Polymyalgia rheumatica: An update (Review)

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Abstract. Polymyalgia rheumatica (PMR) is a chronic inflammatory disease which affects the connective vascular tissue, characterized by pain accompanied by morning stiffness, predominantly of the neck muscles, hip and shoulder girdle. Usually, patients with this disease are >50 years of age and biological inflammatory syndrome is present with an increase in both the erythrocyte sedimentation rate and C-reactive protein levels, aspects similar to giant cell arteritis. The aim of the present review was to depict the current pathogenic hypothesis, diagnostic and treatment approach for patients with PMR, and novelties since the development of the currently used 2012 European League Against Rheumatism and American College of Rheumatology provisional classification criteria. PMR is a prevalent disease that can occasionally prove difficult to diagnose and treat. Possibly, the most abundant type of evidence and data revealed over the past decade have been acquired through musculoskeletal imaging, with implications in diagnosis, disease monitoring and relapse, prognosis and changes with treatment. Further research on pathophysiology is required to gain a deeper understanding of the underlying processes, which will serve as the foundation for future personalized treatments. In addition, there is an increasing demand for improved diagnostic techniques, which should include a further development of various imaging modalities, in order to provide accurate diagnosis and appropriate therapy.

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1. Introduction

Polymyalgia rheumatica (PMR) is a chronic inflammatory disease which affects the connective vascular tissue, characterized by pain and accompanied by morning stiffness, predominantly of the neck muscles, hip and shoulder girdle. The main characteristics included in the majority of definitions are pain and morning stiffness of the hip and shoulder girdle and/or the neck muscles, lasting for >30 min, with a disease onset of >1 month. Usually, patients are aged >50 years and the biological inflammatory syndrome is present, with an increase in both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, aspects similar to giant cell arteritis (GCA) (1).

PMR predominantly affects the elderly, and the median age of disease onset is 73 years. The prevalence is estimated at 700/100.000 individuals aged >50 years. The incidence increases with age and varies depending on the geographical region, with an increased incidence observed in Scandinavian countries. The disease affects females 2-3-fold more frequently than males, as well as individuals of Caucasian ethnicity, as compared with Asian, Latin-American and African-American populations (2).

PMR is frequently associated with GCA in ~30% of cases. From a clinical point of view, 40-60% of patients with GCA can present with symptoms of PMR at the time of diagnosis. PMR and GCA bear multiple similarities, including age at disease onset, an increased prevalence among females and geographical distribution, suggesting that these clinical entities may represent subtypes of the same pathology (3).

The aim of the present review was to depict the current pathogenic hypothesis, the diagnostic and treatment approaches for PMR patients, and novelties since the development of the currently used 2012 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) provisional classification criteria.

2. Pathogenesis

To date, the etiology and pathogenesis of PMR are not clearly understood. This can be attributed to earlier studies, which were conducted in mixed cohorts presenting with both PMR and GCA, impeding the successful evaluation of the patterns involved in the pathogenesis of isolated PMR, as reviewed by Guggino *et al* (4).

HLA-DRB1*04 allele is usually associated with PMR in conjunction with GCA. However, when assessing genotypes and susceptibility to PMR alone, the data presented in literature is controversial. Salvarani *et al* (5) revealed a high incidence of HLA-DRB1*04 alleles in a cohort of patients of Italian descent with 'pure' PMR. Furthermore, Gonzalez-Gay *et al* (6) described an association of HLA-DRB1*04 with more severe disease activity and increased synovial inflammation in patients with PMR from a patient cohort of Spanish descent.

Since PMR is associated with inflammation of the bursae, the cytokines implicated in the inflammatory process may be responsible for some of the pathogenic traits of this disease. It has been suggested that PMR is associated with various TNF polymorphisms. Also, higher levels of interleukin (IL)-1, IL-6 and intercellular adhesion molecule-1 (ICAM-1) have been associated with increased risk of disease development or increased disease severity in PMR (7).

The role of infectious and environmental factors has been postulated in PMR pathogenesis. Among several of the investigated infectious factors, *Mycoplasma pneumoniae*, parvovirus B19 and *Chlamydia pneumoniae* have been more frequently incriminated in the development of PMR (8-10). Additionally, Cimmino and Zaccaria (11) indicated that antibodies to adenovirus and respiratory syncytial virus may also trigger PMR, due to their high prevalence in the bloodstream of PMR patients.

Another factor involved in the development of PMR is the use of immune check-point inhibitors in cancer patients, due to their antagonizing effect on cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed death cell protein 1 (PD-1). The therapeutics that have been implicated in the pathogenesis of PMR are ipilimumab, nivolumab and pembrolizumab (12).

The pathophysiology of PMR may entail an abnormal immune response, particularly one involving T cells. An increase in T-helper 17 (Th17) cells was observed in a group of individuals with PMR and/or GCA, and a concurrent decrease was also discovered in regulatory T cells. Also, an increase of memory-effector T cells was noted, revealing an alteration in T-cell subpopulation no longer expressing the co-stimulatory molecule ($CD4^+CD28^-$ and $CD8^+CD28^-$). These subtypes of T cells are known to be increased in elderl; however, as compared to sex and age-matched controls, the observed levels of T cells were increased in those with PMR/GCA. Memory-effector T lymphocytes contribute to the pro-inflammatory cascade in PMR, due to the ability to produce interferon (IFN)-γ and tumor necrosis factor (TNF)-α in large quantities (13,14) (Fig. 1).

IL-17 has also been recently linked to PMR and GCA, due to the subsequently incited activation of Th17 responses. Additionally, there is a correlation between higher IL-6 levels and PMR disease activity. IL-6 inhibitors are presently being trialed for the treatment of PMR after demonstrating effectiveness in GCA (15).

van der Geest *et al* (16) also demonstrated a decrease in the numbers of B lymphocytes which presented an inverse association with ESR, CRP, and B-cell activating factor (BAFF) levels.

Pro-inflammatory cytokines could be markedly implicated in PMR pathogenesis as well. When comparing symptomatic vastus lateralis and trapezius muscles of PMR patients to healthy individuals included as a control, higher interstitial concentrations of IL-1α, IL-1β, IL-1 receptor antagonist, IL-6, IL-8, TNF-α, and monocyte chemoattractant protein-1 have been detected in the serum of the PMR population. The etiology of the illness may thus be influenced by the elevated interstitial concentrations of pro-inflammatory cytokines in the affected muscles (17,18). JAK/STAT signaling pathway has been studied in GCA and PMR. The inhibition of JAK 1 and JAK2 may lead to the downregulation of Th1 and Th17 pathways and also IL-6 (19).

The clinical symptoms of PMR may be attributed to immune cell infiltration in the muscles and periarticular areas. Patients with PMR and GCA were demonstrated to present immune complexes in their muscles. PMR has also been associated with synovitis. In comparison to healthy individual controls, deltoid muscle biopsies from patients with PMR exhibited increased microvascularization. The evaluation of arthroscopic samples used to study synovitis of the shoulder, it was revealed that only macrophages and T cells, infiltrate the extracted fragments, whereas B cells, NK cells, or γ/δ T cells were not detected (20,21). A strong adhesion molecule expression, including vascular cell adhesion molecule (VCAM)-1 and ICAM-1, has been observed in PMR subjects with synovitis and may be important for the recruitment of several immune system components in PMR synovial infiltration (22).

Also, the process of endocrine senescence that produces decreased levels of dehydropiandrosterone and alterations of hypothalamic-pituitary-gonadal axis with adrenal cortex insufficiency and decreased cortisol secretion in response to the inflammatory status was incriminated as an etiopathogenically important mechanism (23).

Deregulation of the immune system may result in a vicious cycle, with the immune system remaining activated and in a permanent state of inflammation, as is frequently observed in inflammatory autoimmune diseases. However, it should also be considered that chronic inflammation gradually causes dysregulation of the immune system (24).

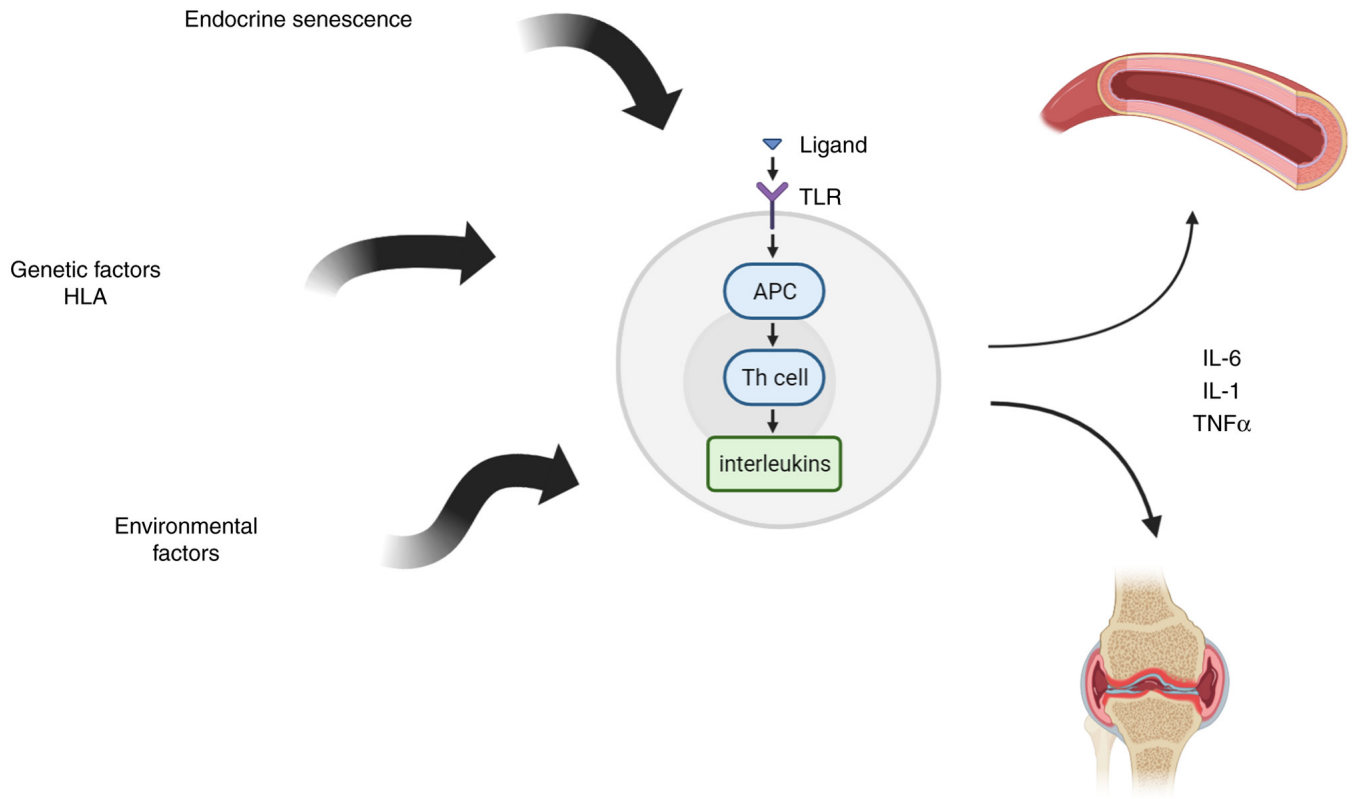

Figure 1. Schematic diagram of the pathogenesis of polymyalgia rheumatica. APC, antigen presenting cell; Th cell, T helper cell; HLA, human leukocyte antigen.

The immune system dysregulation may lead to a higher risk of cancer occurrence in PMR patients. Nevertheless, the data in literature regarding the development of cancer in PMR patients is controversial. According to a follow-up study in Sweden, there was discovered a link between malignant diseases and PMR. Furthermore, some specific types of cancers such as skin cancers and hematologic malignancies such as acute myeloid leukemia, multiple myeloma or myeloproliferative diseases have been associated with PMR (25). A more recent study on 80 patients diagnosed with PMR, which were observed for >40 weeks and screened using positron emission tomography/computed tomography (PET/CT) revealed a higher prevalence of cancer in PMR patients, in comparison to the general population (26). Also, the treatment for cancer such as immune checkpoint inhibitors may trigger PMR (27).

3. Clinical manifestations

PMR manifests in patients >50 years of age, leading to discomfort, a reduced range of motion and stiffness of the shoulder girdle may, which is a fundamental clinical hallmark of PMR. Furthermore, neck, hip girdle and thigh symptoms may also occur. Patients also frequently complain about difficulties in movement, with the symptoms being bilateral in most cases (28).

In total, up to 40-50% of patients may exhibit established symptoms, including low-grade fever, lethargy, asthenia, anorexia and weight loss. In some cases, the first sign of isolated PMR is a fever >38˚C (3).

The onset of symptoms is frequently unforeseen, occurring typically within a few days; however, in rare cases, symptoms may develop suddenly overnight. Aching and early morning stiffness lasting for >30 min are two of the most common symptoms occurring in the musculoskeletal areas that are involved in the inflammatory process. The symptoms of inflammatory pain and stiffness are often most aggravated in the morning, gradually improving during the course of the day, and then relapsing to their baseline level after the patient has rested or has been inactive (also known as 'gelling') for an extended period of time.

Hip girdle symptoms are described as pain in the groin area and lateral sides of the hip and often radiate to the posterior thigh region (29).

Performing tasks necessary for the activities of daily living, including clothing, combing hair, getting out of bed, or getting up from a chair are examples of actions that become challenging and are often coupled with debilitating pain. Nocturnal pain is also common, and patients frequently face difficulties in falling or staying asleep (30).

At disease onset, symptoms may be unilateral, rapidly becoming symmetrical and bilateral. During a physical examination, the active mobility of a patient, particularly concerning the abduction of the shoulders, may be restricted due to tenderness. In addition, there is no clinically apparent joint swelling. A passive range of motion that is facilitated by the examiner may, in certain cases, approximate a healthy phenotype. The discomfort in the shoulder is widespread, and it is not localized in specific shoulder structures (31).

Under normal circumstances, a painful limitation in the active range of motion of the neck and hips also occurs. Even though pain in the muscles manifests, it is not typical for the muscles to exhibit any weakness, despite the existence of muscular discomfort (32).

There is a possibility that other joint symptoms may also be present. Clinical signs of peripheral synovial inflammation can be observed in various cases, approximating to ≤23-39% of patients. Arthritis is characterized by asymmetrical presentation, a non-erosive character, mainly affecting the knees and wrists. Following the initially administered therapy with glucocorticoids (GCs), the symptoms appear to subside in the majority of patients. Inflammation of the periarticular structures, including tendons and bursae, may also be present in patients with peripheral synovitis. Tenosynovitis and bursitis can be evidenced by musculoskeletal ultrasound (MSUS) and other imaging techniques, including magnetic resonance imaging (MRI). It has been reported that ~15% of patients with PMR exhibit ultrasonographic evidence of carpal tunnel syndrome, and 3% of patients have been reported to exhibit distal tenosynovitis (33).

PMR may, in certain instances, manifest clinically as distal swelling and edema, which may be analogous to the symptoms experienced by individuals diagnosed with remitting seronegative symmetrical synovitis with pitting edema syndrome (34).

4. Laboratory features

Laboratory analyses are non-specific. The increase in acute phase reactants is dominant from a paraclinical point of view, with values of ESR that vary from moderate to high, often >100 mm/h, with <20% of patients presenting with values below 40 mm/h. By contrast, CRP levels are constantly increased, representing a reliable inflammatory monitoring marker, normal values being incompatible with the diagnosis of PMR (35,36). The study by Cantini *et al* which evaluated 177 patients with PMR, revealed that 6% of the patients presented with normal ESR values at the time of diagnosis, while CRP levels were normal in only 1% of cases. Even in several cases of relapse, ESR levels were normal in 68% of cases, whereas CRP levels were elevated in 62% of cases (37).

Increased levels of markers of non-specific inflammation, including α2 and α1-globulins, gamma globulins, fibrinogen, α1-antitrypsin, α1-antichemotrypsin and haptoglobin may also be detected (38).

Blood count changes indicate an inflammatory biological profile with the presence of mild or moderate normocytic normochromic anemia, reactive leukocytosis or thrombocytosis (38).

Rheumatoid factors (RFs), anticitrullinated protein antibodies and antinuclear antibodies are usually absent. However, a weak positivity of RFs must be considered in ~10% of elderly population, without any clinical significance (39).

On occasion, anticardiolipin antibodies may be detected in increased titers as an independent predictive marker for the risk of vascular complications (40).

Indications of hepatic damage are often present with increases in the levels of alkaline phosphatase, γ-glutamyl transpeptidase, 5'-nucleotidase, and occasionally, moderate increases in transaminase levels. Serum levels of creatine kinase and lactate dehydrogenase are within a normal range and exclude myositis-type involvement. IL-6 and von Willebrand factor levels are increased, with significant decreases following treatment administration (36,41).

The examination of the synovial fluid may reveal mild inflammation, including an increase in the total number of leukocytes with levels ≤20,000/mm^3, 40-50% of which being polymorphonuclear (42). Also, neuropeptides such as vasoactive intestinal peptide were found in the synovial fluid of PMR patients which may contribute to the immunomodulation of synovial fluid inflammation, but also extraarticular manifestations such as cardiac rhythm dysregulations (43,44).

5. Imaging

Probably the most abundantly available data and type of evidence in the literature over the past decade have been acquired through musculoskeletal imaging, with applications in diagnosis, disease monitoring and relapse, prognosis and change with treatment. Currently, none of the various sets of classification criteria for PMR are fully validated in clinical practice. The simultaneous presence of inflammation in articular and periarticular structures of the bilateral shoulder or in one shoulder and the hips, as identified by ultrasound, aided in the improvement of the sensitivity and specificity of the clinical criteria in 2012, with the introduction of the ultrasound criteria. Multiple imaging techniques, having advantages and disadvantages, from conventional radiology, scintigraphy to MSUS, MRI and 18-FDG PET/CT have improved the diagnosis of PMR and have made it possible to differentiate this particular pathology from other similar disease, such as elderly onset rheumatoid arthritis (RA; EORA), and to provide a prompt therapeutic intervention (1,33).

Conventional radiology. The use of conventional radiology is considered outdated for the diagnosis of PMR. Due to the inflammatory features of joint and periarticular structures characteristic of the disease and to the non-erosive aspect of the arthritis, the use of this method does not provide useful information. In this setting, it could be used only for differentially diagnosing PMR from other inflammatory, erosive or degenerative joint disease or concomitant diseases. The last guidelines of the British Society for Rheumatology and the Health Professionals in Rheumatology for the management of PMR include a chest X-ray as the bare minimum for the establishment of the diagnosis, being useful for the exclusion of alternative conditions that may mimic the disease (45).

Scintigraphy. The advances in nuclear medicine imaging techniques over the past decade have surpassed the capabilities of conventional scintigraphy. The lack of the high specificity of the method and the use of new nuclear medicine imaging modalities justify the absence of recent publications on this topic over the past decade. Gallium-67 scintigraphy reports in PMR demonstrate intense uptake in both shoulders (46). The high sensitivity of the Technetium pertechnetate scintigraphy was reported by O'Duffy *et al* (47) since 1976. That study, reported that 24 out of 25 patients exhibited positive PMR characteristics with abnormal uptake in both shoulders, as compared with the lack of the PMR characteristics in 26

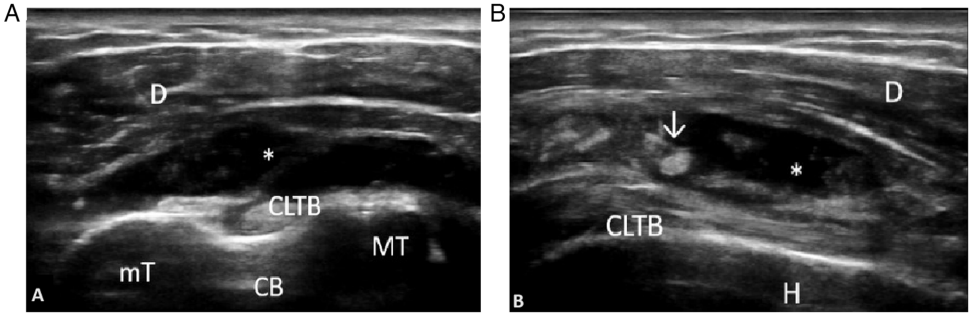

Figure 2. Transverse (A) and longitudinal (B) scan in gray scale of the long head of the biceps tendon, demonstrating anechoic moderate collection in the subacromial/subdeltoid bursa, with the presence of villonodular synovial proliferation in a 79-year old male patient (performed on a MyLabSix Ultrasound machine; Esaote SpA). mT, small tuberosity of the humerus; MT, big tuberosity of the humerus; CLTB, long head of the biceps tendon; CB, bicipital groove; *, collection; d, deltoid muscle; ↓, synovial proliferation.

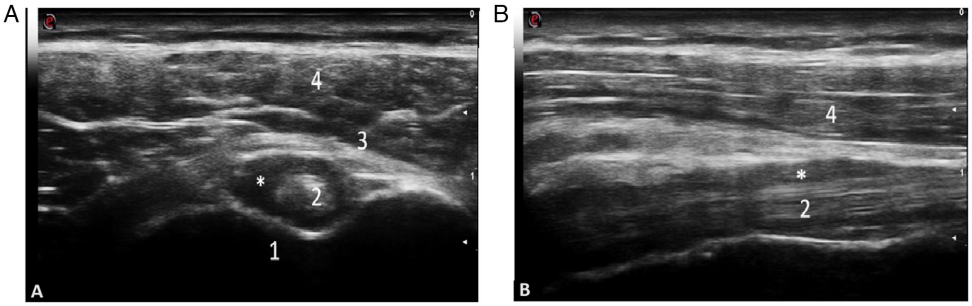

Figure 3. Transverse (A) and longitudinal (B) scan in gray scale of the long head of the biceps tendon illustrating a hypo/anechoic collection at the level of the long head of the biceps tendon in a 79-year old male patient (performed on a MyLabSix Ultrasound machine; Esaote SpA). 1, humerus; 2, long head of the bicep brachialis tendon; 3, transverse humeral ligament; 4, deltoid muscle; *, hypo/anechoic collection.

controls. Nevertheless, the lack of discriminative power currently justifies the absence of recent data regarding the use of the method.

Ultrasound. MSUS has recently become a preferred technique, mainly due to its capacity to visualize in a multi-planar and dynamic way both articular and extra-articular synovial structures, with a relative low-cost and wide availability. Using standardized scanning techniques and defined ultrasound pathology, together with the addition of power- and colour-Doppler, MSUS has improved the ability to detect and assess inflammatory activity in PMR with excellent reliability. In addition, MSUS has been demonstrated to have high intraobserver (k=0.96) and interobserver (k=0.99) reproducibility (48).

Diagnostic accuracy. As a result of several ultrasound studies performed in Europe, with regard to the detection of inflammatory lesions in PMR mostly using B-mode, and to a lesser extent, power Doppler examination, the most frequent ultrasound abnormalities described are bursitis of the subacromial/subdeltoid (SASD) bursae and tenosynovitis of the long head of the biceps tendon (LHBT), ranging from 6.2 to 100% at the shoulder level, with a higher prevalence of SASD bursitis, and less frequently, trochanteric bursitis and synovitis at the hip level (49,50). The importance of this data determined the inclusion of an ultrasound criteria for the first time in rheumatology in the 2012 EULAR/ACR Provisional Classification Criteria for PMR, increasing the specificity of the clinical diagnosis to 81% (51). Subsequently, Macchioni *et al* (52) revealed that the addition of ultrasound to clinical criteria increased the diagnostic performance from 81.5 to 91.3% in patients with PMR, while comparing PMR to other types of inflammatory arthritis, including RA. The diagnostic specificity in this case increased from 79.9 to 89.9% (Figs. 2 and 3). The images were obtained by examining a patient with PMR at the Emergency Clinical County Hospital of Craiova.

A recent study by Kobayashi *et al* (53) demonstrated that ultrasound of the shoulder and knee, improves the accuracy of the 2012 EULAR/ACR Provisional Classification Criteria for PMR; however, this does not apply for the hip. Considering that the assessment of the hip joint by ultrasound is not a patient or physician-friendly procedure, due to limited sensitivity in the detection of abnormalities, in comparison to MRI and that inflammatory knee lesions are frequently detected in PMR using MRI and PET/CT, particularly in tendons and ligaments besides bursas and synovia, it was concluded that bilateral involvement of the shoulder (LHBT, supraspinatus or subscapularis tendon) and the bilateral involvement of the knee [popliteus tendon (PopT) or medial or lateral collateral ligament] provided numerically increased sensitivity (90 vs. 87%), specificity (83 vs. 68%), positive predictive value (79 vs. 67%) and negative predictive value (92 vs. 87%) compared with the 2012 EULAR/ACR criteria without ultrasound. In the PMR-definite group the dominant ultrasound lesions were the tenosynovitis of LHBT and that of PopT, with 85% exhibiting both abnormalities (53).

In a systematic review by Mackie *et al* (54) in 2015 regarding the accuracy of musculoskeletal imaging for the

diagnosis of PMR, the use of ultrasound was associated with several strengths. It is worth mentioning that according to that review, control patients with other inflammatory diseases were included in order to estimate the diagnostic accuracy compared to MRI and PET/CT studies only in ultrasound-related studies. Bilateral SASD bursitis had the most discriminative value for PMR diagnosis, with a specificity of 89% and sensitivity of 66%, superior to glenohumeral synovitis, according to data from four ultrasound-related studies. The ultrasound detection of trochanteric bursitis demonstrated a sensitivity ranging from 21 to 100% (54).

Ultrasound in PMR may be of particular assistance in establishing positive diagnosis in cases with normal ESR, as recorded in 7-22% of patients at time of diagnosis (3). Manzo *et al* (55) suggested a 4-point guidance on how to investigate a suspicion of PMR, ultrasound being of real positive value when bilateral SASD bursitis, LHBT tenosynovitis or trochanteric bursitis are present.

Differential diagnosis. The role of ultrasound in differential diagnosis of PMR is supported by several studies. When analyzing the diagnostic outcome in patients with polymyalgic symptoms, Falsetti *et al* (56) suggested the importance of ultrasound in the identification of the most predictive ultrasound model for PMR. This particular model is represented by the detection of the presence of bilateral SASD bursitis, a low frequency of wrist, metacarpophalangeal and metatarsophalangeal effusion/synovitis, a low frequency of knee menisci chondrocalcinosis or tendinous calcaneal calcifications, Achilles enthesitis and low-power Doppler ultrasound (PDUS) scores at wrist level.

Ruta *et al* (49) compared shoulder ultrasound abnormalities in patients with PMR and RA and detected bilateral SASD bursitis in 36% of patients with PMR and only in 3% of patients with RA, with a similar difference noted for LHBT tenosynovitis, which was observed in 30% of patients with PMR and was not observed in the RA control group.

Furthermore, the presence of moderate to severe proliferative synovitis of the shoulder bursae, particularly in the subacromial bursa, is a key ultrasound feature for discriminating EORA from PMR-like onset EORA (pm-EORA) from PMR. Higher scores of gray scale and the power Doppler evaluation of synovitis were obtained by Suzuki *et al* (57) in 2017 in patients with PMR compared to those with pm-EORA. The same authors further extended the comparison between pm-EORA and PMR by proposing a semi-quantitative PD scoring system for the hyperemia on the subscapularis tendon, with good intraobserver and interobserver reproducibility, demonstrating that inflammation in PMR is predominantly localized in extrasynovial soft tissue or shoulder bursa, as compared to pm-EORA (58).

In a recent study by Ottaviani *et al* (59) which analyzed 94 patients with polymyalgic syndrome, it was concluded that the screening of the acromioclavicular joint may help distinguish PMR from calcium pyrophosphate disease (CPPD), as patients with CPPD demonstrated humeral bone erosions, synovitis and CPPD of the AC joint more frequently, with a sensitivity of 85.2% and specificity of 97.1%. By contrast, despite a low specificity, the most sensitive US features for PMR diagnosis were subacromial-subdeltoid bursitis (96.3%) and biceps tenosynovitis (85.2%).

Treatment efficacy. Consistent information to support the role of ultrasound in monitoring the response to treatment in PMR is still lacking. Jiménez-Palop *et al* (48) performed a prospective study in a cohort of 53 patients with PMR treated with corticosteroids, assessing as main objective the ultrasound inflammatory changes at the shoulder and hip level. Their study concluded that an ultrasound may be a useful additional tool for monitoring the response to corticosteroid treatment, due to the significant decrease in the ultrasound inflammatory parameters having been detected at week 4, whereas after 4 and 12 weeks of treatment were more prone to the alteration of their levels in comparison with clinical and laboratory markers of the disease activity (48). However, according to another study by Miceli *et al* (60) in 2017 on 66 patients with PMR that underwent ultrasound evaluation at baseline and after 12 months of GC therapy, the presence of subdeltoid bursitis and/or biceps tenosynovitis at baseline was not a predictive marker either for GC response or for the requirement for the administration of an increased GC dose to maintain remission at 12 months. Nevertheless, in the prospective open-label outcomes and treatment regimens (TENOR) study that included 18 patients with PMR treated with tocilizumab infusions without corticosteroids, ultrasound and MRI demonstrated notable improvements in inflammatory lesions. At week 12, ultrasound examinations proved that bursitis improved significantly in all four joints (P=0.029), although intra-articular effusions/synovitis exhibited less improvement (P=0.001). By the end of week 12, 37% of ultrasound-detected abnormalities improved (61).

MRI. MRI has extensive applications in rheumatology and its use in PMR is not an exception to this. Due to the accurate visualization of deep structures, including spine, peripheral joints, tendons, bursae and periarticular tissue, several studies over the past decade have provided novel insight into the anatomical origin of inflammation in PMR, with emphasis on extra-articular involvement of enthesis, bursae or periarticular tissues.

Diagnostic accuracy. Several MRI studies have facilitated the diagnosis of PMR. Fruth *et al* (62) in 2018 investigated the presence of disease-specific patterns in 40 patients with PMR using contrast-enhanced MRI (ceMRI) of the pelvis. The predominantly occurring characteristic for all patients with PMR was the peritendinous enhancement of pelvic girdle tendons. All cases exhibited bilateral involvement of the common ischiocrural tendon, gluteus medius and minimus tendons, proximal rectus femoris origin and in 90% of cases enhancement of the adductor muscles at the inferior pubic bone. Therefore, bilateral involvement of at least four extracapsular sites in the pelvic region detected in patients with PMR by using ceMRI suggests that it may be relevant for diagnostic purposes (62). The same authors performed in 2020 pelvis ceMRI in 40 patients with confirmed diagnosis of PMR, including 80 individual healthy controls. That study confirmed a distinct pattern of extracapsular inflammation including bilateral peritendinitis and pericapsulitis of the proximal origins of the rectus femoris muscle and adductor longus muscle, characteristic for PMR, with significant diagnostic capability of the method, an excellent sensitivity of 95.8% and a specificity of 97.1% (63).

MRI has been proven to be useful for the diagnosis and the identification of inflammatory sites difficult to evaluate, including lumbar interspinous bursae in patients with PMR, as demonstrated by Salvarani *et al* (64). The authors of that study reported evidence of interspinous lumbar bursitis found in 9/10 patients with PMR and that lumbar pain may be supportive of predominantly extra-articular synovial involvement (64). Although the use of MRI aids in identifying additional areas of inflammation in the spine and pelvis, the number of controls with inflammatory disease was insufficient for precise specificity estimates, as demonstrated by Mackie *et al* (65) in a systematic review of the literature regarding the accuracy of musculoskeletal imaging for the diagnosis of PMR. Although MRI appears to be of particular interest in identifying deep structures with a limited acoustic window for ultrasound examination, including the spine and pelvis, its use may be limited by increased costs and limited availability, particularly for repeated evaluations in patients with symptom resolution following GC treatment, a limited area of imaging and a longer examination time, as well as limited access to whole-body MRI.

Instead, according to Mackie *et al* (65), whole-body MRI in PMR can identify a distinct subset of patients who are more likely to respond to GC therapy according to the MRI pattern of extracapsular inflammation and high IL-6 and CRP levels. The same study was designed for distinguishing PMR from RA according to the patterns of inflammation. In patients with PMR, extracapsular features of inflammation, including periacetabular inflammation without the involvement of the hip joint, extended from the anterior hip capsule, medial to the gluteus muscle and lateral to the iliac bone, distinct from iliopectineal bursitis, may help distinguishing between PMR and RA. Additionally, it is considered a predictor of response to glucocorticoid therapy. In this particular subset of patients with PMR, the entheseal involvement resembled a seronegative spondyloarthropathy (65).

An MRI study by Cimmino *et al* (66) regarding hand involvement in PMR also demonstrated the prevalent inflammation of extra-articular structures, presenting with extensor and flexor tendons tenosynovitis rather than joint synovitis. Of note, the authors of that study did not identify an association between clinical presentation and MRI, supporting the presence of extensor tenosynovitis as an epiphenomenon suggestive for subclinical disease (66).

Differential diagnosis. In support of the use of MRI in differential diagnosis, Ochi *et al* (67) evaluated shoulder and hip joints in PMR and RA patients. The MRI parameters analyzed were thickness and abnormalities of the supraspinatus tendon, effusion around the glenohumeral joint, subacromial-subdeltoid bursa, the biceps tendon in the shoulder and effusion around the acetabulofemoral joint, iliopsoas bursa and trochanteric bursa in the hip (67). The supraspinatus tendon was significantly thicker in PMR patients than in RA and control patients ($P<0.05$). Patients with PMR exhibited increased scores for effusions (joint, bursa, and tendon sheath in the shoulder and bursa in the hip), as well as more frequent periarticular soft tissue edema ($P<0.05$) as compared with RA cases.

A recent article by Nakamura *et al* (68) analyzed whether gadolinium-enhanced MRI in shoulders of patients with PMR could increase the diagnostic value and predict recurrence. Supporting the findings of extra-synovial involvement detected at hip level by Ochi *et al* (67), MRI abnormalities, including capsulitis, rotator cuff tendinitis and focal bone edema in the shoulder improved diagnostic accuracy in PMR with 76% sensitivity and 85% specificity. In addition, in patients with recurrence of the disease, rotator cuff tendinitis and synovial hypertrophy were predictive signs (68).

Treatment efficacy. In a previous study, the response to treatment with tocilizumab was evaluated in a post hoc MRI analysis of the data from the TENOR study, at baseline, following 2 and 12 weeks of treatment. Myofascial lesions were characteristic for recent onset PMR in the shoulder and hip. Resolution of inflammatory lesions was observed at week 12 in 41.7% of the 103 groups of muscles studied, while improvements were depicted in 64.1% of the examined muscle groups (69).

PET/CT. PET/CT scans using an analogue of glucose known as 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG-PET/CT), are a type of imaging technique that use a radioactive isotope, often implemented in the diagnosis and monitoring of oncological patients. By contrast, other clinical applications excluding cancer diagnosis are currently being used in clinical practice, since FDG accumulates in tissues that are not exclusively malignant. FDG also accumulates in inflammatory areas of the tissues, due to elevated activity levels in cells involved in inflammation, including lymphocytes, neutrophils and macrophages (70). In 2018, Slart *et al* (71) established recommendations for the application of PET/CT in improving the diagnostic and monitorization process in individuals with large vessel vasculitis (LVV), as well as PMR.

PET/CT can be used for the detection of mural inflammation and/or luminal changes in extra-cranial arteries to support the diagnosis of large vessel-GCA, as stated in the EULAR recommendations for the use of imaging in LVV, also revealing PMR lesions that remain elusive when other techniques are used. Even though it is not routinely used in PMR, PET/CT can reveal PMR lesions that are difficult to detect using other methods (72).

Numerous studies have been conducted in an effort to define a particular pattern of 18F-FDG uptake that may aid in the diagnostic process. Yuge *et al* (73) conducted a study on 60 individuals who initially diagnosed with PMR, enthesitis, arthritis, or myopathy. However, after applying the criteria established by the ACR/EULAR in 2012, the total number of patients diagnosed with PMR was limited to 16 individuals. In the final PMR group, the highest incidence of 18F-FDG was detected in the glenohumeral and sternoclavicular joints (88%), followed by the spinous processes and greater trochanters, ischial tuberosities and the last acromioclavicular joints, wrists and elbows. An enhanced 'Y-shaped' uptake along the interspinous bursae was a characteristic pattern for patients with PMR (73,74). In the study by Kaneko *et al* (75), 20 patients with PMR were enrolled, detecting isotope accumulation specifically in the proximal joint structures (glenohumeral, coxofemural and sternoclavicular joints) and in the extra-articular synovial structures (greater trochanter, ischial tuberosity, and the area anterolateral to the rim of acetabulum). Furthermore, another study conducted by Rehak *et al* (76) discovered an

accumulation of the isotope in the prepubic region in specific individuals. This finding was most likely the result of pectineus and adductor longus enthesitis. In addition to this, the authors of that study demonstrated that the areas with high accumulation of the tracer revealed no uptake after PMR therapy (76). This provides support to the utilization of 18F-FDG-PET/CT in the management of PMR not only for the diagnosis but also for the monitoring of treatment.

Sondag *et al* (77) demonstrated that considerable absorption in three or more sites in the joints, bursae, or entheses (acromioclavicular, sternoclavicular, glenohumeral; ischial, trochanteric, iliopectineal, and interspinous; pubic symphysis, respectively) was related to the diagnosis of PMR with a sensitivity of 74%. This method also assists in the process of differentially diagnosing PMR and RA, particularly EORA (77).

In a previous study by Takahashi *et al* (78), a typical pattern for PMR and EORA was established. In patients with PMR, a high sensitivity (92.6%) and a high specificity (90%) was observed when three out of five characteristic regions exhibited either an increased or an absent ^{18}F-FDG accumulation. An increase in uptake was detected in the ischial tuberosities, vertebral spinous processes, glenohumeral joints, and iliopectineal bursitis, and was not observed in the wrists (78).

Moreover, a retrospective study was conducted by Wendling *et al* (79) at a single center on patients diagnosed with PMR according to the criteria established by the ACR and EULAR in 2012. A control group of individuals who did not present with rheumatological symptoms, but were tested as part of neoplastic research, or patients with neoplastic disorders who were followed-up were also analyzed. A total number of 201 cases were investigated, including 101 patients with PMR and 100 healthy individual controls. Overall, PET muscle injury was observed in 34% of patients with PMR, as compared with 10% of the individuals in the control group. In total, 19, 14, 13 and six afflicted muscle sites were detected in the spinal region, the scapular girdle, the pelvic girdle and the thighs, respectively. On three occasions, fasciitis was also observed. In individuals diagnosed with PMR, age, CRP levels, or an overall PMR PET score were not linked to muscle involvement detected by PET (79).

In conclusion, although PET/CT is not a routine investigation as this imaging method exposes patients to increased levels of radiation, PET/CT may prove to be a useful diagnostic and monitoring tool for patients with PMR.

Role of imaging in PMR. The use of modern imaging techniques provides novel information regarding the anatomical and pathophysiological basis of PMR. Novel sites of inflammation were discovered with the use of MRI and PET/CT as compared to the use of MSUS alone. Thus, in addition to SASD bursitis and biceps tenosynovitis, inflammation of the peritendon of muscle insertions at the hip and interspinsous bursae are findings that may aid clinicians in differentially diagnosing PMR from other elderly-onset inflammatory diseases.

Additional studies on larger patient cohorts are required; however, these imaging techniques may be valuable for the diagnosis and monitoring the response to treatment in patients with PMR.

6. Diagnosis

When common signs and symptoms, as well as increased levels of inflammatory markers occur, the diagnosis of PMR is not a difficult process for a clinician with an extensive knowledge in this research field. However, there is a certain risk for less experienced clinicians to over- or underdiagnose PMR, particularly in situations involving illnesses that mimic PMR or in patients with many comorbidities, due to the absence of a diagnostic gold standard and the lack of specificity of the signs, symptoms, and laboratory data associated with PMR.

Over the years, several classification criteria have been proposed for PMR, the latest being the 2012 European League Against Rheumatism and American College of Rheumatology provisional classification criteria (Table I) (80).

The required inclusion criteria are the following: An age ≥50 years, bilateral shoulder pain and abnormal CRP and/or ESR levels. A score ≥4 strongly indicates PMR manifesting without MSUS, whereas a score ≥5 is indicates the presence of PMR with MSUS.

Prior to the development of the aforementioned criteria, other four research groups developed classification criteria for PMR, as follows: i) Bird criteria in 1979; ii) Jones and Hazleman criteria in 1981; iii) Chuang and Hunder criteria in 1982; and iv) Healey criteria in 1984 (Table II) (80-83).

7. Differential diagnosis

Conditions that afflict adults aged >50 years and are linked with bilateral shoulder pain should be considered for the differential diagnosis of PMR, since it is also a condition that causes discomfort in the neck and shoulders. This is important, considering the fact that there are no specific diagnostic tests for PMR. A misinterpretation of any disease as PMR may lead to inappropriate exposure to GCs for extended periods of time. Rheumatic diseases and non-rheumatic diseases should also be included in the differential diagnosis. With the emerging of new diagnostic criteria and the use of MSUS, PMR is easier to detect, making the differential diagnosis less complicated (84).

The different diseases that should be considered for differential diagnosis are the following: i) Rheumatic diseases, including rheumatoid arthritis, particularly the seronegative form, spondyloarthritis, microcrystalline arthritis, systemic lupus erythematosus, vasculitis and inflammatory myopathies; ii) non-inflammatory musculoskeletal pathologies, including fibromyalgia, osteoarthritis-glenohumeral and coxofemoral osteoarthritis, rotator cuff pathologies, subacromial/subdeltoid bursitis and adhesive capsulitis; iii) remitting symmetrical seronegative synovitis with puffy edema; iv) endocrinopathies, including thyroid pathologies and pathologies of the parathyroid glands; v) viral, bacterial infections and infectious or mycobacterial endocarditis; vi) solid or hematological neoplasia; and vii) other pathologies, including Parkinson's disease, depression, hypovitaminosis D and medication-induced myopathy (e.g. statin-induced myopathy) (85,86).

8. Treatment

The treatment of PMR is currently based on the 2015 EULAR/ACR recommendations. There is no validated

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

Criteria/symptoms	Points without MSUS	Points with MSUS
Morning stiffness lasting for >45 min	2	2
Hip pain or limited mobility	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and/or bicep tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

Adapted from the Dasgupta *et al* 2012 (51) provisional classification criteria for polymyalgia rheumatica: A European League Against Rheumatism/American College of Rheumatology collaborative initiative. EULAR, European League Against Rheumatism; ACR, American College of Rheumatology; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; MSUS, musculoskeletal ultrasound.

definition of remission and/or relapse for patients with PMR. However, the majority of definitions encountered in the literature comprise a combination of the absence of clinical symptoms/myalgias/improvement of clinical symptoms with ESR levels <20-40 mm/h and CRP levels <0.5-1 mg/dl. Regarding the therapy, the patients should have discontinued the GCs or these should be administered at a reduced dose (87).

Thus, the use of GCs is recommended instead of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with PMR, with the exception of the short-term use of NSAIDs and/or analgesics for the improvement of the symptoms of other associated pathologies, including coexisting osteoarthritis. According to the guidelines, a minimum effective dose of equivalent of prednisone ranging from 12.5 to 25 mg/day is recommended. Dose tapering is required to be individualized, according to the clinical and biological profile of each patient. The following principles for dose tapering are recommended to be administered: i) initial tapering ≤10 mg/day equivalent of prednisone in 4-8 weeks; ii) for relapse therapy, the dose of GCs is increased to the previous dose before the relapse, followed by its gradual tapering in 4-8 weeks up to the dose at which the relapse occurred; and iii) when tapering the dose in the case of remission, the dose of prednisone should be decreased by 1 mg every 4 weeks until the discontinuation of therapy, as long as remission is maintained.

The administration of intramuscular methylpredisolone should be considered as an alternative to administering GCs orally; however, this decision remains at the discretion of the attending physician (88). Concerning recently diagnosed patients, Dejaco *et al* (88) compared the efficacy of the oral administration of prednisolone (initial dose of 15 mg/day gradually reduced to 10 mg/day) with the administration of intramuscular methylprednisolone acetate (120 mg every 2 weeks for 12 weeks followed by injections every month, with dose tapering by 20 mg every 3 months). The prednisolone dosage was gradually decreased at levels <10 mg per day at a rate of 1 mg every 8 weeks. Both courses of treatment successfully induced and maintained the patients with PMR in remission. By contrast, oral prednisolone administration trended towards managing symptoms more rapidly and effectively than intramuscular injections of methylprednisolone (88).

Patients to whom oral prednisolone was administered received a larger cumulative GC dose, being prone to more GC-related adverse events than those who were administered injectable methylprednisolone; however, higher rates of stopping the medication were observed (88).

A single dose of prednisone per day is recommended, except for cases in which nocturnal pain is severe following the reduction the dose of GCs administered to <5 mg/day equivalent of prednisone (88).

The early introduction of synthetic disease modifying therapy with methotrexate (MTX) in doses of 7.5-10 mg/week is conditionally recommended, particularly in patients with an increased risk of relapse, as well as in cases with risk factors, comorbidities and/or with concomitant treatments that predispose to adverse reactions in combination with GCs (78). In the study by Ruediger *et al* (89) in 2020 conducted on 70 patients with PMR, out of which 31% were prescribed MTX in combination with GCs, MTX was associated with a reduction in steroidal anti-inflammatory drugs use and an improvement in inflammatory biological profile. A multicenter randomized, double-blind, placebo-controlled trial performed by Caproali *et al* (90) on 72 patients newly diagnosed with PMR proved that the administration of 10 mg/week of MTX in combination with GCs compared to GCs alone was associated with the earlier cessation of prednisone therapy, rendering it useful in patients at a high risk for steroid use. Furthermore, an ongoing multicenter double-blind placebo-controlled clinical trial is currently conducted by Marsman *et al* (91) aiming to evaluate the efficacy of the administration of 25 mg/week MTX in patients with PMR in an early disease phase.

Studies on other conventional synthetic immunosuppressive drugs are limited, usually based on small study groups or case series. Hydroxychloroquine and azathioprine have been tested in patients with PMR. The study by de Silva *et al* (92) involving 31 patients with PMR and/or GCA tested the efficacy of azathioprine, suggesting that patients who received azathioprine required a reduced GC dosage. However, the majority of the patients fulfilled the criteria for GCA and the

Table II. Classification criteria for PMR.

Bird criteria 1979 (at least 3 out of 6 criteria stated below are required for classification as PMR)	Jones and Hazleman criteria 1981 (all criteria stated below are required for PMR classification)	Chuang and Hunder criteria 1982 (all criteria stated below are required for PMR classification)	Healey criteria 1984 (required criteria: Age ≥50 years and at least 3 out of 5 of the remaining criteria required for classification as PMR)
Bilateral shoulder pain and/or stiffness	Shoulder or pelvic girdle pain without muscle weakness	Age ≥50 years	Age ≥50 years
Disease onset <2 weeks	Morning stiffness lasting for more than 1 h	Bilateral pain and stiffness persisting for 1 month or more involving two of the following areas: neck or torso, shoulders or upper arms, hips or thighs	Persistent pain for 1 month or more involving two of the following areas: neck, shoulders, or pelvic girdle
Initial ESR ≥40 mm/h	Disease duration of more than 2 months per year		Morning stiffness lasting for more than 1 h
Morning stiffness duration >1 h	ESR >30 mm/h or CRP >6 mg/l	ESR >40 mm/h	Rapid response to prednisolone (≤20 mg per day)
Age >65 years	Absence of rheumatoid arthritis	Exclusion of other diagnoses with the exception of giant cell arteritis	Absence of other joint or musculoskeletal diseases
Depression and/or loss of weight	Absence of objective signs of muscle disease		ESR >40 mm/h
Bilateral upper arm tenderness	Fast and dramatic response to systemic glucocorticoids		

PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

number of patients was limited (92); thus further extensive studies are required in order to attest the efficacy of azathioprine. Hydroxychloroquine was also tested in a retrospective study performed by Lee *et al* (93), demonstrating no benefits for patients with PMR.

The use of anti-TNFα biological therapy is not recommended for the treatment of PMR as it has not proven to be beneficial to the patients. The administration of the antagonist of the receptor for IL-6, tocilizumab, has been demonstrated to improve symptoms and attenuate the inflammatory syndrome in patients with PMR in several series of cases and retrospective studies. In the study performed by Lally *et al* (94) on 10 patients with PMR, with only 9 patients having been assessed at the time of the primary endpoint, it was concluded that tocilizumab may be an efficient, well-tolerated drug, with a good safety profile and a great steroid-sparing effect. All the patients did not present relapse without GC therapy at the primary endpoint (94). Overall, 20 patients with active PMR of recent onset were included in a prospective open-label study performed by Devauchelle-Pensec *et al* (95). These patients received three tocilizumab infusions at 4-week intervals, without receiving GC therapy, followed by the administration of oral prednisone. At the end of the 12th week, all of the patients reported clinical improvement in their PMR symptoms (95). Furthermore, in a more recent randomized, double-blind, placebo-controlled trial on 101 patients with PMR, steroid-dependent patients were treated with tocilizumab. GC therapy was terminated by week 24 in 49% of patients in the tocilizumab group as compared to the placebo group, of which only 9% terminated the GC (96). In a series of cases presented by Mori and Koga (97), three patients presenting with GC-resistant PMR were administered tocilizumab in addition to GCs, with all of the patients achieving remission. A phase 2/3 randomized controlled trial on 36 patients with new-onset PMR conducted by Bonelli *et al* (98) proved that tocilizumab was superior to the placebo when attesting to the sustained GC-free remission, time to relapse and the cumulative GC dose. Out of the 36 patients enrolled in that study, 19 received subcutaneous tocilizumab in doses of 162 mg per week, while 17 were administered the placebo. All the patients received prednisone doses tapered from 20 mg to 0 mg over the course of 11 weeks (98).

Limited research has been conducted on the administration of other biological therapeutics in individuals diagnosed with PMR. In a proof-of-concept, single-blind, three-arm study, 16 patients with PMR were administered either secukinumab or canakinumab, as a single dose of 3 mg/kg/body weight, or oral prednisone at a dose of 20 mg per day (99). Patients were randomly assigned 1:1:1 to receive either secukinumab or canakinumab or GCs. Patients who were administered GCs demonstrated significant reductions in their levels of pain, whereas those who were treated with secukinumab and canakinumab only exhibited a slight improvement in their range of motion. On day 15, none of the patients who were receiving biological treatment and only one of the patients who were receiving GCs obtained a full response. In the group that received secukinumab, in 4 patients, this was replaced by GCs. A dose of GCs that was 40% lower on a monthly basis was then required, as compared with individuals who were not treated with biological therapeutics. Additionally, this also applied

Table III. Ongoing clinical studies in PMR.

Clinical study	Accession no./year	Type	Primary outcome	Secondary outcome	Status/results
A study to evaluate the change in disease state and adverse events in adult participants with PMR, dependent on glucocorticoid treatment, and receiving subcutaneous injections of ABBV-154 (AIM-PMR).	NCT0497296/2021	A phase 2, randomized, double-blind, placebo-controlled clinical trial	Time to flare (time frame 52 weeks)	Percentage of patients who achieve flare free-state; cumulative glucocorticoid dose change from baseline in glucocorticoid dose.	Recruiting
Clinical trial of prednisolone in combination with SPI-62 or placebo in subjects with PMR.	NCT05436652/2022	Interventional	Erythrocyte sedimentation rate; CRP; Plasma fibrinogen; Timeframe, baseline to day 28.		Not yet recruiting
Treatment with leflunomide in patients with PMR (PMRLEFRCT).	NCT0357679/2018	Prospective, randomized, double-blind, placebo-controlled treatment study during 12 months (part I) and an additional open-label follow-up of 12 months (part II)	PMR relapse.	Time until first relapse within the first 24 months; Percentage of patients with at least one relapse in the first 12 or 24 months; number of relapsing patients within the first 24 months; time until glucocorticoid free remission; glucocorticoid-sparing effect; number of participants with adverse events and serious adverse events as assessed by MedDRA V21.0.	Recruiting
Abatacept in earLy onset PMR: Study ALORS (ALORS)	NCT03632187/2018/2018	Multicenter double blinded randomized placebo controlled trial.	Following of one biological parameter (CRP) for a time frame of 12 weeks.	Emergence of adverse events; following of the PMR activity score; medical resource evaluation; following of the cumulative dosages of glucocorticoids; The flare of the PMR (PMR-AS); following of the medical exam using the ultrasound Scoring; evaluation of FDG uptake using TEP scanner in regions of interest; following the proportion of patient relapse; biological marker levels (interleukin, cytokines, immune cells); following of patient quality of life	Active, not recruiting

Table III. Continued.

Clinical study	Accession no./year	Type	Primary outcome	Secondary outcome	Status/results
BAriCitinib Healing Effect in earLy pOlymyalgia Rheumatica (BACHELOR)	NCT04027102/2019	Multicenter double blinded randomized placebo-controlled trial.	Following of the PMR activity score (time frame 12 weeks)	Following of the PMR activity score (time frame 36 weeks); Emergence of adverse events (safety and tolerability); following of the cumulative dosages of glucocorticoids; ultrasound of synovitis and tenosynovitis; levels of biological markers (interleukin, cytokines, immune cells); following of the quality of life using SF36; following of the quality of life according to HAD; following of the quality of life according to the scale EuroQol 5 dimensions.	Recruiting

PMR, polymyalgia rheumatica; CRP, C-reactive protein; FDG, 2-[fluorine-18]-fluoro-2-deoxy-D-glucose; SF36, the short form 36; HAD, the hospital anxiety and the depression scale.

for 3 patients who were treated with canakinumab prior to changing the treatment to GCs. Overall, it was suggested that the application of these biological therapeutics in patients with PMR requires further investigation (99).

A prospective open-label 52-week pilot study investigated the efficacy of baricitinib, which is a JAK1 and JAK2 inhibitor, in treating relapsing forms of GCA in patients (100). Baricitinib was well-tolerated and the majority of patients were able to terminate GCd administration as a consequence. It is probable that JAK inhibition may be also important for the treatment of PMR (100).

The BRIDGE-PMR, a double-blind, randomized, placebo-controlled, proof-of-concept trial included 47 patients with PMR randomized 1:1 to a single intravenous infusion of rituximab 1000 mg or the placebo (101). All the patients received a 17-week GC tapering scheme. That study revealed that rituximab was more efficient in combination with GCs than the placebo and GCs (101). In extension of that study, the 47 patients included in the original study were followed-up from 2019 to 2021, and it was proven that the patients treated with rituximab were in GC-free remission at 1 year after the infusion (92). Thus, rituximab may be considered a valid treatment option for PMR, although studies on larger groups of patients are required (102).

Sarilumab, a recently approved drug for the treatment of PMR, was studied the SAPHYR trial which compared sarilumab and 14-week GC tapering with placebo and 52-week GC tapering. The arm treated with sarilumab demonstrated improved clinical status than the GC arm (103).

There are several ongoing studies evaluating the efficacy of certain conventional synthetic and/or biological agents for PMR treatment (Table III). The website https://clinicaltrials.gov/ was used as research for the ongoing studies evaluating treatment options in PMR.

The optimization of the benefit-to-risk ratio of GCs in order to achieve durable remission, while minimizing the occurrence of side-effects is an ongoing issue. Subsequently, the creation of novel GC preparations and/or GC receptor ligands may be able to improve the benefit-to-risk ratio of GCs. Accordingly, selective GC receptor agonists and modulators may be potential therapeutics targeted at selectively enhancing anti-inflammatory cellular pathways. As consequence, the undesirable effects associated with these medications would not be triggered by the pathways that these pharmaceuticals could prevent from being activated (104).

9. Conclusions and future perspectives

Although the present review was a narrative one, which could be considered a limitation, it provides important insight into the new diagnostic techniques and treatment options for PMR. In conclusion, PMR is a prevalent disease that can occasionally impose marked diagnostic and therapeutic difficulty. Further research into its pathophysiology is required in order to elucidate the underlying processes further, which will serve as the foundation for future tailored treatments. In addition, there is a demand for improved techniques of diagnosis, which should include the further improvement of various imaging modalities, in order to assist in accurate diagnosis and appropriate therapy. Other potential therapeutic agents including JAK inhibitors have to be further evaluated in PMR.

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Ethics approval and consent to participate

Written informed consent was acquired from the patients associated with the images presented in Figs. 2 and 3.

Patient consent for publication

Patients provided consent for the publication of their personal data in Figs. 2 and 3.

Competing interests

The authors declare that they have no competing interests.

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