The New and Evolving Science of Polymyalgia Rheumatica

Optimizing Care for PMR: Advances and Challenges in Diagnosis and Treatment

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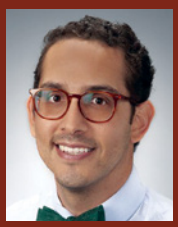

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Dear Colleagues,

This is a very exciting time in the field of polymyalgia rheumatica (PMR). With an increased focus on basic and clinical research regarding the pathogenesis of PMR, we now understand more about this disease than ever before. We know that cytokines play many key roles in the inflammation that drives PMR. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to local and systemic inflammation in patients with PMR.

Sanofi and Regeneron Pharmaceuticals are excited to bring you additional educational materials describing some of the fundamental aspects of PMR through a series of scientific monographs entitled *The New and Evolving Science of Polymyalgia Rheumatica*. In the first installment, we discussed the pathophysiology of PMR and the role IL-6 plays as a key driver in the disease. In the second installment, we focused on how glucocorticoids have shaped the treatment landscape in a range of rheumatic diseases, and how we can refine their use through the Glucocorticoid Toxicity Index (GTI) and its related clinical outcome assessments. In this third edition of the series, we provide you with the latest insights to deepen your understanding of PMR, a complex disease requiring accurate and timely differential diagnosis as well as tailored management and monitoring plans.

We hope you find this installment both informative and engaging.

Sincerely,

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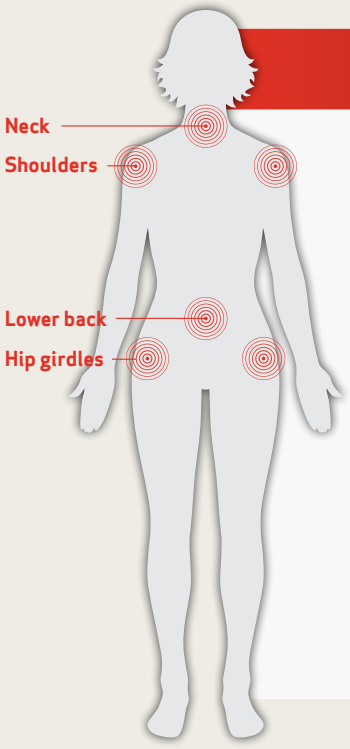
I. Introduction to Polymyalgia Rheumatica (PMR)

Epidemiology

PMR is an inflammatory rheumatic disease characterized by pain and stiffness, primarily affecting the neck, shoulders, and hip girdle (Figure 1).[1,2] PMR is the second most common inflammatory rheumatic disease in the general population, after rheumatoid arthritis.[3,4] However, among older adults, PMR incidence surpasses that of rheumatoid arthritis and other inflammatory rheumatic diseases, making it the most common inflammatory rheumatic disease for those older than 50.[4,5] PMR generally affects individuals aged 50 and older, with an annual incidence of 64 new cases per 100,000 people in this age group.[6,7] Women are disproportionately affected, with a prevalence 2 to 3 times higher than in men.[5] In both sexes, PMR incidence increases with age, with the peak between 70 and 79 years.[8] PMR is more common among individuals of Northern European descent but can affect individuals of any race and from any region.[5]

Inflammatory patterns in PMR

Although PMR commonly presents as pain and stiffness in the neck, shoulder, and hip girdle,[1,2] recent imaging studies have shown that PMR can affect other musculotendinous structures, including parts of the spine, elbows, hands/wrists, and knees (Figure 2).[9] Inflammation in PMR typically affects the connective tissues surrounding muscles and tendons, particularly the contiguous perimysium and peritenon.[9] It is common for adjacent structures such as the bursa (which reduces friction at large joints), joint capsules, and ligaments to be involved.[9]



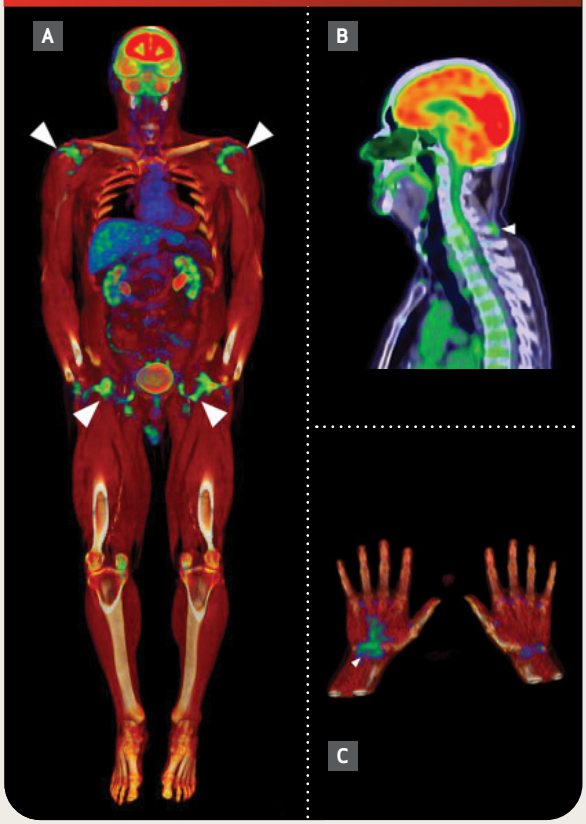
Polymyalgia Rheumatica Facts

- Second most common inflammatory rheumatic disease after rheumatoid arthritis[3,4]
- Typically affects people aged 50 years and older[6,7]
- More prevalent in women and in individuals of Northern European descent[5]
- Commonly presents as pain and stiffness in the neck, shoulder, and hip girdle, though other areas may also be affected (Figure 2)[1,2,9]
- ~10% to 30% of patients with PMR also develop giant cell arteritis, an ischemic disease needing urgent medical treatment[6,10]

Figure 1: Common facts about polymyalgia rheumatica.

As a result, patients may experience severe movement limitations in the shoulder and hip joints, pain during movement in the glenohumeral and coxofemoral joints, painful impingement from subacromial bursitis in the shoulders, and discomfort in key musculotendinous sites such as the biceps, ischial tuberosities (sit bones), and hamstrings.[9]

Distinct Patterns of Inflammation at Various Musculotendinous Sites in PMR[9]



Owen CE, Characterising polymyalgia rheumatica on whole-body ^{18}F-FDG PET/CT: an atlas, Rheumatology Advances in Practice, 2024, 8, 1, 1-12, by permission of Oxford University Press

Figure 2: Whole-body ^{18}F-FDG PET/CT imaging in a patient with PMR reveals inflammation patterns in various musculotendinous structures. Peri-articular ^{18}F-FDG uptake is seen in the shoulders and hips (A), cervical spine (B), and hands (C), as indicated by the white arrows.

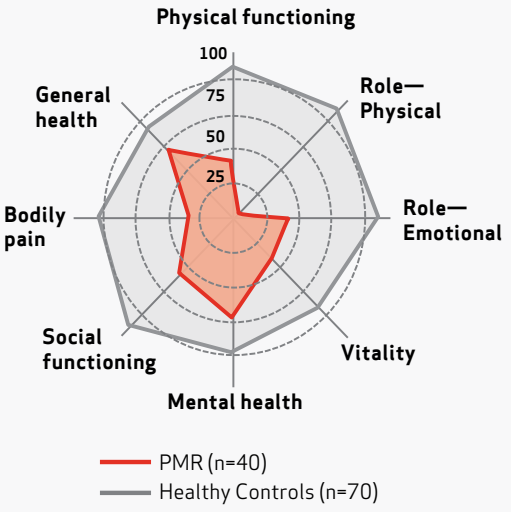
CT, computed tomography; ^{18}F-FDG, fluorodeoxyglucose ^{18}F-PET, positron emission tomography.

The impact of PMR on patients' quality of life

PMR often has a rapid onset, characterized by acute or subacute onset of the disease for up to 2 weeks, leading to the patient experiencing a sudden deterioration of daily performance and reduced quality of life (QoL).[11] Pain from PMR can interfere with sleep at night, while morning stiffness can make it difficult for patients to get out of bed and perform daily activities.[3] A 2007 study of 129 PMR patients revealed substantially lower physical and mental QoL compared to the general population aged 65 to 74 years.[12] In a primary care cohort of 654 patients with PMR, fatigue was greater compared to the general US population, along with high levels of pain, stiffness, functional impairment, insomnia, anxiety, depression, and polypharmacy.[13]

A 2021 study monitored 40 patients with PMR for up to 5 years after diagnosis, administering

Living With PMR Can Substantially Reduce Health-Related Quality of Life[14,15]



Patient Reported Outcomes on Quality of Life in Patients with Giant Cell Arteritis and Polymyalgia Rheumatica, van Sleen Yannick, et al. © 2021. Reproduced with permission of John Wiley & Sons, Inc.

Figure 3: Scores of the 8 domains of the 36-item SF-36 in treatment-naïve PMR patients (n=40) in a study presented in 2021. Data were compared with age- and sex-matched healthy controls (n=70) who were also followed for up to 5 years. Scores range from 0 to 100, with lower scores indicating lower health status.

the 36-item Short Form Health Survey (SF-36) at each visit. Results showed that PMR patients consistently scored lower across 8 domains of the SF-36 (physical functioning, limitations due to physical problems, bodily pain, general health perception, vitality [ie, energy/fatigue], social functioning, role limitations due to emotional problems, and mental health) compared to age- and sex-matched healthy control subjects, who were also followed for up to 5 years (Figure 3).[14,16]

Even though patients with PMR experience pain and disability, the absence of any visible, external symptoms can present challenges for healthcare providers in managing the condition and may leave patients feeling that their symptoms and experiences are not fully recognized.[9,11]

The central role of IL-6 in PMR pathophysiology

Although the pathophysiology of PMR is not completely understood, PMR pathogenesis is driven by inflammation. Both innate and adaptive immunity contribute to the inflammatory process seen in PMR.[17] Various proinflammatory cytokines secreted by innate and adaptive immune cells are implicated in PMR pathogenesis. Elevated serum levels of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-17 (IL-17), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), were observed in patients with PMR compared to healthy controls or those with inactive PMR, although IL-6 is the only cytokine whose levels correlate with both disease activity and risk of relapses (Figure 4).[17-19] In contrast, interleukin-10 (IL-10) may play a protective role in PMR, in which higher IL-10 concentrations have been associated with a milder form of PMR.[17]

Among proinflammatory cytokines, IL-6 has been extensively studied in PMR, and since its levels correlate with disease activity, IL-6 is believed to be a major driver of PMR pathogenesis.[17,19] IL-6 is secreted by immune cells, such as activated CD4+ T cells, and can exert its effects in multiple tissues to affect both *local* and *systemic* inflammation.[1,5]

IL-6 has been detected in noninflamed arteries, as well as in the synovial tissue of patients with PMR, where it is thought to drive local inflammation.[1,20] Additionally, serum levels of IL-6 are increased in PMR, and IL-6 drives systemic inflammation, as measured by elevated levels of C-reactive protein (CRP) and other biomarkers in the plasma.[5]

In one study, patients with newly diagnosed PMR had significantly increased concentrations of plasma IL-6, whereas healthy control subjects had minimal detectable levels of IL-6 in the plasma. Without exception, all PMR patients had IL-6 levels that were at least fourfold higher than those in healthy controls, suggesting that elevated IL-6 levels serve as a marker for disease activity.[19] Additionally, levels of soluble IL-6 receptor (sIL-6R) have been suggested to be a prognostic marker for PMR outcomes, since higher relapse rates were found to correlate positively with higher levels of sIL-6R.[21]

PMR and giant cell arteritis (GCA) are closely related conditions

PMR is frequently associated with GCA, the most common form of vasculitis affecting adults older than 50, with an incidence of 18 new cases per 100,000 people per year.[6,22] GCA primarily affects the large arteries, notably the cranial arteries, presenting symptoms such as headache, fatigue, fever, vision loss, and jaw claudication.[22,23] One of its most dreaded complications is permanent vision loss, which can occur in 15% to 20% of patients with GCA and is commonly caused by anterior ischemic optic neuropathy. The risk of anterior ischemic optic neuropathy is decreased with early diagnosis and treatment.[24]

PMR may begin simultaneously or consecutively with GCA. Approximately 40% to 50% of patients diagnosed with GCA have PMR manifestations, and 10% to 30% of patients diagnosed with PMR are also found to have GCA.[6,25] Patients with PMR should always be examined for GCA. Early detection of GCA is crucial because this form of vasculitis can cause blindness; stroke; and aortic aneurysm, dissection, and rupture.[26,27] Due to risks of serious ischemic complications and vision loss, GCA should be treated as a medical emergency.[10]

Nonetheless, delays in diagnosis of GCA are common, even in cases with classic symptoms, highlighting the need for fast-track diagnostic pathways in clinical settings.[26]

II. PMR Diagnosis and Challenges

Diagnosing PMR often presents challenges since it is diagnosed clinically, with no specific confirmatory test.[28] Therefore, the diagnosing clinician needs to consider clinical history, inflammatory markers, and other laboratory results.[29] The 2012 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria provide standardized guidelines to aid in the classification of individuals with suspected PMR, requiring inclusion criteria such as age of at least 50 years, bilateral shoulder aches, morning stiffness lasting longer than 45 minutes, and elevated acute-phase reactant levels (CRP/ESR) (Figure 4).[30] While ESR and CRP are commonly used acute-phase reactants included in these criteria, it is worth noting that some patients may exhibit normal levels of these markers.[27] Normal ESR values were observed in 7% to 22% of patients with PMR at time of diagnosis, although these patients usually have high CRP levels.[31] The occurrence of patients with PMR who have normal ESR and CRP varies among different studies, ranging from 1.2% to 14.8%, adding to the diagnostic challenge.[31,32]

The hallmark of PMR is a sudden onset of symptoms, such as sudden-onset bilateral shoulder pain and stiffness, which occurs in about 95% of cases. Early morning stiffness lasting more than 45 minutes is typical, along with pelvic girdle pain, which is seen in up to 70% of patients. However, not all cases fit this pattern, which can make diagnosis challenging.[33]

About half of patients may exhibit peripheral musculoskeletal involvement, complicating diagnosis.[33] This can manifest as peripheral arthritis, often asymmetric and affecting wrists and knees.[33] Although the arthritis associated with PMR is nonerosive and highly responsive to steroids, distinguishing these cases from late-onset rheumatoid arthritis can be challenging.[33] Other peripheral manifestations include carpal tunnel syndrome and tenosynovitis, resembling remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome.[33] These symptoms may also suggest other inflammatory arthropathies, necessitating consideration of alternative diagnoses.[33]

Additionally, constitutional symptoms, such as low-grade fever, fatigue, anorexia, and weight loss, may occur in up to 40% of PMR patients.[33]

Furthermore, PMR diagnosis presents additional challenges because there is significant heterogeneity in how patients describe their symptoms.[34] Some describe their symptoms as severe pain, whereas others describe muscle ache similar to aches caused by exercise or being sick with an infection. Other patients mention stiffness as the predominant symptom, with pain secondary to stiffness.[34]

PMR: Challenges in differential diagnosis

Several conditions can mimic PMR symptoms.[33] Since there is no specific test, a differential diagnosis to exclude other diseases is the basis for identifying PMR (Figure 4).[27,35] Given that PMR is a type of inflammatory pain, determining whether the pain is inflammatory or mechanical (noninflammatory) is the first important step.[35-38]

Inflammatory pain in PMR can be worse in the morning, abate with activity, and worsen with rest; can manifest systemically; and can respond to corticosteroids. On the other hand, mechanical pain is characterized by intermittent pain throughout the day that worsens with activity and improves with rest.[35-38]

Once inflammatory pain is confirmed, the differential diagnosis process for PMR begins by ruling out various conditions, including inflammatory and noninflammatory rheumatic disorders, as well as infections and malignancies (Figure 4).[27,33,39] Among PMR mimickers with prominent musculoskeletal manifestations are systemic disorders, such as rheumatoid arthritis, inflammatory myopathies, and fibromyalgia, along with local regional disorders

that can cause proximal musculoskeletal pain, such as rotator cuff pathology, frozen shoulder, or greater trochanteric pain syndrome (Figure 4).[27,33,39] Throughout the process, it is important to determine if the patient has GCA, a medical emergency that requires immediate and aggressive treatment to prevent serious complications, such as blindness; stroke; and aortic aneurysm, dissection, and rupture.[26,39] Immediate referral to a rheumatologist is advised, especially when patients present with symptoms such as headache, jaw claudication, or vision problems, to promptly assess and manage potential GCA.[39]

Patient journey to PMR diagnosis

The journey to PMR diagnosis can be significantly complex and long for some patients; many patients go weeks to months without proper diagnosis (and therefore treatment), experiencing poor quality of life as a result. A survey of 270 physicians showed various paths to PMR diagnosis for patients (Figure 5).[11,40] Upon developing symptoms, some patients may go to see their primary care physician (PCP), while others may see orthopedic or other specialists to treat their underlying symptoms. These patients could be receiving treatment for their symptoms without a definitive diagnosis for 6 to 24 months. During this time, several patients could potentially receive a PMR diagnosis, while others could be misdiagnosed due to confounding factors.[33,40,41]

The risk of misdiagnosis in PMR could be as high as 30%, according to a peer-reviewed study that pooled results from 3 separate studies.[41] Common misdiagnoses include age-related aches or pains, fibromyalgia, and rheumatoid arthritis.[40]

In cases in which PCPs may suspect PMR or a rheumatic disease in general, they may refer the patient to a rheumatologist who, based on history, clinical/physical exam, and blood tests, would arrive at a diagnosis of PMR, typically within 1 to 3 weeks.[40]

Receiving a PMR diagnosis can bring relief to patients, particularly for those who have struggled to obtain an accurate diagnosis.[34]

"I was just glad to get a diagnosis, you know, and I was euphoric, you won't believe this! But the day they told me I'd got PMR, I was euphoric, I was picking the phone up to my sister and said, 'I've got an answer now, I've got this.'"[34]

- a patient with PMR

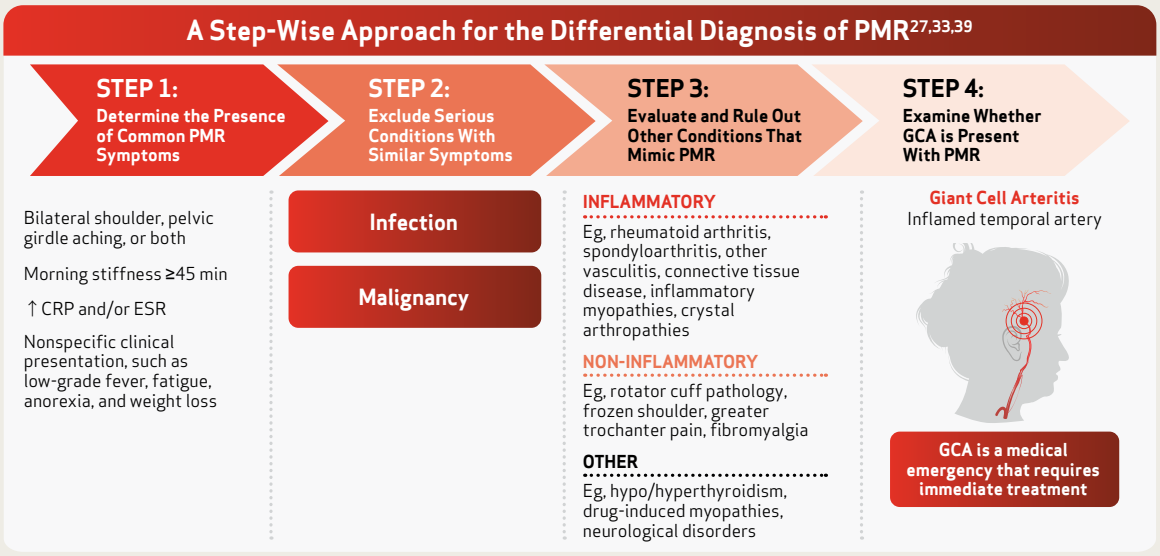


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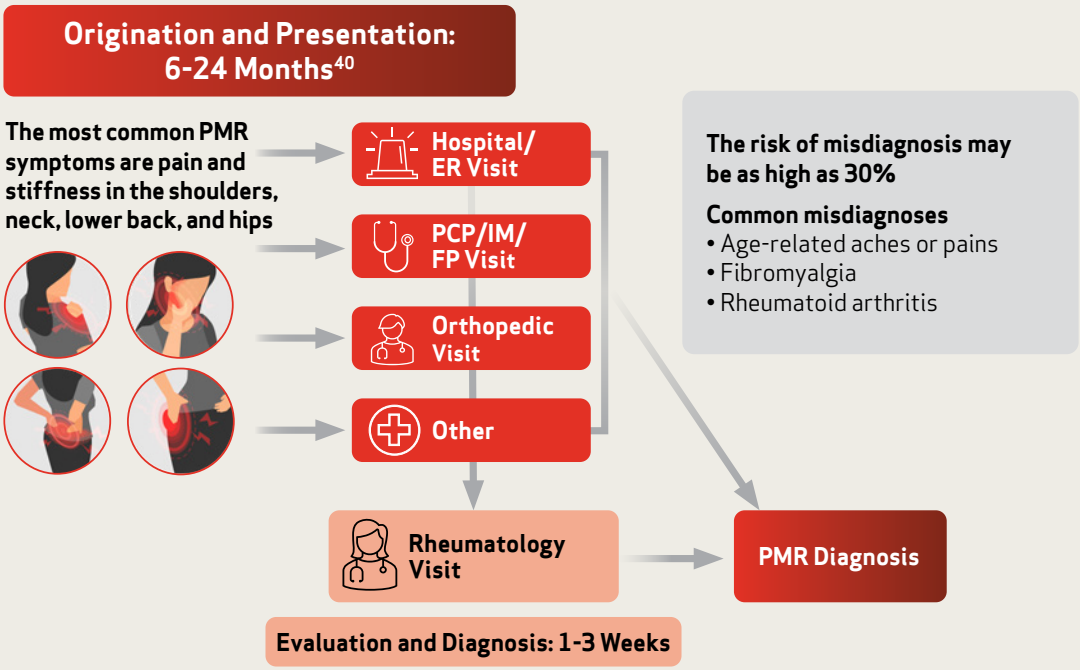
Figure 4: The differential diagnosis of PMR involves evaluating common PMR symptoms, ruling out infection and malignancies, and considering other conditions that mimic PMR, such as RA, other forms of vasculitis, and fibromyalgia, among others. Additionally, it is important to consider the possibility of GCA both during and after the PMR diagnosis.

Referral to rheumatologists

Since a thorough evaluation—including a detailed history, comprehensive examination, and sometimes imaging—is necessary to differentiate PMR from other conditions, PMR diagnosis could be facilitated by assessment from a rheumatologist.[41] There are 3 broad situations in which referral to a rheumatologist is recommended (Figure 6).[27,41] In the first scenario, there are atypical clinical presentations causing diagnostic uncertainties, such as in younger patients (less than 60 years of age); chronic onset, lack of shoulder involvement, or lack of inflammatory stiffness; "red flag" features such as prominent systemic symptoms, weight loss, night pain, or neurological signs; or peripheral arthritis or other features of autoimmune and muscle disease. In the second scenario, referral is recommended when PMR is initially suspected but the diagnosis remains unclear, as indicated by normal or very high inflammatory markers (eg, ESR ≥100 mm/h or CRP >100 mg/dL); lack of or ill-sustained response to corticosteroids; or prominent constitutional symptoms such as fever, weight loss, fatigue, and night sweats. In the third scenario, referral to a rheumatologist is warranted in treatment situations in which corticosteroid therapy is contraindicated, when dose reduction is not feasible, or when there is a need for prolonged corticosteroid therapy (Figure 6).[27,42]

In 2023, the EULAR/ACR task force provided recommendations for early referral of patients with suspected or newly diagnosed PMR, a stance further reinforced by the 2024 recommendations from the French Society of Rheumatology.[41,42]

Both the 2023 EULAR/ACR task force and the 2024 French Society of Rheumatology recommendations highlight the need to promptly consider specialist assessment in all individuals with suspected or newly diagnosed PMR. Particularly for those experiencing severe symptoms, expedited referral and access protocols, preferably within 1 week, were recommended.[41,42]



In 2023, a EULAR task force provided the recommendation that every individual with suspected or newly diagnosed PMR should be considered for specialist assessment.

ER, emergency room; FP, family practitioner; IM, internal medicine; PCP, primary care physician; PMR, polymyalgia rheumatica.

Figure 5: A survey of 270 physicians showed that the journey to a PMR diagnosis can be long for many patients and can often include misdiagnoses.

A delay beyond 1 week in specialist care evaluation may lead to a greater number of patients receiving unnecessary corticosteroid treatment, which may complicate further evaluation and is associated with frequent adverse effects.[41,43] Recognizing the importance of this coordination of care in PMR, a partnership between primary care and rheumatology providers is important to facilitate the implementation of rapid access protocols for effective PMR management.[41]

III. PMR Management

Treat-to-target recommendations in PMR

The first treat-to-target recommendations in PMR were developed by an international multidisciplinary task force in 2023.[10] The concept of treat-to-target involves defining a specific treatment target for a specific individual case, regular monitoring of progress toward this target, and adjusting treatments as needed to achieve the lowest possible disease activity or remission.[10] This approach has been demonstrated to yield superior outcomes compared to conventional care in various rheumatologic conditions such as rheumatoid arthritis, spondyloarthritis, gout, and systemic lupus erythematosus.[10]

The PMR treat-to-target recommendations underscored several overarching principles, including recognizing the interconnectedness of PMR and GCA, defining remission as the absence of clinical symptoms and systemic inflammation, tailoring treatments based on individual conditions and comorbidities, adjusting treatment as necessary during follow-ups, and aiming to sustain remission using the lowest effective dosage of medications.[10] The task force emphasized the importance of avoiding overtreating PMR with corticosteroids, which can happen when initiating or maintaining doses that are too high, prolonging treatment duration excessively, or failing to consider steroid-sparing agents.[10]

Corticosteroid treatment in PMR

Once PMR is diagnosed, the EULAR/ACR recommendation is to start a patient with PMR on a 12.5 mg to 25 mg daily dose of prednisone for 2 to 4 weeks, which typically leads to a dramatic improvement in symptoms within the first few days (Figure 7).[6,29] Once the clinical symptoms are under control, gradual tapering of prednisone is started until the patient is off prednisone completely (Figure 7).[29,35] Although it is advised to taper prednisone to 10 mg/day within 4 to 8 weeks, achieving this is often difficult due to the high risk of relapses.[29,44] Patients who successfully taper according to this schedule should continue reducing their dosage until they can discontinue the medication and their disease is in remission.[29] However, observational studies suggest that long-term corticosteroid-free

PMR Patients Should be Considered for Referral to Rheumatologists[27,41]

Diagnostic Uncertainty: Atypical Clinical Presentations

- Younger patient (<60 years)
- Chronic onset
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- "Red flag" features: prominent systemic features, weight loss, night pain, neurological signs
- Peripheral arthritis or other

Diagnostic Uncertainty: PMR Initially Suspected, but Remains Unclear

- Normal or very high inflammatory markers (eg, ESR >100 mm/h or CRP >100 mg/dL)
- Lack of response to corticosteroids
- Ill-sustained response to corticosteroids
- Prominent constitutional

Treatment Dilemmas

- Contraindications to corticosteroid therapy
- Unable to reduce corticosteroid dose due to flares (ie, recurrence of symptoms)
- Need for prolonged corticosteroid therapy

Figure 6: PMR patients should be considered for early referral to rheumatologists.

remission may be achieved in 30% to 60% of patients, and many patients will experience relapse during tapering.[10,35]

If patients experience relapses and flares while tapering, prednisone can be increased to the previous effective dose, and eventually gradual tapering can be attempted again.[35] These patients would benefit from consultation with a specialist to explore alternative treatment approaches, such as steroid-sparing options.[27,35] The EULAR/ACR group recommends that patients with PMR be monitored every 4 to 8 weeks in the first year, every 8 to 12 weeks in the second year, and as indicated in case of relapse or as prednisone is tapered and discontinued.[29]

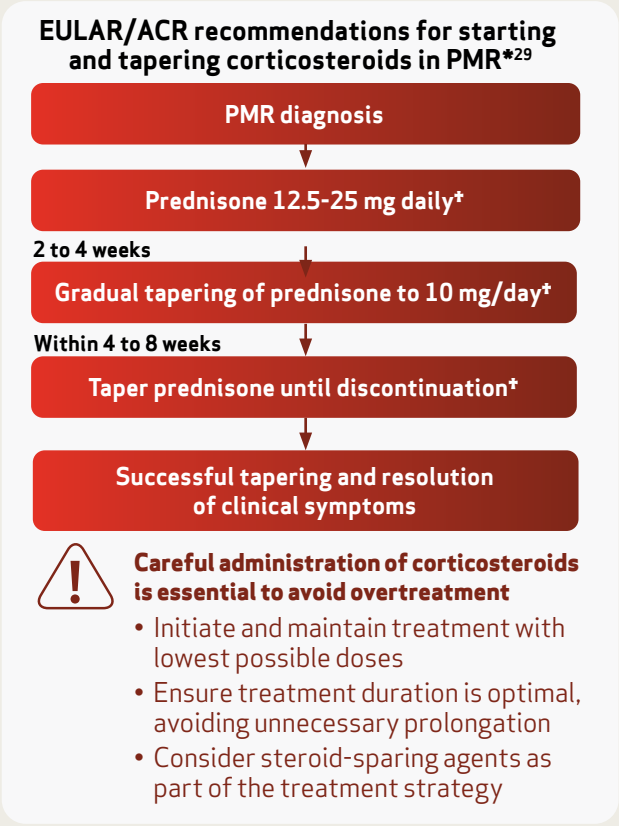
Corticosteroids should be used with caution, ensuring that the initial dosage does not exceed 25 mg daily before tapering as soon as possible. Higher doses can confound diagnosis by rapidly reducing inflammatory symptoms in patients with serious immune-mediated inflammatory diseases as well as other constitutional symptoms secondary to systemic infections and malignancies.[27,41] Furthermore, not all patients can tolerate corticosteroids due to preexisting comorbidities such as osteoporosis, diabetes mellitus, glaucoma, joint infection, and uncontrolled hypertension.[43] Additionally, corticosteroids carry greater risks in patients with peptic ulcer disease, congestive heart failure, and active infections.[43] Given the prevalence of these conditions among older adults, many patients with PMR may benefit from steroid-sparing treatments.[42,45,46]

Prior to administering corticosteroids, consider conducting relevant lab tests based on the patient's symptoms. Labs may include complete blood count (CBC), ESR/CRP/plasma viscosity, urea and electrolytes, liver function tests, calcium, alkaline phosphatase, urine protein electrophoresis, thyroid-stimulating hormone, creatine kinase, rheumatoid factor, antinuclear antibody, chest radiograph, and dipstick urinalysis.[27]

IV. Challenges in PMR Management

Navigating corticosteroid tapering amid flares and relapses

Although standard treatment of PMR aims for a gradual tapering of corticosteroids until discontinuation, stopping or tapering corticosteroids can be challenging due to the potential for relapse and flares.[29,35] In fact, pooled data from 7 studies showed that approximately 43% of patients (n=384) experienced relapse within 1 year of starting corticosteroid treatment.[44] This could be attributed to the mechanism of action of corticosteroids; these agents temporarily reduce inflammation,



ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

*Adapted from the 2015 Recommendations for the management of PMR: a EULAR/ACR collaborative initiative.

†Variable doses based on HCP preference.

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Figure 7: EULAR/ACR recommendations for starting and tapering corticosteroids in PMR.

including reducing IL-6 levels, but stopping corticosteroids can bring the levels back up, leading to a resurgence of symptoms.[1,47]

Tapering corticosteroids could be a long process, and many patients may require prolonged corticosteroid treatment to control their PMR symptoms. A large US-based study using electronic health record data of 16,703 patients who were new to rheumatology practice found that through 24-month follow-up, 63.8% of patients remained on corticosteroids beyond 1 year, despite guideline recommendations to limit corticosteroid use. Furthermore, steroid-sparing agents were utilized in only 39% of patients in this study. [29,46]

Risks of long-term corticosteroid use

Long-term corticosteroid use poses significant risks of cardiovascular disease, osteoporosis, and diabetes mellitus (Figure 8).[43] These risks of adverse events increase with higher cumulative doses of corticosteroids. In an observational study involving 175 PMR patients with a median cumulative prednisone dose of 5400 mg, a cumulative prednisone dose of ≥1800 mg was shown to increase the risk of adverse events.[48] Specifically, these patients had a 2 to 5 times increased risk of diabetes and bone fracture compared to age- and sex-matched control subjects.[48] However, it is important to recognize that individual risk may vary due to various factors, and some patients may experience considerable adverse events while others may not.[49]

In another longitudinal study, anti-osteoporosis treatments could not prevent bone loss in patients receiving 5 mg/day or more of prednisone. Even glucocorticoid doses as low as 2.5 mg/day of prednisone equivalent were found to decrease bone mineral density.[50] This highlights the importance of using glucocorticoids with caution because they may contribute to significant bone loss despite concurrent treatments aimed at preserving bone health. Even at low doses of prednisone, the risk of steroid-related complications still exists.[51,52] In fact, in one study, the relative risk of fractures was 1.86 times higher in patients receiving ≤10 mg/day of corticosteroids for ~1-2 years compared to an unexposed control group of patients. The relative risk of hip, vertebral, wrist/forearm, and nonvertebral fractures is 1.73, 2.73, 1.09, and 1.81 times higher than for control subjects.[51] In another study, the risk of cataracts was more than 3 times greater in patients taking corticosteroids <5 mg/day when compared to patients who did not take corticosteroids in the past 12 months.[52] The possibility of significant adverse events even at low doses makes it challenging to determine what dose of prednisone, if any, is acceptable for long-term use.[46]

The risks of long-term corticosteroid use[43]

Cardiovascular Disease

Bone Loss/Fracture

Diabetes Mellitus

Cataract

- Caution should be used when considering CS treatment in patients with comorbidities such as osteoporosis, diabetes, glaucoma, joint infection, and uncontrolled hypertension
- CSs pose greater risks for patients with peptic ulcer disease, congestive heart failure, and active infections
- CSs may not be suitable for people with frailty
- Since these conditions are common in older adults, many patients with PMR may not tolerate CSs and would benefit from steroid-sparing options

Figure 8: Long-term corticosteroid use, even at low doses, poses several risks and should be used with caution in patients with comorbidities.

The threshold for "low-dose" steroids (ie, safely acceptable levels of steroids) has been decreasing over time to the minimum needed for effective therapy.[46,53] When starting corticosteroid treatment, proper considerations include weighing these risks against benefits to determine appropriate strategies for short-term vs long-term use, as well as for tapering and discontinuation.[53]

Considerations for patients with comorbidities

Considering these risks and side effects, the appropriateness of corticosteroid use should be evaluated based on comorbidities, concomitant medications, and risk factors for steroid-related adverse events (Figure 8).[54] Patients with conditions such as osteoporosis, diabetes, glaucoma, joint infection, and uncontrolled hypertension may not tolerate corticosteroids well and may require alternative treatment (Figure 8).[43] Since these conditions are common in older adults, many patients with PMR may benefit from steroid-sparing options.[42,45,46] Moreover, corticosteroids can increase risks in individuals with peptic ulcer disease, congestive heart failure, and active infections and may have unwanted psychological effects such as psychosis, anxiety, insomnia, and mood disturbances.[43,55]

PMR patients may also present with frailty, a condition associated with chronic low-grade elevation of inflammatory markers such as CRP and IL-6, and marked by a decrease in physiologic reserve and homeostatic balance. Frailty heightens susceptibility to disability, falls, hospitalization, and mortality.[56] A study in a single-center cohort of PMR patients showed higher prevalence of frailty and pre-frailty compared to that reported in community-dwelling older adults.[56] PMR patients with frailty had reduced quality of life, which manifested as worsened physical function and increased pain that disrupted their daily activities.[56] Identifying frailty in PMR patients is important because this consideration affects the course of treatment.[42] Since patients with frailty are more susceptible to corticosteroid toxicity, alternative steroid-sparing options should be considered in these cases.[42,56,57]

The need for alternative therapies beyond steroids

Despite the risks and cautions about corticosteroid use, a pooled analysis of studies showed that 77%, 51%, and 25% of PMR patients were taking corticosteroids after 1, 2, and 5 years, respectively.[44] This finding highlights the unmet need for effective steroid-sparing agents. However, alternative options to corticosteroids such as methotrexate lack robust support for use in PMR.[58] In fact, methotrexate is only conditionally recommended by the EULAR/ACR 2015 guidelines due to the small number of patients in randomized trials, contradictory results, and no clearly demonstrated reductions in GC-related adverse events.[29] Since methotrexate is not FDA approved for use in PMR and is associated with various side effects, it is important to assess the risk-vs-benefit profile for individual patient cases.[59,60] Emerging data highlight the efficacy of steroid-sparing alternate treatments in PMR patients requiring extended GC use or experiencing relapses. These findings align with the evolution in treat-to-target PMR approach and recent guidelines from the French Society of Rheumatology.[10,42,57,61]

According to recent guidelines from the French Society of Rheumatology, alternate steroid-sparing treatments are prioritized for PMR patients who are unable to taper off corticosteroids.[42]

V. Conclusion

Managing PMR, the most common inflammatory rheumatic condition in older adults, requires a comprehensive and individualized approach to optimize patient outcomes (Figure 9).[4,5,10,54,62] Accurate and timely diagnosis of PMR is important, particularly if there is a potential overlap with GCA.[27,41,42] While corticosteroids have historically been considered standard treatment, they come with significant adverse effects, necessitating a careful evaluation of patients' conditions and vigilant monitoring for adverse events and drug interactions.[29,53,54]

Although PMR treatment aims for a gradual tapering of corticosteroids until discontinuation, stopping or tapering corticosteroids can be challenging due to the potential for relapses and flares.[29,35]Additionally, complete discontinuation of corticosteroids may not be possible for several patients.[44]

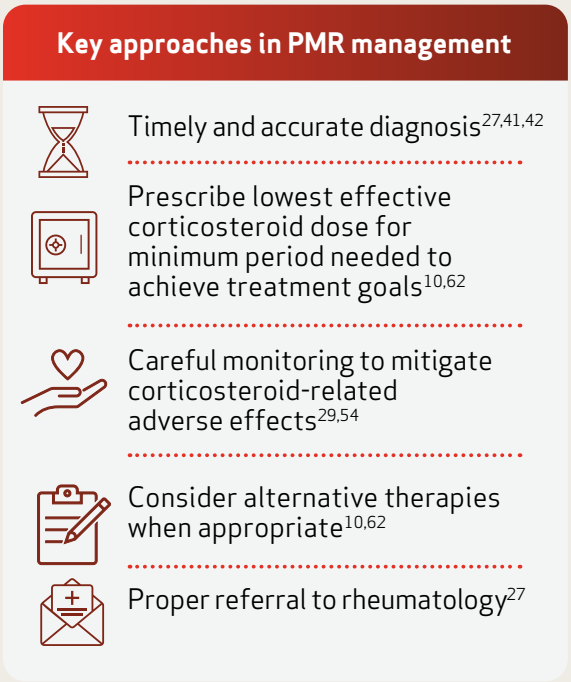

Figure 9: Key approaches in PMR management.

The current treat-to-target strategy in PMR that involves prudent use of the lowest effective dose of corticosteroid for the shortest possible duration, potentially supplemented by alternative therapies, represents a paradigm shift in PMR management.[10,62] This strategy, tailored to individual patient needs and comorbidities, is crucial for optimizing outcomes.[10,54,62] Early referral to rheumatology is needed, especially when there is diagnostic uncertainty or treatment dilemmas, such as contraindications to or problems with tapering/discontinuation of corticosteroids, to ensure that patients get appropriate access to alternative therapies beyond steroids.[27]

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