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Review

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Polymyalgia rheumatica - an up-to-date review on diagnosis and management

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Abstract

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in those over the age of 50 years. Previously it was considered to be a benign clinical syndrome characterised by subacute onset bilateral shoulder and pelvic girdle pain and stiffness, with a corresponding rise in acute phase reactants, and distinctive rapid resolution of symptoms with the instigation of moderate doses of glucocorticoids. However, over the past decade, with the advancements and, indeed, wider application of imaging modalities in PMR, we have garnered an increased understanding of the anatomic predilection of inflammation and, subsequently, disease pathogenesis. Moreover, our appreciation of the relationship between PMR and giant cell arteritis (GCA) has strengthened. Glucocorticoids have formed the cornerstone of the management of PMR for decades, with often protracted treatment durations and associated high cumulative steroid burden and adverse effects. However, we are now on the cusp of a new era in the management of PMR, with our therapeutic armamentarium expanding with the recent FDA approval of the interleukin -6 antagonist sarilumab for the management of refractory disease. It is an exciting time for PMR, and this review aims to explore the recent advancements in both diagnosis and management, while also providing an updated perspective on the relationship between PMR and GCA.

Keywords: Polymyalgia rheumatica, giant cell arteritis, vasculitis

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory disorder characterised by early morning stiffness and severe pain of the shoulder and pelvic girdle[1]. It is the most common inflammatory rheumatic disease of those over the age of 50 years[2,3]. The incidence increases progressively with age, with a peak incidence occurring in those between 70-79 years of age, suggesting that aging is central to its pathophysiology[4,5]. There is a female preponderance, with more than two-thirds of those diagnosed with PMR being female[6]. The lifetime incidence risk of PMR is estimated at 2.43% for females and 1.66% for males[7].

Until recently, PMR, in the absence of concomitant giant cell arteritis (GCA), was considered a relatively benign and straightforward condition. However, we now understand it is a source of much disability, and indeed, the ubiquitous use of glucocorticoids renders those with it susceptible to increased morbidity. Unfortunately, compared with other inflammatory rheumatic diseases, PMR remains understudied. However, it appears that we are on the cusp of a new era in its diagnosis and management, with the evolution of imaging modalities and resultant improved understanding of disease pathogenesis, and subsequent identification of new therapeutic targets. The objective of this review is to summarise the recent advances in PMR, including its diagnosis and management, and identify future areas for research.

GCA/PMR OVERLAP

Giant cell arteritis (GCA) is the most common form of vasculitis affecting adults, with an incidence rate of approximately 10 per 100,000 in those over the age of 50 years[8]. It is a granulomatous vasculitis that has a predilection for medium and large calibre arteries. Classically, it affects the cranial arteries, so-called cranial GCA (c-GCA), with the pathognomonic constellation of symptoms including headache, scalp tenderness, jaw claudication, and the most feared complication of sudden painless visual loss secondary to anterior ischaemic optic neuropathy. However, with the advancements in diagnostic imaging, we are increasingly aware of the large vessel subtype (LV-GCA), which typically presents with non-specific constitutional symptoms including weight loss, fatigue, fever, and drenching night sweats. C-GCA and LV-GCA are frequently present together, with a reported concomitant rate as high as 83%[9-12]. Moreover, a reported 40%-60% of patients with GCA report symptoms of PMR, and 15%-20% of those with PMR have a concomitant GCA, either at disease onset or throughout the course of their disease[3,13]. Additionally, subclinical vascular involvement has been described in approximately one-third of patients with PMR if systemically screened for by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET), and in 22%-23% if screened for by ultrasound (US)[14-17]. Due to this significant clinical overlap, in addition to the fact that both conditions occur solely in those > 50 years of age and have an IL-6 signature with an excellent initial response to glucocorticoids, there is a move to recognise these conditions not as separate entities, but instead as different manifestations of a common, albeit complex spectrum. To reflect this, the emerging concept of "GCA-PMR spectrum disease" (GPSD) has been proposed by Tomelleri *et al.*[18]. In GPSD, patients are stratified using clinical, laboratory, and imaging criteria, which are proposed to capture the often intertwined heterogeneous disease phenotypes and their resultant different outcomes[18]. The current treatment paradigm of both GCA and PMR has glucocorticoids at the cornerstone, but the dose used to treat PMR is significantly lower than that used to treat GCA. Tomelleri *et al.* hypothesise that there are, in fact, five clinical subsets including cranial GCA, ischaemic GCA, LV-GCA (on its own, or with c-GCA and/or relapsing PMR), isolated pure PMR, and PMR with peripheral arthritis and/or distal involvement such as remitting seronegative symmetrical synovitis with pitting edema (RS3PE)[18]. They propose that each of these subsets can then be used to stratify and personalise appropriate management, by encapsulating each subset's risk of developing acute ischaemic complications, chronic vascular tissue damage, relapse risk, and likely response to available therapeutics[18]. However, this concept is in its infancy, and an international multicentre prospective cohort is needed to map the various disease subsets within the GPSD, with disease

course and long-term critical outcomes.

Moreover, although we have an increased awareness of the prevalence of subclinical GCA in those with PMR, there are a number of unanswered questions surrounding it. At present, in most centres, routine screening of those with PMR to identify subclinical GCA is not considered a standard of care[19]. Subclinical GCA is typically identified through vessel wall imaging, with both US and FDG-PET computed tomography (CT) offering superior diagnostic accuracy *vs.* temporal artery biopsy[20-22]. This results in routine screening being limited by cost, imaging expertise and availability. Given the likelihood that greater than 1 in 5 patients with PMR may have subclinical vasculitis, the routine implementation of screening most certainly warrants consideration. However, prior to this, it is imperative that the implications of the presence of subclinical vasculitis in disease management are determined. To date, there has been no prospective blinded study demonstrating a prognostic difference between those with isolated PMR and those identified as also having subclinical GCA.

Standard lower-dose glucocorticoid tapers employed in PMR treatment are usually sufficient to relieve PMR symptomatology. However, with an increased awareness of the prevalence of subclinical GCA, there is a heightening debate regarding the efficacy of this low-dose steroid regimen in this cohort of patients. While some studies have suggested a potential higher glucocorticoid requirement in those with subclinical GCA, these are all unblinded and thus susceptible to clinician bias, and therefore must be interpreted with extreme caution, especially considering the substantial toxicity associated with glucocorticoids.

Controlled, blinded prospective studies exploring the stratification of patients with subclinical PMR are of utmost urgency and indeed importance, in order to best manage these patients and potentially prevent long-term vascular complications. Until then, the consensus is that these patients should be managed as per those with isolated PMR, using a lower to moderate dose glucocorticoid regimen.

DIAGNOSIS

Clinical diagnosis

Until recently, the perception of PMR as a relatively benign rheumatological condition has resulted in its significance being underestimated and, subsequently, its care being primarily executed in the hands of non-specialists. In reality, the diagnosis of PMR can be extremely complex, with many mimics and, indeed, marked heterogeneity in disease presentation, arguably necessitating the expertise of a specialist. There is no definitive diagnostic test for polymyalgia rheumatica, making it a diagnostic challenge, often associated with much uncertainty. The typical presenting symptom is sudden onset bilateral shoulder pain and stiffness, a feature which is present in up to 95% of those diagnosed with PMR[23]. Patients also typically experience prolonged early morning stiffness, lasting greater than 45 minutes, with pelvic girdle pain observed in up to 70% of patients[23]. However, not all patients present with this typical constellation of symptoms. Up to 50% of patients may have peripheral musculoskeletal involvement[24], a feature which most certainly heightens the diagnostic difficulty. Such distal manifestations include peripheral arthritis, most commonly asymmetric, affecting the wrists and knees[25,26]. Differentiating these patients from those with late-onset rheumatoid arthritis (LORA) can be problematic; however, the combination of bilateral wrist synovitis, and metacarpophalangeal or proximal interphalangeal synovitis is more indicative of a diagnosis of rheumatoid arthritis over PMR[27]. Moreover, the peripheral arthritis typically associated with PMR is non-erosive and very steroid-responsive[28]. Other peripheral manifestations of PMR include carpal tunnel syndrome[28], in addition to tenosynovitis causing distal swelling and edema, resembling those with RS3PE syndrome[29,30]. Although these can be a feature of PMR, they can also often herald the diagnosis of other forms of inflammatory arthropathy and thus their presence requires active consideration of an alternative diagnosis.

Constitutional symptoms including low-grade fever, fatigue, anorexia, and weight loss can also occur in up to 40% of patients with PMR[31].

As described, the presentation of PMR can be nonspecific, and there are numerous so-called "mimics" of PMR including inflammatory arthropathies, inflammatory, and drug-induced myopathies, connective tissue diseases, vasculitis, degenerative musculoskeletal disorders, rotator cuff pathologies, fibromyalgia, malignancy, paraneoplastic syndromes, and infection[31-33]. [Figure 1] Therefore, there is a significant risk of misdiagnosis, which, among other potential devastating consequences, can also lead to unnecessary glucocorticoid exposure, with its associated morbidity.

Consequently, it is imperative that all patients undergo a thorough evaluation including a careful history and comprehensive physical examination, in order to distinguish PMR from other conditions with similar features, which is arguably best done in specialist rheumatology clinics. [Figure 2] A recent international survey of the current practices for PMR by general practitioners and rheumatologists revealed that only approximately 25% of those with a suspected diagnosis of PMR were referred to a rheumatology clinic for assessment, of whom 50% were already on glucocorticoid therapy prior to referral, which undeniably complicates specialist evaluation[34]. Alarmingly, 30% of patients referred for specialist evaluation were initially misdiagnosed[34].

A proposed method of optimising early diagnostic accuracy and, indeed, overall patient outcomes is the implementation of fast-track clinics[35]. The use of such fast-track clinics in GCA has been widely reported, with benefits including rapid and accurate diagnosis, reduced risk of permanent visual impairment, in addition to overall increased cost-effectiveness *vs.* standard care[35-39]. To date, only two studies have reported on the use of fast-track clinics in PMR, with both demonstrating that providing timely and easily accessible specialist care improves diagnosis and, indeed, patient outcomes[40,41]. The patients assessed in the fast-track clinics had a faster time to diagnosis of PMR, decreased the total number of days of inpatient hospitalisations[40,41], and in one study, had a reduced starting dose of prednisolone *vs.* those managed by standard care[40]. Moreover, the implementation of fast-track clinics also appears to be more cost-effective by reducing the annual cost for patients[41]. However, it is worth noting that both of these studies used historical cohorts as their comparator, and both studies were undertaken in Denmark, potentially limiting the transferability of results to other countries.

Laboratory tests and serum biomarkers

It is evident that PMR often proves a diagnostic challenge, and undeniably, one of the most significant unmet needs in its management is the lack of a disease-specific serum biomarker for diagnosis and disease prognostication. Unfortunately, compared to other rheumatological conditions, there is a paucity of data pertaining to serum biomarkers in PMR. The non-specific acute phase reactants, erythrocyte sedimentation rate (ESR), and c-reactive protein (CRP) are the most commonly used serum inflammation markers in PMR, and form part of the 2012 EULAR/ACR classification criteria for PMR[42]. [Table 1] However, although both of these markers are typically elevated in PMR, there is a subpopulation of patients in whom these markers remain normal[43-45]. Additionally, their role in disease prognostication and identification of those with concomitant vasculitis is at present limited. Moreover, with the potential integration of interleukin -6 (IL-6) antagonists into the management algorithm of those with PMR in the near future[46-49], and their associated normalisation of both ESR and CRP[50], novel biomarkers are needed, not only for diagnosis but also for the identification of disease relapse.

Table 1. 2012 EULAR/ACR provisional classification criteria for polymyalgia rheumatica

Criteria	Points
Morning stiffness duration > 45 min	2
Hip pain or limited range of motion	1
Absence of rheumatoid factor and/or anti-citrullinated protein antibody	2
Absence of other joint involvement	1
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	0/1*
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	0/1*
Required: age ≥ 50 years, bilateral shoulder aching and abnormal c-reactive protein and/or erythrocyte sedimentation rate	
Required score for the diagnosis of Polymyalgia Rheumatica: 4 or more without ultrasound, and 5 or more with * ultrasound	

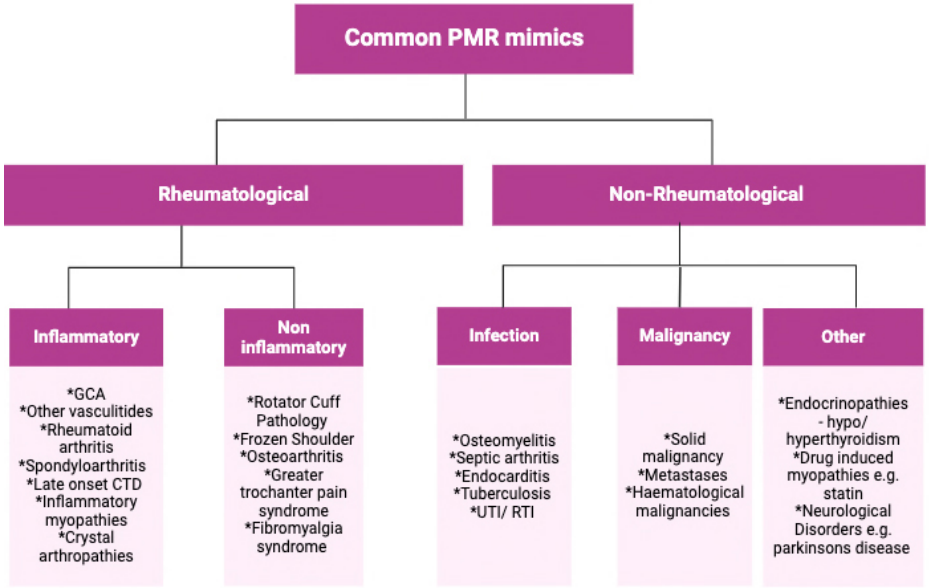

Figure 1. Common conditions that mimic Polymyalgia Rheumatica that must be excluded prior to diagnosis. GCA: Giant cell arteritis; CTD: connective tissue disease; UTI: urinary tract infection; RTI: respiratory tract infection. Created in BioRender.com.

Perhaps the most studied potential serum biomarker in the diagnosis of PMR is serum interleukin-6 (IL-6)[51-53]. IL-6 is a soluble mediator that exerts a pleiotropic effect on inflammation, immunological reaction, and haematopoiesis. Multiple studies have demonstrated its elevation in those newly diagnosed with active PMR, and its levels have been shown to correspondingly decrease with remission[51-53]. However, its potential role in the routine management of PMR is limited by both its non-specificity and the fact that it is currently not a readily available test in all laboratories. Moreover, its interpretation for those on IL-6 receptor blockade has not been evaluated or standardised, and thus its advantage for clinical decision making over the more widely available CRP and ESR has as of yet to be determined.

Levels of serum B-cell activating factor (BAFF) have also been demonstrated to be elevated in the serum of those with PMR *vs.* healthy controls[51]. It offers promise, particularly as its regulation is via a distinct pathway to that of IL-6 and CRP[54]. BAFF is constitutively produced by stromal cells; however, in a proinflammatory setting, it is produced by monocytes and exerts an important regulatory role on B cell responses[54]. However, its levels correspond with circulating B cells that have been reported to be reduced in those with active PMR[55]. A further limitation in its applicability is its lack of specificity, with elevated levels

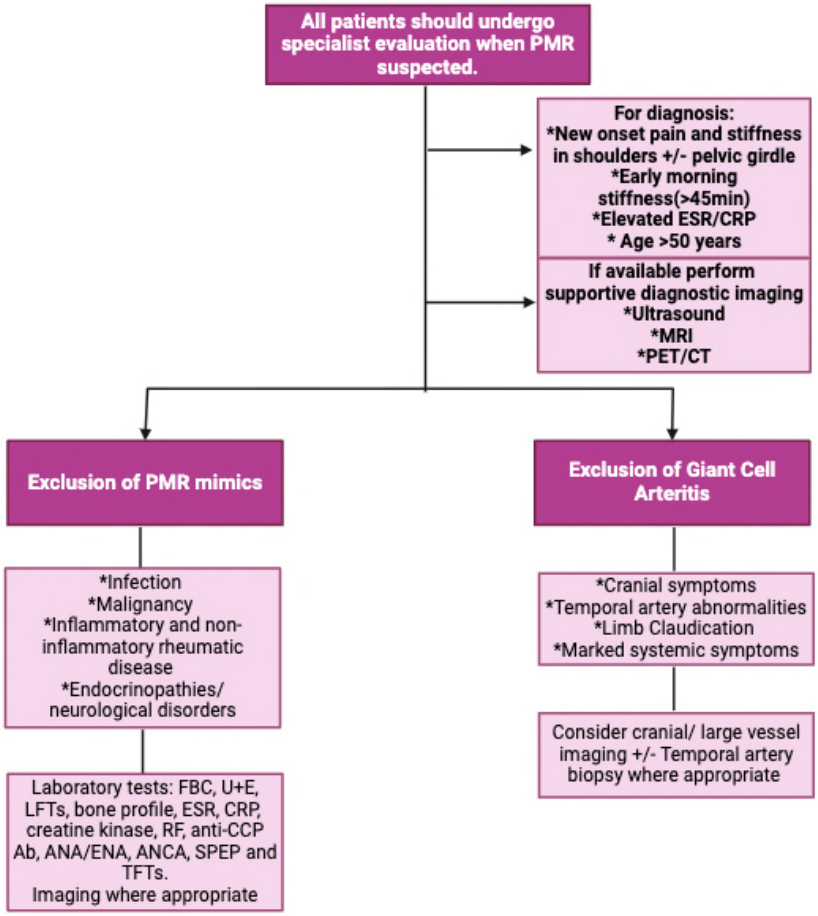

Figure 2. An up-to-date stepwise approach to the diagnosis of Polymyalgia Rheumatica. ESR: Erythrocyte sedimentation rate; CRP: c-reactive protein; MRI: magnetic resonance imaging; PET/CT: positron emission computed tomography; FBC: Full blood count; U+E: urea and electrolytes; LFTs: liver function tests; RF: rheumatoid factor; anti-CCP Abs: anti-cyclic citrullinated peptide antibody; ANA: antinuclear antibodies; ENA: extractable nuclear antigen; ANCA: anti-neutrophil cytoplasmic antibody; SPEP: serum protein electrophoresis; TFTs: thyroid function tests. Created in BioRender.com.

also reported in the setting of malignancy and infection[54].

Two further serum biomarkers, namely CXCL9 and CXCL10, have also been demonstrated to be elevated in those with active PMR[51]. Both CXCL-9 and -10, among other functions, play a pivotal role in Th1 polarisation[56], and interestingly, both of these markers remained high even in those with glucocorticoid deemed remission[51], supporting the previously reported concept of Th1 response resistance to glucocorticoid[57]. This somewhat precludes the usefulness of both CXCL9 and CXCL10 as suitable biomarkers, as they fail to modulate with disease activity, rendering them potentially ineffective for monitoring disease relapse or treatment response.

Serum calprotectin has also been studied as a serum biomarker in PMR[58,59]. It has the potential to serve as a reliable marker of disease activity, with elevated levels observed in those with PMR (*vs.* healthy controls) and subsequent declining levels observed in those treated with glucocorticoids[59]. However, it also lacks specificity, with similarly high levels found in those with other inflammatory rheumatic diseases, thus limiting its role in diagnosis[60-62]. Regarding disease stratification, multiple different serum markers have been evaluated to predict disease relapse. Despite the identification of novel markers, including soluble IL-6

receptor (sIL-6R)[63], plasma fibrinogen levels[64], and high neutrophil-to-lymphocyte ratio[65] as predictors of disease relapse, serial CRP and ESR measurements remain the main predictors of worse disease outcome in PMR in clinical practice[66,67].

As we previously discussed, the identification of subclinical GCA in those with PMR has become an area of increased interest. Several studies have explored the role of serum biomarkers in the identification of those with subclinical GCA. One retrospective study demonstrated how low serum levels of matrix-metalloproteinase 3 (MMP-3) were an excellent positive predictor of subclinical GCA in those with PMR[68]. This was subsequently evaluated using two international cohorts, with lower MMP-3 levels again showing a strong correlation for the presence of concomitant GCA in those with PMR[69]. Moreover, this study also supported a previous finding of high angiopoietin-2 levels in those with concomitant GCA[70], with high angiopoietin-2/-1 ratios found in those with PMR and concomitant GCA[69].

A meta-analysis that included studies up until the year 2020 did not find any positive correlation between acute phase reactants, namely CRP and ESR, and the presence of subclinical GCA in those with PMR[15]. However, subsequent studies have reported the potential of a higher ESR at baseline to distinguish those with and without subclinical GCA[69,71]. Larger, multicentre studies are most definitely needed.

Imaging

Over the past decade, there have been significant advancements in imaging techniques in PMR, with subsequent improvements in our diagnostic ability. Moreover, by employing a wider array of imaging modalities, we have garnered novel insights into the anatomical predilection of inflammation and, subsequently, disease pathogenesis. The most superior imaging modality for the diagnosis of PMR remains elusive; however, musculoskeletal US is the only modality to be incorporated into classification criteria, precisely the optional 2012 EULAR/ACR classification criteria[42]. [Table 1] Musculoskeletal US is rapidly becoming integral to a rheumatologist's clinical armamentarium, and its role in the diagnosis of PMR is continually evolving. US, in addition to magnetic resonance imaging (MRI) and FDG-PET, enables the assessment of not only articular and periarticular PMR-related changes, but also the identification of potential vascular involvement.

Bilateral subacromial-subdeltoid bursitis, although non-specific, is considered a distinctive US finding in those with PMR[72]. It has a reported sensitivity of 66% and specificity of 89% for the diagnosis, and reinforces the view that PMR has an anatomical predilection for extra-articular rather than intra-articular synovial structures[72]. Other US features suggestive of a diagnosis of PMR include long head of biceps tenosynovitis and/or glenohumeral synovitis[73]. Less frequently, trochanteric bursitis and hip synovitis can occur[74]. While these findings are non-specific, the use of US most certainly adds diagnostic value and aids a clinician in discriminating PMR from other musculoskeletal diseases. In one study, 94 patients with suspected PMR underwent US of their shoulders, and in almost one-quarter of patients (n = 25), calcium pyrophosphate deposition disease (CPPD) was found[75]. LORA is one of the most common mimics of PMR, and perhaps the most difficult to differentiate clinically from PMR. One study compared the semiquantitative scoring of both grey scale and power Doppler US changes in the subacromial and subdeltoid bursae of those with PMR to those with LORA[76]. They demonstrated significantly higher grey scale and power Doppler US grades of both subacromial and subdeltoid bursitis in those with LORA *vs.* those with PMR[76]. The authors postulate that the differing degrees of synovial proliferation are the key pathological difference driving the contrasting US changes, with the synovitis in PMR being primarily exudative in nature *vs.* the predominantly proliferative synovitis observed in rheumatoid arthritis[76]. A recent retrospective study demonstrated the prognostic value of bilateral hand US in discriminating PMR

from LORA, with the presence of at least one of the following increasing the probability of a diagnosis of LORA within 1 year from PMR diagnosis: rheumatoid factor positivity, grey scale synovitis in 2 of hand joints, and power Doppler positivity in 1 hand joints[77]. Notably, the presence of at least one of the aforementioned factors had an 88.9% sensitivity and a 92.6% specificity for the diagnosis of LORA[77].

The increased use of imaging modalities has also increased our awareness and, indeed, understanding of the phenotypic overlap between PMR and GCA, and most recently, the presence of subclinical GCA[15]. Performing US of the axillary arteries, in addition to the cranial arteries, increases the sensitivity and diagnostic accuracy of US in the diagnosis of GCA[78]. The pathognomonic US feature of GCA is the "halo sign", which is defined as a "homogeneous, hypoechoic wall thickening, well delineated towards the luminal side, visible in perpendicular planes, most commonly concentric in transverse scans"[79]. The presence of a unilateral halo sign has a sensitivity of 68% and a specificity of 91% for the diagnosis of GCA, with this increasing to a specificity of 100% when bilateral halos are present[79]. Moreover, the thickened wall of a vessel with active GCA typically remains persistently visible upon compression of the lumen with the US probe, giving rise to the so-called "compression sign". In cases of suspected GCA, the use of US is undeniably invaluable, but much is still unknown about its role in those with subclinical GCA, including which patients, if any, should be selected to undergo baseline imaging. Once a greater appreciation of the clinical implications of a finding of subclinical GCA is garnered, a potential paradigm shift in routine imaging may unfold, but further research is needed.

Overall, US is safe, relatively inexpensive, and widely accepted and tolerated amongst patients. Additionally, it also offers the benefit of being a readily accessible modality that can form part of a patient's clinical assessment during a consultation with a rheumatologist, rendering it unique compared with MRI and FDG-PET/CT. This is particularly pertinent in PMR, and indeed those with vasculitis, as treatment can result in the rapid normalisation of imaging findings and thus any delay in diagnostic imaging may affect the accuracy of results. US is advantageous, as in experienced hands, it permits rapid interpretation and immediate decision making. However, US has limitations in PMR, particularly its inability to access certain sites, namely the deep bursae and tendinous structures at the spine and hip[80]. Additionally, US of the hip can be time-consuming, and uncomfortable for the patient, and therefore, it is not always feasible in clinical practice, somewhat limiting the real-world application of the 2012 EULAR/ACR provisional classification criteria. With advancements in imaging modalities, we are coming to appreciate the involvement of anatomical areas outside of the hips and shoulders in PMR, most notably the knees and interspinous processes[27,28,81,82]. Accordingly, one group assessed the role of US of the shoulder and knee in discriminating newly diagnosed PMR from other differential diagnoses, and found that US assessment of the tendon and ligament-related lesions in both shoulders (long head of biceps, supraspinatus or subscapularis tendon) and both knees (popliteus tendon or medial or lateral collateral ligament) increased the diagnostic accuracy of the 2012 EULAR/ ACR provisional classification criteria for PMR[83]. Interestingly, in this study, 95% of patients with definite PMR had some US abnormalities in the knee, despite only 10% having the clinical manifestation of knee swelling[83]. This study provides impetus for the consideration of US of bilateral shoulder and knee as an alternative to US of shoulder and hip for PMR diagnosis, not only due to its proposed equivalent diagnostic accuracy, but also its potential superior acceptability for patients, and clinicians alike. However, a direct comparison study needs to be performed before this can fully garner momentum.

MRI, although more expensive and often poorly tolerated by patients, is superior to US in its visualisation of the pelvic girdle and hip findings in PMR, namely articular synovitis, bursitis, and tenosynovitis[84]. Moreover, over the past decade, MRI studies have increased our understanding of the anatomic basis of

PMR pathology, by identifying its characteristic extra-articular involvement with peritendinous, extracapsular, and myofascial inflammation.

The first study to describe such anatomic predilection was in 2001, where extracapsular soft tissue edema on shoulder MRI differentiated those with PMR from those with RA[85]. A further study comparing MRI of the metacarpophalangeal joints of those with PMR and those with RA revealed similar rates of synovitis, tenosynovitis, and bone erosions, but a significantly higher degree of gadolinium enhancement of extracapsular soft tissue in those with PMR[86]. Both of these studies not only implicate extracapsular inflammation in the pathophysiology of PMR, but also offer an imaging differentiation between PMR and other musculoskeletal conditions which can be exploited diagnostically. This extra-articular predilection of PMR was also confirmed in a study that demonstrated a characteristic peritendinous enhancement of the pelvic girdle tendons in 40 patients using contrast-enhanced MRI[87]. In the majority of patients, the peritendinous involvement was bilateral, with the proximal rectus femoris involved in 100% of patients, and the adductor muscles at the pubic bone involved in 90%[87]. Moreover, all patients had involvement of at least four extracapsular sites[87]. An additional retrospective study by the same group including 120 patients with pelvic girdle pain of unknown origin further confirmed this unique pattern of inflammation in the specific pelvic tendinous and capsular structures in those with PMR[88]. Moreover, MRI has enabled the novel identification of the involvement of interspinous bursa in PMR[81,82].

Further progressing our understanding of the anatomic pattern of inflammation in PMR, localised myofascial inflammation was identified in those with active PMR using MRI of both shoulder and pelvic girdles[89]. Myofascial inflammation was defined as a high T2 STIR signal within the affected muscle or forming a line around it, and in the study, each patient had at least one myofascial inflammatory lesion detected in the pelvic and shoulder girdle[89]. The hip musculature was most frequently involved (86.7%), followed by the adductors at the pubic symphysis (80%), shoulder musculature (71.4%), and muscles adjacent to the ischial tuberosities (60%)[89].

FDG-PET/CT studies have also confirmed the involvement of musculotendinous structures in PMR[90,91]. However, the precise anatomical correlate of the increased uptake observed using FDG-PET/CT is often limited by the inherent low resolution of the imaging modality. Consequently, a fusion study, where MRI was performed to precisely identify the anatomic correlate of abnormal ^{18}F-FDG uptake on FDG-PET/CT, was undertaken[28]. Interestingly, the researchers identified hamstring peritendonitis as the anatomical correlate of ^{18}F-FDG uptake adjacent to both ischial tuberosities and posteromedial knee structures[28]. Furthermore, a high frequency of wrist and/or hand involvement was also reported, with abnormal ^{18}F-FDG uptake in a volar distribution at the hand corresponding with flexor tenosynovitis on MRI[28]. This further supports musculotendinous inflammation as the defining pathology in PMR. However, histological studies are required before a definitive conclusion is drawn. Despite its low resolution, FDG-PET/CT is undoubtedly an enticing imaging modality in PMR, as it enables the simultaneous assessment of the multisite distribution of inflammation typical of PMR, in addition to the detection of a concomitant large vessel vasculitis, while also identifying potential differential diagnoses including infection and malignancy[92]. One of its primary limitations is the lack of a standardised and widely accepted definition for both PMR and large vessel vasculitis based on the intensity of ^{18}F-FDG uptake. Various studies have assessed the diagnostic value of composite PET-PMR scores and diagnostic algorithms[93,94]; however, further research is required.

MANAGEMENT

Glucocorticoids

Glucocorticoids have served as the cornerstone of the management of PMR for decades. Characteristically, patients with PMR undergo a rapid resolution in their symptomatology upon commencement of a low to moderate dose of prednisolone (15-25 mg OD)[19]. There is no evidence-based, standardised protocol for steroid taper, with it primarily being physician-led and patient-specific, and indeed, the optimal approach to steroid taper remains controversial, augmented by the paucity of studies addressing it[95]. The disease course of those with PMR is heterogeneous. Some patients complete their steroid course within one year, whereas for others, their disease is marked with frequent relapses and subsequent huge steroid burden over a number of years. Despite the perception that most individuals complete their steroid taper within one to two years, the reality appears to be different[96]. A recent systematic review and meta-analysis demonstrated a high glucocorticoid persistence rate over time[97]. The pooled proportions of individuals from observational studies still taking glucocorticoids at 1,2, and 5 years was 77% (95%CI: 71%-83%), 51% (95%CI: 41%-61%), and 25% (95%CI: 15%-36%), respectively[97]. Moreover, the pooled proportion of those experiencing at least one relapse at 1 year from treatment initiation was 43% (95%CI: 29%-56%)[97]. This highlights not only the high relapse rate, but also emphasises the presence of other factors influencing glucocorticoid tapering, as this relapse rate does not fully account for the high glucocorticoid persistence in patients at the various time points outlined above. A further study using the ACR Rheumatology Informatics System for Effectiveness (RISE) registry recently examined 16,703 patients with PMR[98]. At 12-24 months, 63.8% of patients remained on glucocorticoids[98]. Interestingly, only 39% of these individuals had a steroid-sparing agent prescribed[98].

Alternative methods of glucocorticoid administration have been explored in PMR. Intra-articular bilateral shoulder injections of 6-methylprednisolone every 4 weeks in those newly diagnosed with PMR did result in a rapid improvement in shoulder and systemic symptoms, but the effects at 6 months were sustained in only 50% of patients[99].

The use of intramuscular (IM) methylprednisolone acetate (120 mg 3 weekly for twelve weeks, followed by a steroid taper) was trialed against a glucocorticoid oral taper beginning at 15 mg of prednisolone[99]. IM methylprednisolone had similar remission rates to oral glucocorticoids at week 96[100]. Furthermore, there were fewer side effects including less weight gain, and a lower fracture rate in those treated by the IM route[100]. Despite this, it appears that this alternative route of steroid administration has failed to gain momentum in clinical practice.

The long-term use of glucocorticoids is indeed a cause for concern, particularly in those with PMR, who are typically an older cohort of patients, for whom the well-recognised adverse effects of steroid therapy can be even more devastating. Up to 65% of patients with PMR experience at least one steroid-associated adverse effect, including but not limited to osteoporosis with fragility fractures, arterial hypertension, diabetes mellitus, infection, ischaemic heart disease, cataract, and glaucoma[101]. Therefore, glucocorticoid-associated complications are causative of significant morbidity in this population. It is imperative that the dose and duration of glucocorticoid exposure are limited.

Disease modifying anti-rheumatic drugs

In order to aid steroid reduction in those with refractory or relapsing disease, a number of different glucocorticoid-sparing agents have been studied. At present, oral or subcutaneous methotrexate is the most widely used steroid-sparing agent[19]. Its clinical efficacy for the initial management of PMR has been assessed in three randomised controlled trials (RCTs), albeit with mixed results[102-104]. Two of the studies

demonstrated the efficacy of methotrexate[102,103], but the third did not show any steroid-sparing effect[104]. Most certainly, a higher quality of evidence was present in the studies demonstrating the efficacy of methotrexate; however, the total number of patients investigated in the RCTs is low (n = 194), and this, coupled with the conflicting results and the lack of evidence demonstrating any true reduction in glucocorticoid-related adverse events, has resulted in a hesitancy to assign methotrexate a stronger recommendation in the management algorithm. It should be noted that only low dosages of methotrexate, equivalent to or less than 10 mg, were evaluated in these trial populations, and thus perhaps a higher dosage would yield alternative findings. Currently, a multicentre, double-blind, placebo-controlled trial, "PMR MODE" (NL8366), is underway to assess the efficacy of methotrexate at a dose of 25mg per week in addition to a 24-week prednisolone taper to answer this question[105].

Azathioprine is another conventional synthetic disease-modifying anti-rheumatic drug (cs-DMARD) that has undergone evaluation in an RCT[106]. Although the investigators reported a significant difference in the mean prednisolone dose of patients given azathioprine (1.9 mg) *vs.* placebo (4.2 mg) at 52 weeks, the use of azathioprine was associated with an increased number of adverse events, and the trial number was small with a high dropout rate[106].

There is some promise for the efficacy of Leflunomide as a steroid-sparing agent in PMR, but to date, the support for it stems solely from two case series[107,108]. Therefore, prior to its incorporation into the treatment algorithm, RCTs are needed.

The use of biological agents in PMR has garnered increased attention over the past few years. [Table 2] We have discussed earlier the consistent findings of elevated levels of serum IL-6 in those with active PMR, which has resulted in the exploration of the efficacy of IL-6 antagonists in PMR gaining momentum, particularly with the recent breakthrough studies[47-49,109], heralding a new era in the therapeutic armamentarium of PMR. Following the SAPHYR study (NCT03600818)[109], sarilumab has been approved for the management of PMR in the United States. This study evaluated the efficacy and safety of sarilumab, a fully human monoclonal antibody against IL-6 receptor alpha, in steroid-refractory PMR patients with active disease on 7.5 mg/ day prednisolone[109]. A significantly higher number of patients in the sarilumab arm (200 mg every 2 weeks, with 14-week glucocorticoid taper) *vs.* the comparator arm (placebo every 2 weeks with 52-week steroid taper) achieved sustained remission from weeks 12 to 52 (28.3% *vs.* 10.3%; P = 0.0193)[109]. Real-world studies are awaited, but this study marks an important transition in the therapeutic management of those with PMR. Two other studies[47,48] examined the role of the IL-6 receptor antagonist, tocilizumab, in those with PMR, one in a treatment naïve population[47] and the other in those with refractory disease[48]. The SEMAPHORE (NCT02908217) trial explored the use of tocilizumab in those with glucocorticoid-dependent PMR, requiring doses of prednisolone 10 mg per day[48]. Patients were randomly assigned to receive tocilizumab at a dose of 8 mg/kg every 4 weeks *vs.* placebo every 4 weeks, with both groups undergoing a predefined standardised tapering of oral prednisolone[48]. The primary outcome of this trial was the attainment of a prednisolone dose 5 mg per day or a reduction in prednisolone dose 10 mg from baseline at week 24, combined with a polymyalgia rheumatica activity score (PMR-AS) computed using the CRP level (CRP PMR-AS) of less than 10[48]. This primary endpoint was achieved in 67.3% of those in the tocilizumab group *vs.* 31.4% in the placebo group[48]. 49% of patients in the tocilizumab arm were no longer receiving prednisolone at 24 weeks *vs.* 19.6% in the placebo arm[48]. The most common adverse event was infection occurring in 46.9% in the tocilizumab arm *vs.* 39.2% in the placebo arm[48]. The PMR SPARE (NCT03263715) double-blind, placebo-controlled, multicentre RCT examined the use of tocilizumab in those newly diagnosed with PMR[47]. Those in the tocilizumab arm received 162 mg subcutaneously every week in addition to an 11-week prednisolone taper commencing at 20 mg[47]. The

Table 2. Completed randomised control trials of biologic agents in the management of polymyalgia rheumatica

Drug	Molecular target	RCT identifier	Year published	Patient population	Sample size	Outcome
Sarilumab	IL-6	NCT03600818 "SAPHYR" Trial [111]	2023	Steroid refractory PMR patients with active disease on 7.5 mg/day prednisolone	118 (60 sarilumab, 58 PBO)	*Sustained remission at 52 wks: - Alt wk Sarilumab 200 mg + 14 wks GC taper: 28.3% - Alt wk PBO + 52 wks GC taper: 10.3% *Mean cumulative GC dose at 52 wks: - 777 mg sarilumab *vs.* 2,044 mg PBO; $P < 0.001$
Tocilizumab	IL-6	NCT02908217 "SEMAPHORE" trial [50]	2022	GC dependent PMR with 10 mg/day prednisolone	101 (51 TCZ, 50 PBO)	*Prednisolone dose 5 mg/day or reduction of GC dose 10 mg with a CRP PMR-AS < 10, at wk 24: -TCZ 8 mg/kg 4 weekly + GC taper: 67.3% - PBO + GC taper: 31.4% *GC free remission at wk 24: - 49% TCZ arm *vs.* 19.6% PBO
Tocilizumab	IL-6	NCT03263715 "PMR SPARE" trial [49]	2022	Newly diagnosed PMR	39 (19 TCZ, 17 PBO)	*GC free remission at 16 wks: - TCZ 162 mg s/c wkly + 11 wks GC: 63.2% - PBO wkly + 11 wks GC: 11.8% *Median cumulative GC dose at wk 16: - 727 mg TCZ *vs.* 935 mg PBO
Tofacitinib	Pan-JAK inhibitor	ChiCTR2000038253 EAST-PMR [118]	2023	Newly diagnosed PMR	67 (35 Tofa, 32 GC)	*PMR-AS 10 at 12 and 24 weeks: - Tofa 5 mg BD: 100% - GC only: 100%
Rituximab	Anti-CD20	EudraCT (2018-002641-11) "BRIDGE-PMR" trial [114]	2021	Newly diagnosed and steroid refractory PMR	47 (38 New Dx, 9 GC refractory) 23 RTX, 24 PBO)	GC free remission at 21 wks: - RTX 1 g once + 17 wks GC: 48% - PBO once +17 wks GC: 21%
Infliximab	Tumor necrosis factor alpha	ACTRN012606000205538 [113]	2007	Newly diagnosed PMR	47 (20 INF, 27 PBO)	Relapse free at wk 52: - INF 3 mg/kg wk 0,2,6,14,22 + 16 wks GC: 30% - PBO wk 0,2,6,14,22 + 16 wks GC: 37%

IL-6: Interleukin 6; wk(s): week(s); Wkly: weekly; GC: glucocorticoid; PBO: placebo; TCZ: tocilizumab; INF: infliximab; RTX: rituximab; JAK: janus kinase; PMR-AS (CRP): PMR activity score (c-reactive protein); Tofa: tofacitinib.

placebo arm received a weekly placebo, in addition to an identical glucocorticoid taper to the treatment arm[47]. Glucocorticoid-free remission at 16 weeks was achieved in 12 out of the 19 patients on tocilizumab (63.2%) *vs.* 2 out of 17 patients receiving placebo (11.8%, $P = 0.002$)[47]. The cumulative glucocorticoid dose was also less in the tocilizumab arm, with a median (IQR) cumulative dose of 727 (721-842) mg *vs.* 935 (861-1244) mg ($P = 0.003$) in the placebo arm[47]. Similar to the success of such IL-6 antagonists in GCA[110], a number of uncertainties surrounding their use remain. The patients in whom these agents should be preferenced in lieu of the standard glucocorticoid taper have not been adequately defined, and given the effects that these agents have on the acute phase reactants CRP and ESR, there is a significant unmet need for a reliable serum biomarker to assess disease activity with their use. Moreover, much uncertainty surrounds the optimal therapeutic duration, and the optimal means of withdrawing such therapeutic agents. Therefore, while there is much promise in the future management of those with PMR, several unanswered questions need to be addressed to ensure optimal patient outcomes.

Other biologic agents have also been evaluated in RCTs. The anti-tumor necrosis factor alpha agent, infliximab, was the first to be evaluated in a multicentre, randomised placebo-controlled trial of 40 newly diagnosed patients with PMR[111]. Similar relapse and recurrence rates were demonstrated in both the infliximab arm (infliximab and 16 week prednisolone taper) and the placebo arm (placebo and 16 week prednisolone taper)[111].

The proof-of-concept BRIDGE-PMR trial demonstrated the benefit of a single 1,000 mg dose of the anti-CD20 monoclonal antibody, Rituximab, in addition to a 17-week prednisolone taper, in achieving a significant number of glucocorticoid remissions at 21 weeks (48% *vs.* 21% in the placebo arm; $P = 0.049$)[112]. Notably, this effect was most pronounced in the newly diagnosed PMR patients *vs.* those refractory to therapy. Following on from the 21-week study, patients were followed in a double-blind extension until 1 year after infusion, where 47% of those in the rituximab arm remained in glucocorticoid remission *vs.* 23% in the placebo group ($P = 0.12$)[113]. 26% in the rituximab arm and 22% in the placebo arm had adverse events[113]. While this does foster promise for the future application of Rituximab as a steroid-sparing agent in those with PMR, a larger trial, with the potential for further doses of rituximab, is warranted prior to its incorporation into routine management.

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The Janus kinase (JAK) family of intracellular tyrosine kinases is comprised of JAK 1-3 and tyrosine kinase (TYK) 2[114,115]. In association with signal transducers and activators of transcription (STAT), they have a pivotal role in mediating the downstream signalling of a significant number of proinflammatory cytokines[114]. Subsequently, the role of the JAK/STAT pathway, and more precisely, its intracellular inhibition through the orally administered small molecule JAK inhibitor (JAKi), has garnered much interest in the management of immune-mediated rheumatic diseases. Recently, the first open-label RCT (EAST-PMR) on a pan-JAKi, namely, tofacitinib, in treatment naïve PMR patients was published[116]. In the first cohort of patients from this single-centre study in China, gene expression from peripheral blood mononuclear cells of 11 treatment naïve PMR patients *vs.* 20 healthy controls was evaluated[116]. In those with PMR, they observed increased expression of IL6R, IL1B, IL1R1, JAK2, TLR2, TLR4, TLR8, CCR1, CR1, S100A8, S100A12, and IL17RA, all of which have the potential to trigger janus kinase signalling[116]. Moreover, in vitro, tofacitinib suppressed both IL-6R and JAK2 expression of CD4+T cells from the PMR patients[116]. In the second cohort of patients, those with PMR were randomised and treated with either tofacitinib or glucocorticoids for 24 weeks[116]. There was no statistically significant difference in primary outcome between each group, with all patients in each group achieving a PMR-AS 10 at 12 and 24 weeks[116]. Furthermore, no severe adverse events were observed in either group[116]. This most certainly supports the potential utility of tofacitinib in the management of PMR, but larger blinded RCTs are needed.

Finally, another phase three RCT, "REPLENISH" (NCT05767034), is currently ongoing, evaluating the efficacy and safety of the interleukin-17 A antagonist, secukinumab, in those with relapsing PMR. This may provide another potential biological target for those with refractory disease.

CONCLUSION

Over the past decade, there has been an increased number of novel insights into PMR owing largely to the increased application and advancements in imaging modalities. PMR is now recognised as a musculotendinous condition. Moreover, there is an increased appreciation of the relationship between GCA and PMR. However, many questions remain unanswered regarding this relationship, particularly the clinical and, indeed, prognostic significance of subclinical vasculitis in those with PMR.

The FDA approval of sarilumab for those with refractory PMR most certainly heralds a new era in the management of PMR. While glucocorticoids continue to form the backbone of management for now, there is significant promise for the future therapeutic armamentarium of PMR. One of the most significant unmet needs in the care of those with PMR is the lack of a definitive biomarker for diagnosis and disease activity. This is particularly pertinent given the introduction of interleukin-6 antagonists into the management algorithm, and their neutralisation of the commonly employed acute phase reactants. Finally, there is an impetus to develop disease stratification tools, primarily to characterise the subset of patients that relapse, in order to optimise management strategies and limit overall glucocorticoid burden.

DECLARATIONS

Authors' contributions

Wrote the manuscript: Harkins P

Performed collection and in-depth analysis of the evidence base: Harkins P, McCann L, Harrington R, Cowley S, Kane D, Conway R

Reviewed the progress of the article at each step and finalised the manuscript of the review article: Conway R

Availability of data and materials

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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