to predict which patients are likely to require prolonged corticosteroids, and to devise a pragmatic therapeutic approach for them. <

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Table 2 **Long-term toxicity of prednisolone (≤15 mg daily)**

Toxicity	Details	Implications for screening and management*
Musculoskeletal		
Osteoporosis	Reduced bone density Altered microarchitecture Increased fracture risk	Optimise vitamin D and calcium intake Consider DEXA screening Order plain-film X-rays for new back pain Consider bisphosphonates or denosumab
Osteonecrosis	Possible increased risk	Investigate new hip pain
Myopathy	Risk of painless proximal muscle weakness and atrophy†	Take history, including difficulty with activities above shoulder height or rising from chairs without use of arms
Metabolic		
Diabetes and glucose intolerance	Increased risk of developing type 2 diabetes† Increased fasting glucose	Measure fasting glucose or HbA1c Encourage lifestyle modification Optimise diabetic therapy in patients with diabetes
Body morphology	Increased body weight Altered fat distribution (cushingoid appearance)	Measure height and weight Encourage lifestyle modification
Interference with sex hormone secretion	Increased risk of loss of libido† Hirsutism†	Take appropriate history, including patterns of body hair growth
Adrenal suppression	Increased dosage-dependent risk	Educate regarding staged withdrawal Check biochemical tests if rapid withdrawal required Consider an increased dose of prednisolone on sick days
Cardiovascular		
Dyslipidaemia	Increased dyslipidaemia†	Measure fasting lipids† Encourage lifestyle modification and provide pharmacotherapy
Hypertension	Increased blood pressure†	Monitor blood pressure† Encourage lifestyle modification and pharmacotherapy
Atherosclerosis and ischaemic heart disease	Increased risk of cardiovascular events and subclinical atherosclerosis† Possible increased risk of cardiovascular events	Encourage lifestyle modification
Infections		
Infections	Possible increased risk of general infection† Possible increased risk of opportunistic infection and herpes zoster	Give scheduled vaccinations (inactivated) including influenza vaccination Educate regarding late presentation of symptoms
Dermatological		
Skin atrophy	Increased risk	Educate
Acne, alopecia, bruisability	Increased risk	Educate

Table 2 **Long-term toxicity of prednisolone (≤15 mg daily) (continued)**

Toxicity	Details	Implications for screening and management*
Ophthalmological		
Cataract	Increased risk	Consider ophthalmologic evaluation if symptomatic
Glaucoma	Increased risk in individuals already at risk†	Consider ophthalmologic evaluation with tonometry in at-risk patients
Psychological		
Mood disturbance and psychosis	Increased risk†	Educate, screen and provide therapy as appropriate
Insomnia	Increased risk	Educate, take dose in morning
Gastrointestinal		
Peptic ulcer disease	Possible increased risk	Consider proton pump inhibitor only in patients at risk of ulcers

* Management of all of these adverse events includes minimisation of the corticosteroid dose.
† Applies to moderate doses (prednisolone ≥7.5 mg daily) only, based on References 18–20.
DEXA dual-energy x-ray absorptiometry
HbA1c glycated haemoglobin

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