Polymyalgia rheumatica

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Polymyalgia rheumatica is an inflammatory disease that affects the shoulder, the pelvic girdles, and the neck, usually in individuals older than 50 years. Increases in acute phase reactants are typical of polymyalgia rheumatica. The disorder might present as an isolated condition or in association with giant cell arteritis. Several diseases, including inflammatory rheumatic and autoimmune diseases, infections, and malignancies can mimic polymyalgia rheumatica. Imaging techniques have identified the presence of bursitis in more than half of patients with active disease. Vascular uptake on PET scans is seen in some patients. A dose of 12·5–25·0 mg prednisolone daily or equivalent leads to rapid improvement of symptoms in most patients with isolated disease. However, relapses are common when prednisolone is tapered. Methotrexate might be used in patients who relapse. The effectiveness of biological therapies, such as anti-interleukin 6, in patients with polymyalgia rheumatica that is refractory to glucocorticoids requires further investigation. Most population-based studies indicate that mortality is not increased in patients with isolated disease.

Introduction

Polymyalgia rheumatica is an inflammatory disorder characterised by severe pain and stiffness affecting the shoulders and proximal aspects of the arms bilaterally. Pain and stiffness is also common in the neck. Less frequently these symptoms affect the pelvic girdle and the proximal aspects of the thighs. Patients have morning stiffness that lasts more than 45–60 min and non-specific symptoms such as fatigue and malaise. Increases in acute phase reactants (ie, erythrocyte sedimentation rate and C-reactive protein) is a characteristic feature of the disease.[1]

Bruce first described this condition in 1888.[2] Polymyalgia rheumatica—also known as secondary fibrositis, periarthrosis humeroscapularis, peri-extra-articular rheumatism, myalgic syndrome of the aged, pseudo-polyarthrite rhizomelique, and anarthritic rheumatoid disease—was first reported in the 1940s. The term polymyalgia rheumatica was introduced by Barber in 1957.[2]

Epidemiology: incidence, genetic components, and environmental factors

Polymyalgia rheumatica is a common disease in elderly patients, but rarely arises in individuals younger than 50 years.[3] More than two-thirds of patients are women. Incidence increases progressively with age in both sexes until the age of 80 years.[4] The highest incidence is in people older than 65 years, with a peak in the 70–79 year age group.[3] Polymyalgia rheumatica is most common in Scandinavian countries.[5,6] The mean annual incidence of polymyalgia rheumatica in individuals aged older than 50 years was 50 cases per 100 000 people in Gothenburg, Sweden, between 1985 and 1997.[7]

Notably, Olmsted County, MN, USA, has one of the highest incidence rates of the disease, where the population is predominately of Scandinavian or northern European descent.[8] Data[4] from Olmsted County published in 2016 showed that the age-adjusted and sex-adjusted annual incidence of polymyalgia rheumatica in individuals aged 50 years and older was 63·9 cases per 100 000 inhabitants. A lower incidence of polymyalgia rheumatica is seen in southern Europe.[9,10] In Reggio Emilia, Italy, the mean annual incidence in individuals aged 50 years and older was reported as 12·7 cases per 100 000 people between 1980 and 1988.[9] Furthermore, in Lugo, Spain, the mean annual incidence in individuals aged 50 years and older was 18·7 cases per 100 000 people between 1987 and 1996.[10]

The prevalence of polymyalgia rheumatica is also higher in northern European populations and individuals of Scandinavian descent than in other populations. Data[11] published in 2017 from Olmsted County have shown that the overall age-adjusted and sex-adjusted prevalence of polymyalgia rheumatica on Jan 1, 2015, was 701 cases per 100 000 people (870 in women and 508 in men per 100 000 people). Prevalence in a UK primary care population was 910 cases per 100 000 people (1040 in women and 780 in men per 100 000 people).[12]

HLA class I and II molecules are implicated in the susceptibility to giant cell arteritis, a vasculitis also common in elderly individuals that is often associated with polymyalgia rheumatica.[13] Although an association is often noted between HLA-DRB1*04 class II alleles and patients with polymyalgia rheumatica associated with giant cell arteritis, this association does not seem to exist in all patients with isolated polymyalgia rheumatica.[14] Genetic polymorphisms associated with other autoimmune inflammatory conditions, such as

Search strategy and selection criteria

We searched the Cochrane Library and PubMed for reports published in English from database inception until Feb 28, 2017, using the term "polymyalgia rheumatica" AND each heading used in our Seminar (eg, "epidemiology"; "genetics"; "pathophysiology"…). We largely selected publications from the past 10 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged most relevant. Review articles and book chapters are also cited to provide readers with more details and references than this Seminar has room for. Giant cell arteritis not associated with polymyalgia rheumatica is not discussed in this Seminar.

polymorphisms in the promoter region of the interleukin-6 gene, might also influence the development of polymyalgia rheumatica.[14–16]

Infectious agents might be implicated in the pathogenesis of polymyalgia rheumatica.[3] Simultaneous peaks in the incidence of giant cell arteritis and polymyalgia rheumatica in different regions of Denmark that occurred in close concurrence with *Mycoplasma pneumoniae*, *Parvovirus B19*, and *Chlamydophila pneumoniae* epidemics support this hypothesis.[6] However, no association between *Parvovirus B19* infection and the onset of polymyalgia rheumatica was found in a 4-year prospective study.[17] A modest association between any infection or herpes zoster infection and the development of giant cell arteritis was reported in the UK.[18]

Pathophysiology

Arthroscopic studies have shown the presence of mild synovitis in the proximal joints (mainly in the shoulders) of patients with polymyalgia rheumatica. The inflammatory infiltrate found in the shoulder synovial membranes and other affected joints was composed mainly of macrophages and CD4 T lymphocytes.[19] This mild synovitis does not fully explain the musculoskeletal manifestations and the diffuse pain in the periarticular structures. In view of the prominent inflammatory involvement of bursae, some authors have suggested that polymyalgia rheumatica might be a disorder predominantly of the extra-articular synovial structures.[20]

MRI and ultrasonography studies have revealed the presence of subacromial and subdeltoid bursitis and tenosynovitis of the biceps in association with synovitis of the glenohumeral joints.[21,22] Although hip joint effusion is more common than peri-pelvic bursitis, either or both might occur in polymyalgia rheumatica. Trochanteric bursitis, and less commonly iliopsoas and ischiogluteal bursitis, might also occur as part of the disease spectrum.[23] However, ischiogluteal bursitis is rather specific for polymyalgia rheumatica. Lower cervical and lumbar spine interspinous bursitis was also reported in patients with polymyalgia rheumatica, and might be partly responsible for the neck and back pain reported by patients with the disorder.[24–26] However, the presence of bursitis in these areas is consistent with, but not specific to, polymyalgia rheumatica.

Proinflammatory cytokines might also be important in polymyalgia rheumatica. Increased interstitial concentrations of interleukin-1α and interleukin-β, interleukin-1 receptor antagonist, interleukin 6, interleukin 8, tumour necrosis factor-α, and monocyte chemoattractant protein 1 have been detected in symptomatic vastus lateralis and trapezius muscles of patients when compared with controls. Hence, increased interstitial concentrations of proinflammatory cytokines in symptomatic muscles might be important in the pathogenesis of the disease.[27]

T-helper-1 and T-helper-17 (Th17) lymphocytes are also implicated in the pathogenesis of polymyalgia rheumatica and giant cell arteritis.[28] Although the suppressive activity of circulating regulatory T cells is not altered, a decrease in the number of regulatory T cells and a noticeable shift in the Th17 cell to regulatory T-cell ratio (towards an increased Th17 cell response) is observed in both conditions.[29] In patients recently diagnosed with polymyalgia rheumatica or giant cell arteritis an inverse correlation exists between the number of B cells and the erythrocyte sedimentation rate, C-reactive protein, and serum B-cell activating factor concentrations.[30] Patients newly diagnosed with giant cell arteritis or polymyalgia rheumatica have decreased numbers of circulating B cells compared with healthy controls, but the number of B cells recovers after therapy in these patients.[30]

Clinical manifestations

The cardinal clinical feature of polymyalgia rheumatica is pain with restricted range of motion and stiffness of the shoulder girdle in patients older than 50 years. Patients often complain of pain and stiffness in the upper arms, neck, pelvic girdle, hips, and thighs.[31] These clinical manifestations are usually bilateral. The onset of symptoms is often rapid, generally over a few days and in some cases acutely overnight. Symptoms are associated with aching and early morning stiffness in the affected musculoskeletal regions. Typical of inflammatory pain and stiffness, symptoms are characteristically worse in the morning and improve progressively over the day, and worsen after rest or when the patient is inactive for a long time. Morning stiffness is typical in polymyalgia rheumatic, lasting at least 30 min and usually for more than 45–60 min.[32] Activities of daily living, such as dressing, brushing hair, getting out of bed, or rising from a chair become difficult and are associated with severe pain. Pain at night is also typical and often patients have difficulties falling asleep.[32]

Shoulder pain is almost invariably present, whereas neck and hip girdle involvement occurs in 50–90% of cases.[10,32] Although in some cases symptoms might be unilateral at disease onset, they soon become bilateral.[10,32]

Constitutional manifestations such as low-grade fever, fatigue, asthenia, anorexia, and weight loss occur in up to 40–50% of patients.[32–34] Fever (temperature ≥38°C) might be a presenting symptom of isolated polymyalgia rheumatica. Persistent high fever is more common in patients with polymyalgia rheumatica associated with giant cell arteritis than in those with isolated polymyalgia rheumatica.[32,35]

On physical examination active motion of the shoulders is restricted because of pain without clinically observable joint swelling. Examiner-assisted passive range of motion might sometimes be almost normal. The shoulder pain is diffuse, and not localised to specific shoulder structures.[36] Painful restriction of active movements of the neck and hips is also present in typical cases. Muscle tenderness might also be present but

muscle weakness is not common despite the presence of muscle pain.[32]

***Panel:* Proposed criteria for the diagnosis and classification of polymyalgia rheumatica**

Bird criteria, 1979[43]
- Bilateral shoulder pain with or without stiffness
- Onset of illness within past 2 weeks
- Initial erythrocyte sedimentation rate (ESR) 40 mm per h or higher
- Age 65 years or older
- Morning stiffness exceeding 1 h
- Depression or weight loss
- Bilateral upper arm tenderness

(Diagnosis of probable polymyalgia rheumatica requires three or more of these criteria)

Jones and Hazleman criteria, 1981[45]
- Shoulder or pelvic girdle pain without muscle weakness
- Morning stiffness lasting for more than 1 h
- Disease duration of more than 2 months
- ESR greater than 30 mm per h or C-reactive protein concentration of more than 6 mg/L
- Absence of rheumatoid arthritis
- Absence of objective signs of muscle disease
- Fast and dramatic response to systemic glucocorticoids

(Diagnosis requires the fulfilment of all criteria)

Chuang and Hunder criteria, 1982[34]
- Age 50 years or older
- Bilateral aching and stiffness persisting for 1 month or more involving two of the following areas: neck or torso, shoulders or upper arms, hips or thighs
- ESR greater than 40 mm per h
- Exclusion of other diagnoses with the exception of giant cell arteritis

(All the above criteria are required for a diagnosis of polymyalgia rheumatica)

Healey criteria, 1984[44]
- Persistent pain for 1 month or more involving two of the following areas: neck, shoulders, or pelvic girdle
- Morning stiffness lasting for more than 1 h
- Rapid response to prednisolone (≤20 mg per day)
- Absence of other joint or musculoskeletal diseases
- ESR greater than 40 mm per h

(Diagnosis of polymyalgia rheumatica requires individuals to be aged 50 years or older and the fulfilment of three or more of the criteria)

American College of Rheumatology and European League Against Rheumatism classification criteria, 2012[38]

Patients aged 50 years or older with bilateral shoulder aching and abnormal C-reactive protein concentrations or ESR, plus at least four points (without ultrasonography) or five points or more (with ultrasonography) from:
- Morning stiffness for more than 45 min (two points)
- Hip pain or restricted range of motion (one point)
- Absence of rheumatoid factor or anti-citrullinated protein antibodies (two points)
- Absence of other joint involvement (one point)
- If ultrasonography is available, at least one shoulder with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis (either posterior or axillary); and at least one hip with synovitis or trochanteric bursitis (one point)
- If ultrasonography is available, both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis (one point)

Other joint manifestations might also be seen.[32] Clinical manifestations of peripheral synovitis occurs in a variable percentage of patients, ranging from low to present in as many as 23–39% of patients.[37,38] Arthritis is often asymmetrical and not associated with cortical bone erosions,[39,40] most commonly occurring in the knee and wrist.[40] Joint manifestations resolve in most patients when treatment with glucocorticoids is started.[39,40] Peripheral synovitis might also include inflammation of the periarticular tissues (tendinitis, bursitis), especially of the arms and hands, and can be confirmed by ultrasonography and other imaging techniques. Carpal tunnel syndrome detected by ultrasonography has been reported in 14% of patients with polymyalgia rheumatica and distal tenosynovitis in 3% of patients.[38] In a 1998 study,[39] asymmetric peripheral arthritis predominantly affecting the knees and wrists on ultrasonography was reported in 25% of 117 patients.[39]

In some cases, polymyalgia rheumatica might present with distal swelling and oedema that can be similar to that in patients with remitting seronegative symmetrical synovitis with pitting oedema syndrome.[41,42] The syndrome is characterised by synovitis and extensor tendon synovitis of the hands and feet. Patients with this condition have distal extremity swelling with pitting oedema mostly over the dorsum of the hands and wrists and less commonly over the ankles and feet, and it has been described as a complication of polymyalgia rheumatica in 12% of patients.[41] Similar to the inflammatory arthritis in patients with polymyalgia rheumatica, these symptoms resolve rapidly after the onset of glucocorticoid therapy.[41]

Laboratory abnormalities

Rises in acute phase reactants is a typical feature in patients with polymyalgia rheumatica. An erythrocyte sedimentation rate of 40 mm or higher per h is regarded as a classification criterion by some[34,43,44] (panel). Other authors recommend an erythrocyte sedimentation rate of more than 30 mm per h or a C-reactive protein concentration of more than 6 mg/L as a classification criterion for polymyalgia rheumatica diagnosis.[45] The 2012 European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) provisional classification criteria[38] also included abnormal erythrocyte sedimentation rate or abnormal concentrations of C-reactive protein as an essential criterion for the diagnosis of the disease (panel).

The initial erythrocyte sedimentation rate is lower than 40 mm per h in up to 20% of patients with polymyalgia rheumatica.[46,47] The percentage of patients with a low erythrocyte sedimentation rate ranges between 7% and 20%.[46,47] Patients with polymyalgia rheumatica and low erythrocyte sedimentation rates have similar clinical characteristics and disease course to those with high erythrocyte sedimentation rates.[46,47] However, those with low erythrocyte sedimentation rates are usually younger with a lower frequency of fever, weight loss, and anaemia than those with erythrocyte sedimentation rates of 40 mm

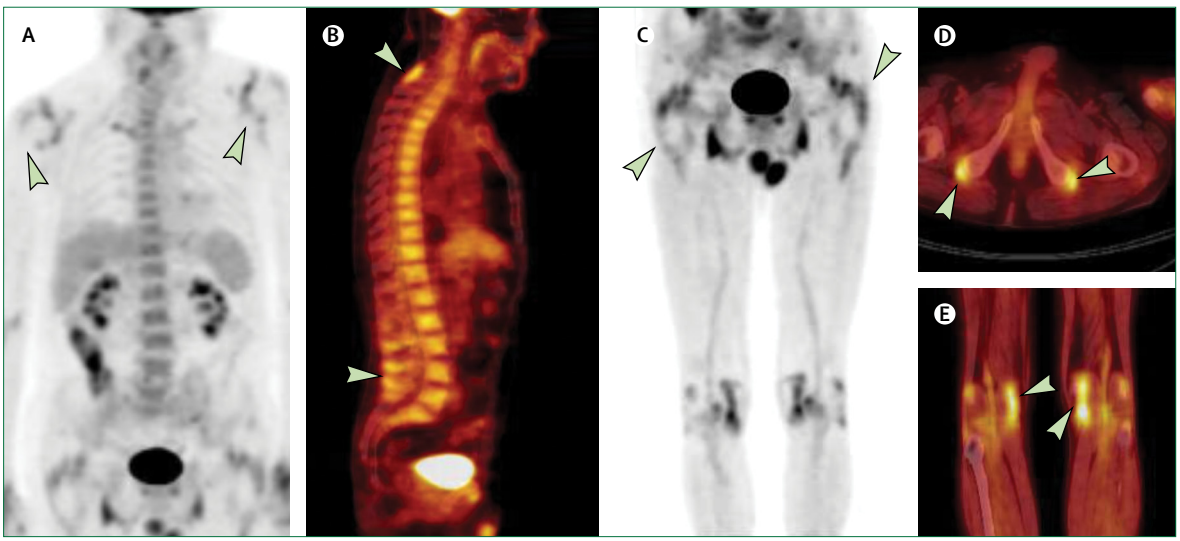

***Figure 1*: FDG-PET integrated with CT images in a 75-year-old man with polymyalgia rheumatica**
(A) PET image showing extensive inflammatory involvement of the shoulders (arrows). (B) PET-CT image showing the cervical and lumbar interspinous processes (arrows). (C) PET image of the hips showing a small increase in FDG uptake in the peritrochanteric bursae (arrows). (D) PET-CT image of the greater trochanter and ischial tuberosity bursae (arrows). (E) PET-CT image of the knees at periarticular level (arrows). FDG=^{18}F-fluorodeoxyglucose.

or higher per h.[46] C-reactive protein might be more specific and more sensitive than the erythrocyte sedimentation rate for the detection of inflammation and assessing disease activity.[48,49] Whether the measurement of C-reactive protein concentration is more useful than erythrocyte sedimentation rate for the initial diagnosis of polymyalgia rheumatic is unclear. C-reactive protein production is mainly induced by interleukin 6. Concentrations of this cytokine are typically increased in patients with polymyalgia rheumatica before treatment is started. This is also the case for serum concentrations of B-cell activating factor.[50] Both serum biomarkers have a strong association with disease activity,[50] but no evidence is available that they are more useful than C-reactive protein for clinical decision making.[51] Alternative diagnoses should be considered in patients with normal C-reactive protein concentrations and erythrocyte sedimentation rates.

IgG antibodies against ferritin peptide are present in most patients with active giant cell arteritis and polymyalgia rheumatica,[52] but their usefulness in clinical practice is not well established.

Other laboratory abnormalities associated with inflammatory response, such as the presence of increased concentrations of α-2 globulin proteins, normochromic, normocytic anaemia, thrombocytosis, and hypoalbuminaemia can be found in patients with active disease, but are not specific for polymyalgia rheumatica.[50]

Generally, autoantibodies more specific for rheumatoid arthritis or connective tissue diseases, such as anti-citrullinated peptide antibodies, rheumatoid factor, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies, are not present in patients with polymyalgia rheumatica. Nevertheless, low titres of rheumatoid factor can arise in elderly people, but they are not diagnostically significant.[50]

Polymyalgia rheumatica and giant cell arteritis

Giant cell arteritis is a large blood vessel vasculitis that occurs in elderly people.[1,3] This condition is uncommon in people younger than 50 years and incidence of the disease peaks in the 70–79-year age group.[3,53] Similar to polymyalgia rheumatica, giant cell arteritis has a strong genetic association with the HLA-class region and the disease has a high prevalence in Scandinavian countries and in individuals of Scandinavian descent.[3,13,14]

Giant cell arteritis and polymyalgia rheumatica are often concurrent and overlapping conditions.[54] Therefore, all patients with polymyalgia rheumatica should be carefully assessed for symptoms and examined for signs of giant cell arteritis, including palpation of temporal, radial, and pedal arteries. Polymyalgia rheumatica might be the presenting manifestation of giant cell arteritis. In a series of patients with giant cell arteritis in whom the diagnosis was confirmed by temporal artery biopsy, 40–50% of patients had polymyalgia rheumatica manifestations.[3,53,54]

Data for the frequency of so-called silent giant cell arteritis confirmed by a positive temporal artery biopsy in patients presenting with isolated polymyalgia rheumatica are variable. About 20% of patients with pure polymyalgia rheumatica are diagnosed with giant cell arteritis, and most studies[54] estimate the incidence to be between 10% and 30%. Clinically, patients with isolated polymyalgia rheumatica have lower mean platelet counts and erythrocyte sedimentation rates and higher mean haemoglobin concentrations than those

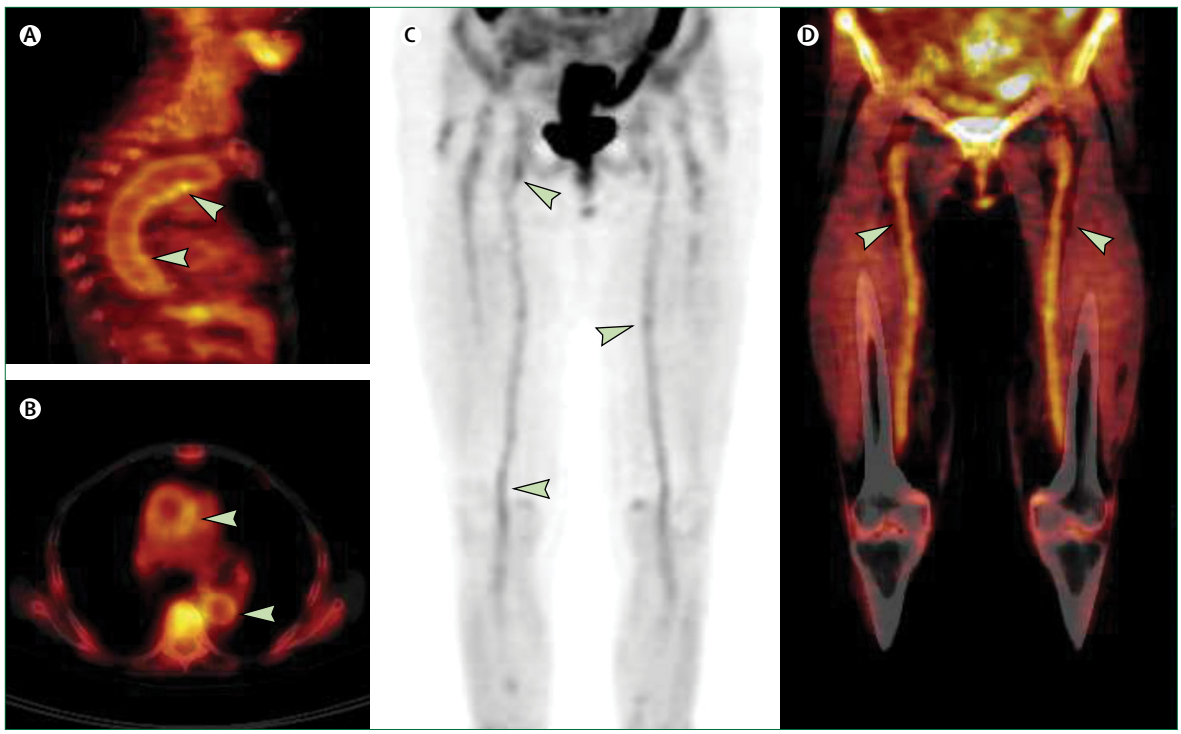

Figure 2: **^{18}F-fluorodeoxyglucose integrated with PET and CT images**
PET-CT images show inflammatory activity (arrows) along the thoracic wall aorta (A, sagittal view; B, transverse view) and PET (C) and PET-CT (D) images show the femoropopliteal arteries (arrows) in a 72-year-old woman with polymyalgia rheumatica and severe pain in the thighs.

with polymyalgia rheumatica associated with biopsy-proven giant cell arteritis.[33] Differences in the genetic profile and gene expression might partly account for disease expression.[55,56]

A major concern is the potential risk of developing severe ischaemic complications of giant cell arteritis in patients who initially present with isolated polymyalgia rheumatica.[54,57] Therefore, close follow-up of patients diagnosed with pure isolated polymyalgia rheumatica is important to identify symptoms of ischaemia.

See Online for appendix

Whether imaging techniques should be considered in all patients with polymyalgia rheumatica to assess for cranial and large-vessel giant cell arteritis requires investigation. However, research is limited by local expertise and availability of relevant imaging modalities, as well as uncertainty about the clinical significance of the findings. Ultrasonography of temporal and axillary arteries might reveal evidence of occult giant cell arteritis, and advanced imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET has revealed that a third of patients with polymyalgia rheumatica without symptoms or signs of giant cell arteritis might have an occult large vessel involvement (figure 1, 2).[58–61] Clinicians should consider assessing patients with polymyalgia rheumatica for aortitis using advanced imaging (ie, PET, CT, or MRI) if they have atypical findings such as low back pain or pain mainly affecting the legs, which are associated with increased acute phase reactants.[62]

Mimics of polymyalgia rheumatica

Symptoms of polymyalgia rheumatica are non-specific and many disease mimics exist. Clinicians should be aware of the most common conditions that mimic polymyalgia rheumatica, including rheumatoid arthritis, shoulder osteoarthritis, polyarticular calcium pyrophosphate deposition disease, rotator cuff disease, and adhesive capsulitis (frozen shoulder).

Additional information about conditions that mimic polymyalgia rheumatica is shown in the table and appendix.[32,37–40,63–77]

Diagnostic investigations and classification criteria

Several sets of criteria for the classification and diagnosis of polymyalgia rheumatica have been proposed (panel). The criteria have common features, such as older age (≥50 years), typical involvement of shoulders, and the presence of raised acute phase reactants.[34,38,43–45] The criterion of older age (>50 years) was proposed by Chuang and colleagues,[34] Healey,[44] and the 2012 EULAR/ACR criteria.[38,78] Bilateral clinical involvement that predominantly involves the shoulders with morning stiffness of at least 45 min to 1 h has been included in the different criteria sets. Increase of erythrocyte sedimentation rate, generally to more than 40 mm per h, or increased C-reactive protein concentration, is also required for the diagnosis and classification of polymyalgia rheumatica.

In addition to these pivotal criteria, several other disease features are important for diagnosis. The 2012 EULAR/ACR classification criteria highlight the importance of hip involvement and the absence of rheumatoid factor and anti-citrullinated peptide antibodies for the diagnosis of polymyalgia rheumatica. Shoulder and hip girdle pain without pain in other joints indicates a diagnosis of polymyalgia rheumatica.[38,78]

Ultrasonography and MRI are useful and equally effective to confirm the presence of bursitis in patients with polymyalgia rheumatica (figure 3).[21,22,79,80] The 2012 EULAR and ACR preliminary classification criteria for polymyalgia rheumatica included, for the first time, the use of ultrasonography data when available. The criteria highlight the importance of ultrasonography findings of bilateral subacromial or subdeltoid bursitis and trochanteric bursitis for the diagnosis of polymyalgia rheumatica in patients with inflammatory pain of the shoulder or pelvic girdle.[38,78]

Macchioni and colleagues[81] compared the performance of the different classification criteria for polymyalgia rheumatica in a single-centre study using ultrasonography. They studied consecutive patients with new-onset polymyalgia rheumatica, in whom the diagnosis was confirmed during a prospective 12-month follow-up. Patients were classified by each of the different classification criteria for polymyalgia rheumatica. Consecutive patients (aged ≥50 years) in whom a diagnosis of rheumatoid arthritis or other inflammatory articular diseases was confirmed after 12 months of follow-up were used as the control group. On the basis of that approach, the most sensitive criteria were the 2012 EULAR and ACR classification criteria (92·6%). With the addition of ultrasonography, the specificity of these criteria increased from 81·5% to 91·3% in patients with polymyalgia rheumatica and from 79·7% to 89·9% in those with rheumatoid arthritis. When compared with the previous classification criteria,[34] the 2012 EULAR and ACR criteria had the highest discriminatory ability. Therefore, the use of ultrasonography increases the specificity of the 2012 EULAR and ACR criteria.[81] However, in the absence of other suggestive clinical features, the presence of isolated ultrasonography abnormalities should not lead to a diagnosis of polymyalgia rheumatica.[82]

A 2015 study[83] with MRI described a subset of patients with polymyalgia rheumatica who had a characteristic pattern of symmetrical extracapsular inflammation adjacent to the greater trochanter, acetabulum, ischial tuberosity, or symphysis pubis. This pattern of inflammation on MRI was associated with raised C-reactive protein and interleukin-6 serum concentrations and complete glucocorticoid response.[83]

^{18}F-FDG-PET integrated with CT has proved useful not only to confirm the presence of vascular involvement but also that of cervical and lumbar spine bursitis.[84] Uptake of ^{18}F-FDG associated with interspinous bursitis is more commonly seen in the lumbar region than in the cervical region (figure 1). However, this increased lumbar ^{18}F-FDG uptake does not correlate with clinical symptoms.[85]

Healey[44] and Jones and Hazleman[45] included a rapid response to glucocorticoids as another criterion for the diagnosis of polymyalgia rheumatica, although this is non-specific and not included in the 2012 EULAR and ACR criteria.[38]

Classification criteria used by the authors of this Seminar and other authors in their epidemiological studies vary.[10,11] For the epidemiological studies[10] of

	Clinical features
Inflammatory rheumatic diseases	
Rheumatoid arthritis, especially late-onset rheumatoid arthritis	Symmetrical and distal joint distribution; rheumatoid factor or ACPA positive; erosions on joint radiographs
Late-onset spondyloarthritis	Low back stiffness and pain; spinal ankylosis or sacroiliitis on radiographs; peripheral arthritis; psoriasis
Remitting seronegative symmetrical synovitis with pitting oedema syndrome	Peripheral hand or foot pitting oedema
Inflammatory myopathies	Proximal muscle weakness, rash; high creatine phosphokinase concentrations
Other connective tissue diseases (late-onset systemic lupus erythematosus, vasculitis, scleroderma, Sjögren syndrome)	Fatigue; multisystem disease; specific autoantibodies depending on every disease; anti-DNA antibodies; low C3 and C4 serum concentrations
Crystalline arthropathies (calcium pyrophosphate and hydroxyapatite deposition disorders)	Shoulder, carpal, and knee involvement; radiography and ultrasound findings; presence of crystals in synovial fluid
Non-inflammatory rheumatic diseases	
Degenerative joint disease, spinal spondylosis	Mechanical joint pain; erythrocyte sedimentation rate and C-reactive protein concentration usually normal; degenerative changes on joint radiographs
Rotator cuff disease, adhesive capsulitis (frozen shoulder)	Periarticular pain, restricted range of motion; characteristic findings on ultrasound and MRI
Fibromyalgia, depression	Fatigue, long-standing pain, multiple trigger points
Infections	
Viral and bacterial infections (eg, bacterial endocarditis and mycobacterial infections)	Fever, weight loss, heart murmur; leucocytosis; urine analysis disturbances; virus serology, blood cultures
Malignant diseases	
Solid tumours (kidney, stomach, colon, lung, others)	Weight loss, fatigue; diffuse aching symptoms not limited to shoulder or hip girdles; evaluation guided by symptoms, abnormal findings on physical examination, sex, and age
Haematological diseases (eg, myeloma, lymphoma, leukaemia)	Weight loss, fatigue; diffuse aching symptoms not limited to shoulder or hip girdles; evaluation guided by symptoms, localising findings, sex, and age
Miscellaneous disorders	
Parkinsonism	Stiffness, rigidity, shuffling gait, gradual onset
Thyroid and parathyroid diseases	Suggestive clinic; abnormal concentrations of thyroid-stimulating hormone, calcium, phosphorus, or parathyroid hormone
Hypovitaminosis D	Low vitamin D concentrations
Drug-induced myopathies (statins, colchicine, others)	Pain and muscle weakness associated with drug use; creatine phosphokinase increases; anti-3-hydroxy-3-methylglutaryl coenzyme A antibodies
Primary amyloidosis	Fatigue, weight loss, systemic and multiorgan dysfunction

ACPA=anti-citrullinated protein antibodies.

***Table*: Mimics of polymyalgia rheumatica**

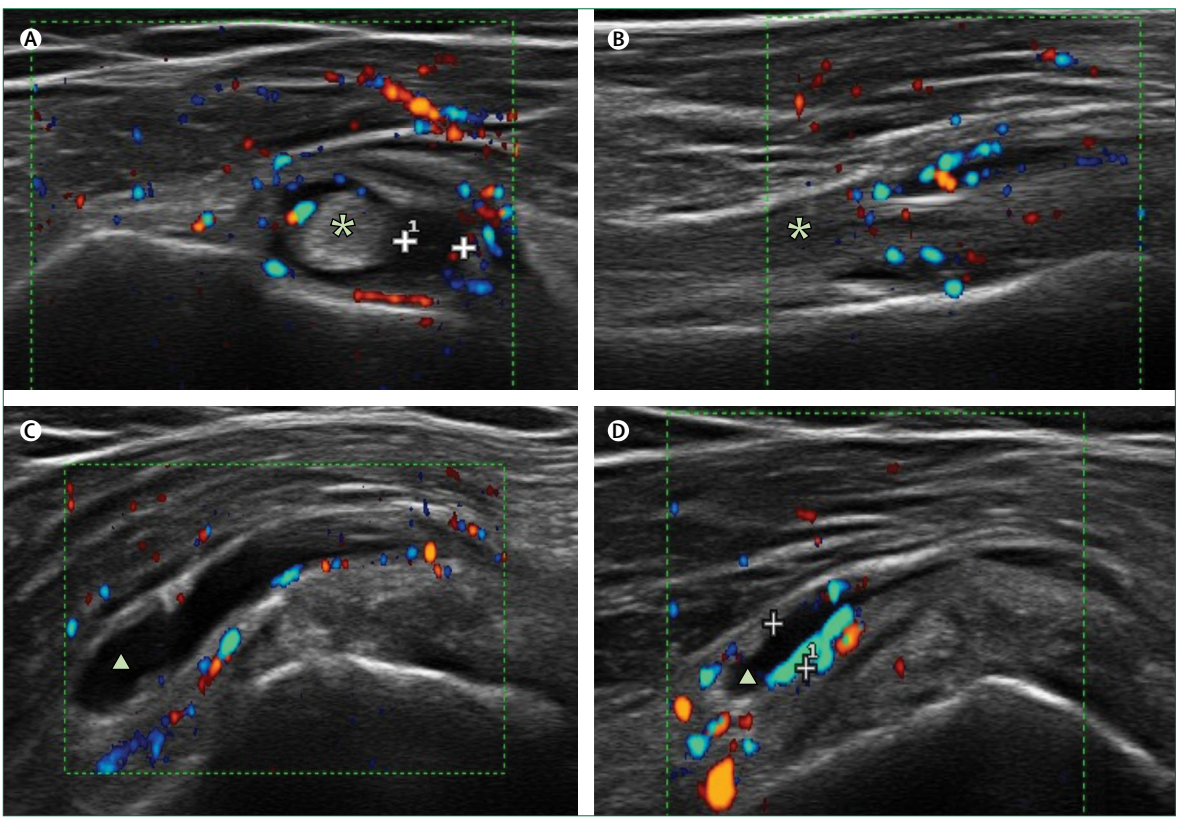

***Figure 3*: Ultrasonography of the shoulders in a patient with polymyalgia rheumatica**
Ultrasonography images show typical findings at periarticular soft tissues. (A) Transverse view of bilateral biceps tenosynovitis. (B) Longitudinal view of bilateral biceps tenosynovitis. (C) Longitudinal view of the subacromial bursa. (D) Longitudinal view of the subacromial bursa with increased vascularisation. In all locations, an increase of power Doppler signal can be seen around the tendon (*) and at the synovial tissue of the tendon sheath and the subacromial bursa. + indicates the margins of the synovial fluid. Δ indicates the interior of the subacromial bursa.

polymyalgia rheumatica in Lugo, Spain, the criteria proposed by Chuang and colleagues[34] were used. Additionally, as proposed by Healey,[44] to make a diagnosis of definitive or pure polymyalgia rheumatica, the rapid resolution of polymyalgia rheumatica symptoms in less than 1 week with a median initial dose of prednisolone of 15 mg per day was required.[10] Consistent with the 2012 EULAR and ACR criteria,[38] the criteria proposed by Chuang and colleagues[34] indicate the importance of older age (≥50 years), the presence of bilateral shoulder pain, and abnormal increase of erythrocyte sedimentation rate.[34] Therefore, we believe that the 2012 EULAR and ACR criteria represent an important step towards standardising the diagnosis of polymyalgia rheumatica.

To address whether the 2012 EULAR and ACR criteria are useful to discriminate polymyalgia rheumatica from other pathological conditions, a prospective multicentre study[86] of patients (aged ≥50 years) presenting with new-onset bilateral shoulder pain and raised erythrocyte sedimentation rate or C-reactive protein concentrations was done in Turkey. Although the clinical classification criteria for polymyalgia rheumatica were very sensitive, their performance was suboptimum for the discrimination of polymyalgia rheumatica from other inflammatory and non-inflammatory shoulder conditions, in particular from seronegative rheumatoid arthritis.[86]

With respect to the applicability of the 2012 EULAR and ACR classification criteria to non-European and non-North American populations, Matsui and colleagues[87] assessed these criteria in Japanese patients diagnosed with polymyalgia rheumatica using the Bird criteria.[43] The authors noted that only 32 (43%) of the 75 patients diagnosed with polymyalgia rheumatica according to the Bird criteria fulfilled the new 2012 EULAR and ACR classification criteria. Morning stiffness lasting more than 45 min was the only independent predictive factor. Therefore, the 2012 EULAR and ACR classification criteria might not be applicable to Asian populations.[87]

The diagnosis of polymyalgia rheumatica in typical cases is fairly straightforward, and is supported by a clinical history, physical examination, and the assessment of routine laboratory markers of inflammation.[40,74] New-onset headache, scalp tenderness, or visual manifestations might indicate that polymyalgia rheumatica is associated with giant cell arteritis.

Clinicians assessing patients with suspected polymyalgia rheumatica must actively search for signs of cancer, infection, and other mimics.[88] Little improvement after treatment with 12·5–25·0 mg per day prednisolone should indicate a diagnosis other than isolated polymyalgia rheumatica.[39,74] The assessment and management of a patient presenting with polymyalgia features is described in the appendix.[40,70,74]

Management of polymyalgia rheumatica

Oral prednisolone is the mainstay of treatment in polymyalgia rheumatica.[89–91]

A prednisolone dose ranging between 12·5 and 25 mg per day is sufficient to yield rapid improvement of polymyalgia features in most cases.[28,51,89,92,93] However, the dose might be individualised according to each patient. Although the biological activity of glucocorticoids is certainly not only bodyweight dependent, generally a heavy person (>80 kg) without risk factors for side-effects such as diabetes mellitus or osteoporosis could receive a starting dose of 20–25 mg per day, whereas a lighter weight person (<60 kg) with risk factors could receive a lower starting dose of 12·5–15·0 mg per day. Although the EULAR and ACR recommendations suggest the use of a single dose of glucocorticoids,[92,93] the half-life of prednisolone is roughly 4 h. In our experience, in some patients a divided dose of prednisolone at the onset of treatment might help to more rapidly improve the symptoms. Patients experience a rapid improvement of symptoms, generally within 24–72 h and in most cases within a week after the onset of therapy.[90,91] However, consistent with a 2012 report,[94] a prospective inception cohort study of polymyalgia rheumatica showed that 3 weeks after starting treatment with prednisolone 15 mg daily, more than 55% of patients failed to achieve a complete response to therapy—as defined by a greater than 70% improvement in pain, morning stiffness for less than 30 min, and normal inflammatory markers.[95] Generally, the erythrocyte sedimentation rate and C-reactive protein concentration also fall to normal values within 2–4 weeks.[28,80]

However, the initial doses of glucocorticoids and tapering regimens have not been adequately investigated.[96] Generally, the initial prednisolone dose is maintained for 3–4 weeks and is then tapered progressively. The recommended glucocorticoid reduction schemes are based on expert opinion because evidence from randomised controlled trials is scarce.[96,97] The EULAR and ACR recommendations suggest reduction steps of 1–1·25 mg at daily doses below 10 mg prednisolone per day. Indeed, 1·25 mg reduction steps apply mainly for countries in which 1 mg prednisolone tablets are not available.[96] In our experience, patients receive an initial prednisolone dose of 15 mg per day, with a tapering scheme of 12·5 mg daily for 2–4 weeks, 10 mg daily for 4–6 weeks, and then the daily dose might be reduced by 2·5 mg every 2–3 months. Alternatively, once the dose has been reduced to 10 mg per day, the daily dose can be decreased by 1 mg each month until discontinuation of glucocorticoid therapy.[10]

Other treatment strategies include bilateral shoulder injections of 6-methylprednisolone every 4 weeks in newly diagnosed patients with polymyalgia rheumatica, which has been reported to result in rapid improvement of shoulder and systemic symptoms, but this effect was sustained in only 50% of patients.[98]

The use of intramuscular methylprednisolone acetate (120 mg every 2 weeks for 12 weeks followed by monthly injections with dose reductions of 20 mg every 3 months) was less effective than an initial daily dose of 15 mg oral prednisolone and led to lower rates of discontinuation of the therapy.[99]

Conventional immunosuppressive drugs might be used in patients who have severe side-effects associated with glucocorticoids or in those who require long-term glucocorticoid therapy because of relapse.

Oral or subcutaneous administration of methotrexate is the most commonly used glucocorticoid sparing drug, used at a starting dose of 10–15 mg per week.[91] Studies of the effectiveness of methotrexate are conflicting, some show no benefit,[100] while others show benefit,[101,102] suggesting that methotrexate is useful to achieve remission, and to reduce the number of relapses, although overall the reported benefits are generally small. Reports of use of other drugs such as azathioprine, are based on small case series with uncertain benefit.[103]

Although a review of 99 patients treated with tumour necrosis factor-α blockers reported good clinical and acute phase reactant response,[104] results from more rigorous studies concluded that they are ineffective, expensive, and potentially harmful in patients with polymyalgia rheumatica. The only randomised clinical trial[105] showed no benefit of adding the antitumour necrosis factor-α monoclonal antibody infliximab to prednisolone for treating newly diagnosed patients. We believe that anti-tumour necrosis factor-α drugs are not indicated in polymyalgia rheumatica.[92,93]

Preliminary data[106–108] suggest that the anti-interleukin-6 receptor antibody tocilizumab might be useful in patients who respond poorly to or have unacceptable adverse side-effects with glucocorticoids. Most of the experience with tocilizumab is based on patients with giant cell arteritis, often associated with polymyalgia rheumatica.[109–111] Tocilizumab was effective in patients with aortitis, some of whom presented with isolated polymyalgia rheumatica that was refractory to prednisolone.[112] In another study,[113] patients with newly diagnosed polymyalgia rheumatica who had been on glucocorticoids for less than 1 month were treated monthly with intravenous tocilizumab (8 mg per kg bodyweight) for 1 year, with rapid tapering of glucocorticoids. Relapse-free remission without glucocorticoids at 6 months was achieved in the nine patients in whom it was assessed. These patients were able to discontinue glucocorticoids within 4 months of

study entry. Persistent remission was also achieved in these patients, throughout the entire 15 month study.[113] Although abatacept has been used in giant cell arteritis, no published data are available on its use in polymyalgia rheumatica.[114]

Osteoporosis prophylaxis should be used to prevent bone loss mediated by glucocorticoids in polymyalgia rheumatica.[115,116] Vitamin D supplementation should be considered.[117] Additional bisphosphonate treatment should be used in patients at risk of fracture, according to glucocorticoid-induced osteoporosis management recommendations and national guidelines.[118] Denosumab, a potent antiresorptive drug that inhibits the receptor activator of nuclear factor-κB ligand, is currently being investigated for the management of glucocorticoid-induced osteoporosis.[119] The medical management of patients with polymyalgia rheumatica is summarised in the appendix.

Relapses

Relapses are defined as the recurrence of polymyalgia rheumatica symptoms that are generally associated with elevation rise in erythrocyte sedimentation rate and C-reactive protein concentration. Persistently high concentrations of C-reactive protein and interleukin 6 were significantly associated with an increased risk of relapse in patients with polymyalgia rheumatica.[120] This association was especially evident for patients with persistently high concentrations of interleukin 6 during the first year of therapy.[120]

In some cases, a relapse indicates the presence of previously unrecognised giant cell arteritis.[121] However, an isolated small increase in erythrocyte sedimentation rate or C-reactive protein concentration in an asymptomatic patient might not be a relapse, therefore increase of acute phase reactants alone is not an indication to raise the dose of prednisolone.[58,90]

Most patients will relapse during the course of their disease, which might be more than 2–3 years in duration, and can be longer. The frequency of relapse in the first year of disease is 20–55%.[10,122,123]

The speed of glucocorticoid tapering has been associated with the risk of relapses.[10,122] Two studies[10,121] showed that a tapering rate of less than 1 mg per month after an initial prednisolone dose of 15 mg per day was associated with fewer relapses of polymyalgia rheumatica. Rapid reduction regimes lead to higher frequency of relapses.[124,125] Relapses generally occur when glucocorticoids have been discontinued or when the dose of prednisolone is less than 5 mg per day.[10] They are generally suppressed by resumption of prednisolone in those patients who had discontinued this therapy. In patients who are still taking prednisolone at the time of the relapse, the dose of prednisolone should be increased. The EULAR and ACR recommendations for management suggest that the oral prednisolone dose is increased to that of the pre-relapse dose, followed by a gradual reduction within 4–8 weeks to the dose at which the relapse occurred.[96] This dose increase is often successful in managing relapse, but it might be necessary to increase prednisolone by 2·5–5·0 mg per day above the dose at which relapse occured.[10] Methotrexate can be considered in patients who have experienced more than two relapses of polymyalgia rheumatica.[90]

Comorbidities and outcomes

Most patients with polymyalgia rheumatica have side-effects associated with glucocorticoid therapy that depend on the duration of treatment and the cumulative dose.[126] Nevertheless, overall cardiovascular mortality does not seem increased in this disease.[127,128] Although patients with isolated disease were reported to be at increased risk for peripheral artery disease,[129] and polymyalgia rheumatica was associated with higher risk for stroke in Chinese individuals,[130] a large registry study of 9776 patients who were followed up between January, 1997, and March, 2010, reported no evidence of increased risk of ischaemic heart disease, cerebrovascular events, peripheral arteriopathy, or any other vascular complication.[131] All long-term population-based studies to date report that polymyalgia rheumatica does not decrease life expectancy.[8,10,132]

Controversies in polymyalgia rheumatica management

No unanimous consensus has been reached on the optimum dose of glucocorticoids to prescribe for patients with isolated polymyalgia rheumatica. Experts from the 2015 EULAR and ACR collaborative initiative[92,93] proposed an initial prednisolone dose between 12·5–25·0 mg daily or equivalent. This group of experts recommends a single dose of prednisolone.[92,93] However, we believe that an initial divided dose might be more effective to improve stiffness and pain in the morning when the patient is diagnosed with polymyalgia rheumatica.

The recommended glucocorticoid reduction schemes are also based on expert opinion because few randomised controlled trials have been done.

Although improvement of pain and stiffness associated with a normalisation of erythrocyte sedimentation rate and C-reactive protein concentration indicates good response to therapy, other data to establish the clinical response are scarce.

Future directions and research questions

Management recommendations should take into account patient perspectives. One way to achieve this is to focus on the severity rather than on the duration of morning stiffness, especially at the time of diagnosis because patients usually find it difficult to measure the exact duration of stiffness.

In addition to a definitive biomarker for diagnosis of polymyalgia rheumatica, better markers of disease activity are needed. These biomarkers could be serological

and imaging techniques that might be better than the current acute phase markers.[133] In this context, a new core set of biomarkers for future clinical trials in polymyalgia rheumatica has emphasised the need for formal validation of instruments to measure disease activity, physical function, glucocorticoid-associated adverse events, and the risk of development of giant cell arteritis in patients with the condition.[133]

The identification of biomarkers that might help to distinguish patients with isolated polymyalgia rheumatica from those with polymyalgia symptoms associated with giant cell arteritis or from conditions mimicking polymyalgia rheumatica is also needed.

Another question to be addressed is that of the long-term clinical and therapeutic implication of findings of increased large vessel uptake on ^{18}F-FDG-PET in patients with apparently isolated polymyalgia rheumatica without structural vascular changes of large vessels when other imaging techniques such as MRI are used.

Studies[96,134] aimed to establish the optimum initial dose, speed of glucocorticoid tapering, and optimum length of treatment should be done, including randomised controlled trials for assessment of the initial glucocorticoid dose and glucocorticoid reduction schemes.

New treatment options are needed for polymyalgia rheumatica. Preliminary data suggest the superior effectiveness of modified-release prednisolone compared with immediate-release prednisolone in patients with polymyalgia rheumatica.[135] Randomised controlled trials of glucocorticoid-sparing drugs, including conventional and biological disease-modifying anti-rheumatic drugs, and more targeted drugs are needed. However, the recruitment of adequate numbers of elderly patients for such trials will present a challenge. Validation studies of the provisional EULAR and ACR classification criteria should be done in a large multinational independent cohort of patients.

Contributors

All authors contributed equally to this manuscript.

Declaration of interests

MAG-G received personal fees from Abbvie, Roche, Sanofi, Jansen, Lilly, Pfizer, Novartis, and MSD, outside of the submitted work. ELM received grants from Novartis, Bristol-Myers Squibb, and Genetech, outside the submitted work, and has been involved in the efforts of the European League Against Rheumatism and American College of Rheumatology to develop classification criteria and management recommendations for polymyalgia rheumatica. SC declares no competing interests.

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