Ann Rheum Dis 000 (2025) 1–16

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Review

Understanding the immunopathophysiology of polymyalgia rheumatica: implications for treatment

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ARTICLE INFO

Article history:
Received 21 March 2025
Received in revised form 9 September 2025
Accepted 11 September 2025

ABSTRACT

Polymyalgia rheumatica (PMR) is one of the most common inflammatory rheumatic diseases in people aged ≥50 years and is characterised by neck pain, bilateral shoulder and hip girdle pain, and morning stiffness. It is closely interlinked with giant cell arteritis (GCA) (potentially considered the GCA-PMR spectrum) and rheumatoid arthritis and shares a common immunopathophysiology with both. Glucocorticoids (GCs) have been the standard of care for PMR for several decades (American College of Rheumatology/European Alliance of Associations for Rheumatology guidelines); however, >50% of patients cannot successfully taper GCs, and long-term treatment is associated with considerable GC-related adverse events. Immunohistological studies using biopsies from subacromial bursae have indicated that various cytokines and cells, including macrophages, interleukin-6 (IL-6), and fibroblast-like synoviocytes (FLS), play an integral role in the immunopathophysiology of PMR. Proinflammatory cytokines, including IL-1, IL-6, IL-17, and tumour necrosis factor-alpha, activate FLS which then secrete IL-6 that can further promote FLS proliferation. Activation of synoviocytes in bursae may result in bursitis which can lead to a high concentration of acute-phase reactants and systemic inflammation. IL-6 also plays a role in sleep disturbances, mood disorders, pain, and fatigue; it is often seen in PMR, via disruption of the hypothalamic-pituitary-adrenal axis, and actions on the peripheral and central pain pathways. Given the diverse roles of IL-6 in the immunopathophysiology of PMR, targeted molecular therapies such as IL-6 receptor inhibitors offer promising alternatives for disease management, distinct from the nonspecific immunosuppressive effects of GCs. In this review, we describe the immunopathophysiology of PMR and discuss unmet medical needs and therapeutic options for PMR.

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Handling editor Josef S. Smolen.

https://doi.org/10.1016/j.ard.2025.09.005

Please cite this article as: E.H. Choy et al., Understanding the immunopathophysiology of polymyalgia rheumatica: implications for treatment, Ann Rheum Dis (2025), https://doi.org/10.1016/j.ard.2025.09.005

INTRODUCTION

Polymyalgia rheumatica (PMR) is the second most common rheumatological condition after rheumatoid arthritis (RA) [1], in the elderly, with incidence increasing with age [2]. Its prevalence ranges from 2 to 113/100,000 person-years in the age group ≥50 years [3] and is higher in individuals of northern European and Scandinavian descent [4] and in women (73 to 125/100,000) vs men (56 to 64/100,000) [1,5,6]. Quality of life (QoL) is substantially impaired in patients with PMR relative to the general population [7].

Clinically, PMR presents with proximal aches and stiffness in the neck, shoulders, and pelvic girdle, which are more prominent after periods of immobilisation (eg, early morning) [4]. Patients may also experience fatigue, drenching sweats, fever, and weight loss [8]. As per the 2012 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) provisional classification criteria, patients aged ≥50 years with new-onset bilateral shoulder pain, not better explained by an alternative cause, can be classified as having PMR in the presence of morning stiffness lasting at least 45 minutes, elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and new hip pain [9]. Pathologically, PMR is characterised by bursitis, tenosynovitis, and inflammation at myofascial junctions [3]. Ultrasound reveals subacromial bursitis, biceps tenosynovitis, and glenohumeral synovitis in shoulders, synovitis and trochanteric bursitis in hips [10], and popliteus tenosynovitis in knees [11].

PMR may often be misdiagnosed due to overlap with other conditions [4] and delayed rheumatology referrals. In a US Medicare claims study, >1/3rd of patients with PMR did not have a rheumatology visit within 3 years of glucocorticoid (GC) initiation [12]. The 2009 British Society of Rheumatology guidelines outline a stepped approach to PMR diagnosis excluding mimicking conditions and state that every patient with PMR may benefit from a visit to a rheumatologist [13]. Furthermore, as per the recommendations for early referral of individuals with suspected PMR, patients exhibiting severe symptoms should be referred for specialist evaluation using rapid access strategies when available, preferably within 1 week after referral [14]. Thus, clinical evaluation of PMR is directed towards excluding mimicking conditions and ensuring early referral.

As per the 2015 ACR/EULAR recommendations, GCs have been the mainstay of PMR treatment [15]. Low-to-moderate GC doses quickly lead to a substantial improvement in PMR symptoms within the first few days [16]. While ~50% achieve remission in 1 to 2 years [17], others may experience chronic/relapsing disease [18], or subclinical vasculitis [19], complicating GC tapering and prolonged treatment [18]. Patients with PMR often remain on long-term GCs [20], with adverse events (AEs) increasing with higher cumulative doses. A US Medicare claims study demonstrated that higher cumulative GC dose was associated with worse outcomes in patients with inadequate response (IR) to GC/GC taper vs non-IR-GC/GC taper group from months 6 to 18 of GC initiation: 8.1 vs 5.5 fractures, 4.7 vs 2.9 type 2 diabetes mellitus, and 13.3 vs 9.2 hospitalised infections/100 patient-years [21]. In rheumatic diseases, each year of GC use raises cardiovascular disease (CVD) and infection mortality risk by 7.5% and 6.8%, respectively, while each year post-GC cessation lowers it by 1.3% and 4.9%. CVD and infection-related mortality never returned to pre-GC use risk in patients who used GC for >2 years [22].

Overall, GCs have many limitations including suboptimal efficacy [7,18], toxicity even at low doses [23], increased morbidity [24], healthcare utilisation [25], and contribution to myopathy [21], and frailty [26]. These limitations emphasise the need for stratified treatment to enable prompt use of efficacious GC-sparing therapies. The 2024 French Recommendations suggest considering alternative therapies when there is a need for either rapid GC withdrawal or avoidance of GC use in patients with PMR with comorbidities, high risk of GC-related AEs, or frailty [27].

Currently, sarilumab, an interleukin (IL)-6 receptor inhibitor (IL-6Ri), is the only approved therapy for PMR [28,29], with a few investigational agents under evaluation. However, a deeper understanding of the disease pathophysiology is essential to identify and stratify patients who may benefit from these therapies, thereby enabling more informed and personalised treatment decisions.

IMMUNOPATHOPHYSIOLOGY OF PMR

PMR is best characterised as an immune-mediated inflammatory disorder with features that suggest a predominantly autoinflammatory nature. This autoinflammatory component is particularly related to the onset and clinical course of the disease. Notably, PMR is associated with marked elevations in inflammatory cytokines, resembling the cytokine profiles observed in other autoinflammatory conditions [30]. The rapid and effective response of PMR to GCs is likely due to their ability to swiftly suppress these proinflammatory cytokines [31].

PMR is considered to be an interplay of age-related, genetic, and environmental factors, along with innate and adaptive immune mechanisms. Given the heterogenicity in clinical features, disease course, and treatment response, different factors may be crucial for individual patients (Table 1) [32–35].

Ageing/immunosenescence plays a crucial role in the pathophysiology of PMR. Ageing causes thymic involution, leading to reduced production of naïve T cells, particularly regulatory T cells (Tregs). This results in an imbalance between proinflammatory T cell subsets (Th1, Th17, memory effector T cells) and anti-inflammatory Tregs. The decrease in Tregs compromises the body's ability to regulate immune responses. Ageing reduces autophagy, leading to the accumulation of cytokines and reactive oxygen species. This triggers the release of damage-associated molecular patterns (DAMPs), further promoting inflammation. These processes contribute to 'inflammaging'—the chronic, low-grade systemic inflammation characteristic of ageing. Ageing cells develop a senescence-associated secretory phenotype, resulting in the overproduction of proinflammatory cytokines [36].

Proinflammatory cytokine network contributes to PMR pathophysiology [35], with increased serum levels of IL-6 [35], tumour necrosis factor-alpha (TNF-α) [37], IL-17 [38], interferon gamma (IFN-γ) [38], and IL-1β [35], reported in patients with active disease. They may drive PMR inflammation by participating in the pathophysiological signalling cascade of PMR.

Signalling pathways in the periphery and the subacromial bursae in PMR

Immune system activation and cytokine involvement in the immunopathophysiology of PMR have been observed in peripheral blood and synovial tissue of the bursae and tendon sheaths of the shoulder and hip girdles (Fig 1) [35,39].

Table 1
Factors influencing PMR pathogenesis

Ageing	An increase in NKG2D—a marker of *immunosenescence*—expressing T cells has been reported in PMR [32,33]
Genetic predisposition	Genes, such as HLA-DRB1, ICAM (G/R 241), RANTES, TNFa2, TNFb3, IL-1RN*2, and IL-6 (−174 allele C), have been found to be associated with PMR [32]
Environmental factors	UV radiation can stimulate macrophages/lymphocytes to produce increased amounts of the cytokines including IL-6, IL-2, IL-1β, and TGFβ1, involved in PMR pathogenesis [34]
Infections	Ageing may increase susceptibility to viral infections, which may induce immune cell activation and cytokines. Furthermore, a potential link has been suggested between parvovirus B19 [32], adenovirus, respiratory syncytial virus [33], and PMR
Innate and adaptive immunity	Both innate and adaptive immunity have been linked to PMR pathophysiology and many of these key players are driven by cytokine activity. PMR disease activity has been correlated with an increase in peripheral blood neutrophils and monocytes. Macrophages and T cells infiltrate temporal arteries and synovial tissues and patients in remission may also present with persistent monocytosis [35]

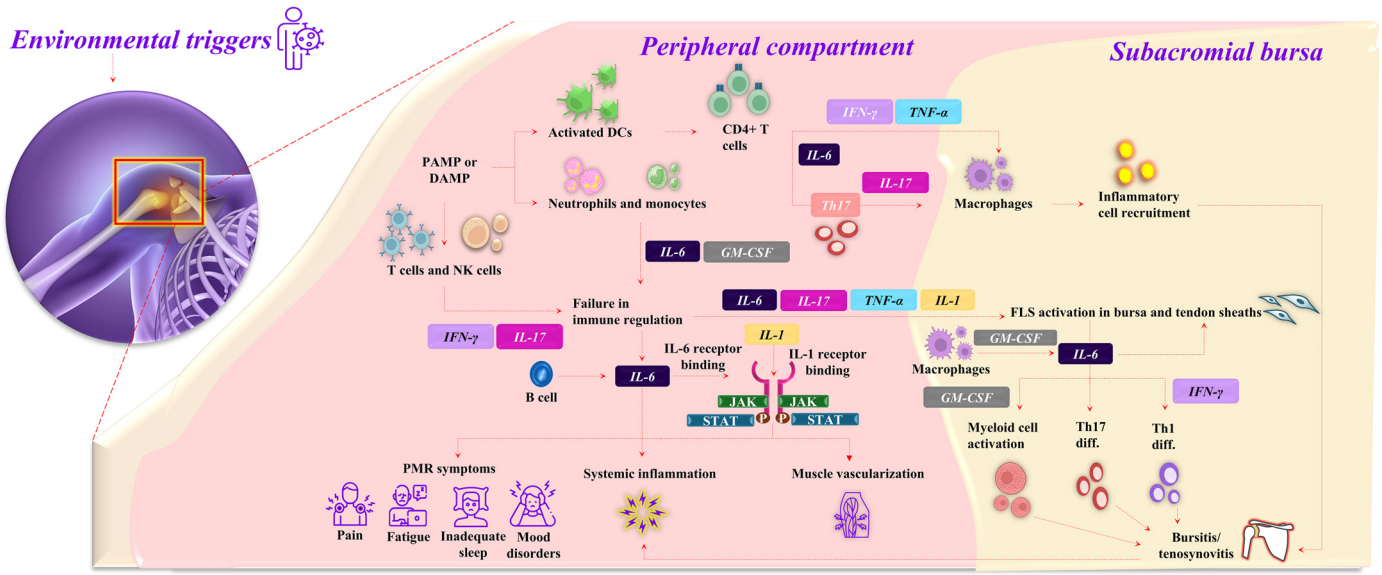
HLA-DRB1, human leukocyte antigen-DR β 1; ICAM, intercellular adhesion molecule; IL, interleukin; NKG2D, Natural Killer Group 2 Member D; PMR, polymyalgia rheumatica; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; TGFβ1, transforming growth factor β 1; TNF, tumor necrosis factor; UV, ultraviolet.

Peripheral compartment

In PMR, circulating dendritic cells (DCs) sense danger signals from triggers, such as environmental factors and infections including adenovirus [33,35] (Fig 1). Upon activation, circulating DCs may settle in the adventitia of the arterial wall and bursae of the shoulder and hip girdles as lower percentages of the conventional DC1 subset have been reported [40]. Toll-like receptors (TLRs) are expressed on the DCs which result in the activation of the latter through pathogen-associated molecular patterns (PAMPs) or DAMPs [33]. PAMPs are released during an immune response to infections caused by viruses or bacteria, while DAMPs are released during tissue damage or stress caused by UV light [41]. These DCs lead to the activation of cluster of differentiation (CD4+) T cells [3], which are polarised to produce Th1 and Th17. Polarisation towards Th1 is driven by IFN-γ and towards Th17 is driven by elevated IL-6 levels [35]. Th17 cells further produce IL-17, which activates macrophages, endothelial cells, and smooth muscle cells. These cells are involved in the tissue damage and chronic inflammation, latter being a key characteristic of PMR [35].

Furthermore, increased senescent T cell and natural killer (NK) cell frequencies are found in PMR. Natural Killer Group 2 Member D on T cells may promote production of proinflammatory cytokines, including IFN-γ, contributing to the pathogenesis of PMR, resulting in failure of immune regulation [42]. Increased peripheral blood neutrophils and monocytes in PMR are associated with disease activity and are considered a major derangement of the innate immune response [35]. B cells are typically implicated in autoimmune diseases associated with autoantibodies such as RA [43]. However, B cells are not only responsible for producing antibodies; they also have a role in modulating T cell responses and secrete cytokines, such as TNF-α and IL-6 [43,44]. Patients with giant cell arteritis (GCA) or PMR had decreased numbers of circulating B cells including IL-6-producing B effector cells which increased when disease improved. B cell numbers also inversely correlated with the acute-phase response [44].

Janus kinase (JAK) signalling is crucial in rheumatic diseases for regulating immune defence and cellular homeostasis. IL-6 activates the JAK-STAT (Signal Transducer and Activator of Transcription) pathway, promoting T cell differentiation and inflammatory responses, granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced JAK-STAT signalling results in erythropoiesis, myelopoiesis, and platelet formation. Additionally, IFN-γ contributes to antiviral defence through activation of the same pathway [45]. In PMR, elevated cytokines like IL-6 and IL-1β activate the JAK-STAT pathway, driving inflammation. IL-6 triggers JAK1/2 activation, while IL-1β additionally acts through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase pathways, amplifying immune responses. This leads to immune cell infiltration in muscles and periarticular tissues, causing pain and stiffness, a hallmark of PMR. Gene expression studies in patients with PMR reveal upregulation of JAK2, IL-6R, IL-1B,



CD, cluster of differentiation; DAMP, damage-associated molecular pattern; DC, dendritic cell; diff., differentiation; FLS, fibroblast-like synoviocytes; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; JAK, Janus kinase; NK, natural killer; PAMP, pathogen-associated molecular pattern; PMR, polymyalgia rheumatica; STAT, signal transducer and activator of transcription; Th, T helper; TNF-α, tumor necrosis factor-alpha.

Figure 1. Overview of the potential immune mechanisms in polymyalgia rheumatica (PMR).

IL-1R1, and TLRs (TLR2, TLR4, TLR8), further promoting inflammatory signalling [46].

These inflammatory processes, characterised by the activation of DCs and T cells, production of proinflammatory cytokines including IL-6, and activation of the JAK/STAT pathway can lead to inflammation that extends to musculoskeletal tissues.

Subacromial bursa/tissue compartment

Inflammation in PMR predominantly occurs in the synovial tissue lining the bursae and tendon sheaths of the shoulder and hip girdles [32,33,35,47]. Imaging has revealed increased evidence of tendonitis in myotendinous junctions [10]. A study by Fruth et al using contrast-enhanced magnetic resonance imaging subsequently confirmed peritendinous enhancement of pelvic girdle tendons to be an imaging hallmark of PMR [48]. Contrast enhancement of musculoskeletal structures, particularly around joints and at musculotendinous junctions, has also been reported [49]. Bursae, like tendon sheaths and synovial joints, are lined by synovial tissue which produces fluid for lubrication [47]. Synovial tissue is composed of type A (macrophage-like) and type B (fibroblast-like) cells [50]. Release of cytokines including IL-6, IL-17, TNF-α, and IL-1 triggers synovial inflammation by activating fibroblast-like synoviocytes (FLS) in bursae [51,52]. Activated FLS secrete IL-6, which can further induce synoviocyte proliferation [53]. In the subacromial bursa, GM-CSF, IFN-γ, and IL-6 result in myeloid cell activation, Th1 differentiation, and Th17 differentiation, respectively. GM-CSF can stimulate macrophages to produce IL-6, resulting in an amplifying loop that can sustain inflammation [54]. IFN-γ-mediated Th1 differentiation promotes macrophage polarisation which stimulates inflammatory cell recruitment and production of proinflammatory cytokines including IL-6, IL-1, and TNF-α, thereby resulting in inflammation of the synovial tissue [39]. Overall, these processes may cause bursitis, tenosynovitis, and systemic inflammation in PMR [3].

IL-17 may also be involved in the pathophysiology of rheumatic diseases, where IL-17A may drive a self-sustaining inflammatory loop by upregulating Src homology 2 domain-containing phosphatase 2, which binds to Act1, an adaptor in IL-17 receptor signalling. This interaction triggers IL-17-independent activation of the IL-17R complex, maintaining inflammation even when IL-17A is therapeutically blocked [55]. However, whether targeting this signalling pathway in PMR can lead to clinical benefits remains to be elucidated.

Role of FLS

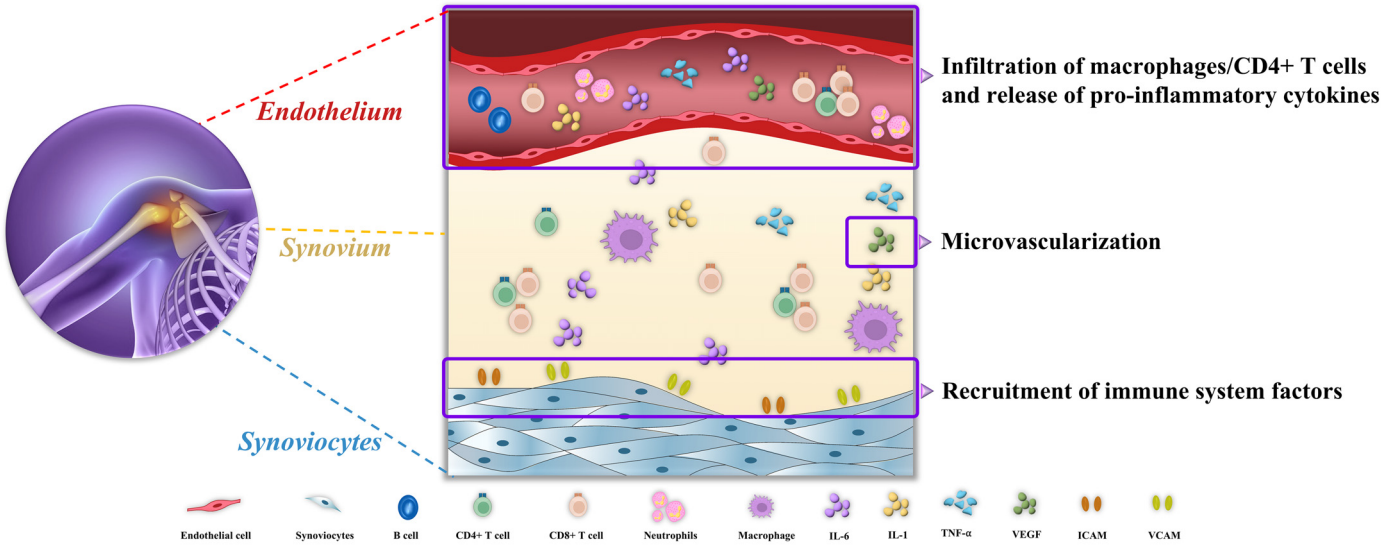
During inflammation in PMR, circulating macrophages and CD4 + T cells infiltrate the synovium of the subacromial and subdeltoid bursae [56], where they release proinflammatory cytokines. Cellular infiltrate also includes NK cells and a few neutrophils [32,33] (Fig 2). Infiltrating T cells produce inflammatory cytokines (IL-1, IL-6, IL-17, and TNF-α), and increased interstitial levels of proinflammatory cytokines (eg, IL-6, IL-1α, IL-1β, IL-8, and TNF-α) [32,33]. Proangiogenic factors (vascular endothelial growth factor) promote microvascularisation [32]. Strong expression of vascular cell and intercellular adhesion molecules at the synovium may recruit immune system factors including vasoactive intestinal peptide, monocyte chemoattractant protein 1, and vascular endothelial growth factor that are involved in synovial infiltration in PMR [32,35]. The release of cells into the synovium is likely to trigger the activation of FLS [51].

Activated synovial fibroblast cells have been identified as a source of IL-6 in PMR. IL-6 released by fibroblasts can stimulate fibroblasts, thus forming an autocrine feedback loop that can sustain inflammation [53]. Furthermore, there is substantial evidence of IL-6 presence in PMR within bursae and in circulation [57]. Hence, IL-6 can be implicated in the chronicity of PMR.

These findings suggest that activation of FLS in bursae/tendon sheaths may lead to bursitis/tenosynovitis, which can further lead to a high concentration of inflammatory mediators such as CRP and ESR. This highlights the importance of conducting further investigations into synovial fluid and tissue from bursae and tendon sheaths to gain deeper insights about the role of FLS in immunopathophysiology of PMR.

Immunopathophysiology of immune checkpoint inhibitor-induced PMR

Immune checkpoint inhibitors (ICIs), used in cancer immunotherapy, can trigger rheumatic immune-related AEs (irAEs), including PMR-like syndrome in 4% to 16% of cases [58,59]. In



CD, cluster of differentiation; ICAM, intercellular adhesion molecule; IL, interleukin; PMR, polymyalgia rheumatica; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

Figure 2. Polymyalgia rheumatica (PMR) pathophysiology in the synovium.

Table 2
Overview of the immunopathophysiology of PMR, GCA, and RA

PMR	GCA	RA
Pathophysiology • Immune-mediated inflammatory disease with synovitis, bursitis, and tenosynovitis [3] • Affects proximal joints [3] • Elevation of proinflammatory cytokines [35]	• Granulomatous vasculitis of large and medium arteries, especially temporal arteries [63] • Granuloma formation [63] • Elevation of proinflammatory cytokines [64] • Vascular wall damage [63]	• Autoimmune chronic inflammatory disease with synovitis [65], tendonitis, and bursitis [66] • Primarily affects joints of hands, wrists, feet, ankles, knees, shoulders, and elbows [65] • Involves autoantibodies like RF and anti-CCP [65,67] • Elevation of proinflammatory cytokines [65] • Joint destruction over time [65]
Genetic risk factors • Association with HLA-DRB1*04 allele [68] • Polymorphisms in IL-6, RANTES, TNF-α genes [32] • Polygenic basis with genetic and epigenetic factors [35]	• Strong association with HLA-DRB1*04 alleles (especially *0401 and *0404) [68] • Polymorphisms in IL-10, VEGF, PTPN22 genes [69–71] • Epigenetic modifications affecting T cell activation genes [63]	• Strong association with HLA-DRB1 shared epitope alleles [68] • RF positivity [65] • Genetic predisposition with environmental triggers [65]
Triggers • Possibly environmental or infectious triggers (eg, viruses) [3]	• Infections (Chlamydia pneumoniae, parvovirus B19, varicella zoster) considered but likely incidental [72]	• Environmental factors including smoking; infections possibly implicated [65]
Clinical manifestations • Bilateral proximal muscle pain and stiffness (shoulders, hips) [4] • Morning stiffness [4] • Systemic symptoms [73] • Elevated ESR/CRP [35]	• New-onset headache [64] • Scalp tenderness [64] • Jaw claudication [64] • Visual disturbances (risk of blindness) [64] • Constitutional symptoms [64] • Elevated ESR/CRP [64] • Temporal artery abnormalities [64] • Possible aortic aneurysm [64]	• Symmetrical polyarthritis affecting joints (hands, wrists) [67] • Joint swelling and pain [65] • Morning stiffness [65] • Systemic symptoms [73] • Elevated ESR/CRP [65] • Possible extra-articular manifestations [67]
Therapeutic options • Low to moderate (12.5-25 mg/d prednisone equivalent) dose, tapering over months to years [15] • Sarilumab (IL-6Ri) is approved for treatment [28]	• High-dose GCs (prednisone 1 mg/kg/d up to 80 mg or equivalent) immediately to prevent vision loss, with gradual tapering [74] • Tocilizumab (IL-6Ri) [75] and upadacitinib (JAKi) [76] are approved for treatment	• MTX [77], LEF [78], sarilumab (IL-6Ri) [28], tocilizumab (IL-6Ri) [75], baricitinib (JAKi) [79], rituximab (B cell depleting agent) [80], etanercept (anti-TNF-α) [81], and infliximab (anti-TNF-α) [82] are approved for treatment

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; csIM, conventional synthetic immunomodulator; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; HLA-DRB1, human leukocyte antigen-DR β 1; IL, interleukin; IL-6Ri, IL-6 receptor inhibitor; JAKi, Janus Kinase inhibitor; LEF, leflunomide; MTX, methotrexate; PMR, polymyalgia rheumatica; PTPN22, Protein tyrosine phosphatase, nonreceptor type 22; RA, rheumatoid arthritis; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; RF, rheumatoid factor; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

ICI-induced PMR, inflammation is primarily driven by T cell infiltration, contrasting with macrophage-driven inflammation in primary PMR [59]. The association of ICI-PMR with other T cell-mediated irAEs (eg, colitis, pneumonitis, vitiligo) suggests a broader role of T cell activation [60,61]. ICI-PMR is often milder, with less morning stiffness, weight loss, and lower acute-phase reactants. It typically responds to lower GC doses (<10 mg) for shorter durations [59]. Differentiating ICI-PMR from primary PMR may improve treatment and classification strategies.

Comparative immunopathophysiology of PMR, GCA, and RA

The immunopathophysiology of PMR overlaps with other rheumatic diseases such as RA (particularly elderly-onset RA [≥60 years] [62]), and GCA (Table 2) [3,4,15,28,32,35,63–82]. About 20% to 39% of patients with PMR have/develop peripheral arthritis [83,84], while 5% to 20% develop RA [84,85].

GCA and PMR are closely interlinked (potentially considered the GCA-PMR spectrum), exhibit significant overlap in inflammation of the arteries and musculoskeletal system, and characterised by a dominant IL-6 signature [64]. Approximately 50% of patients with GCA either have PMR at diagnosis or experience it during relapse, and ~20% have a prior PMR history before developing GCA [86]. PMR and GCA share overlapping immune and systemic features. Clinical features including fever, weight loss, fatigue, night sweats, and peripheral arthritis are common to both conditions [64,86]. CRP, ESR, monocytes, neutrophils, IL-17, IL-6, C-X-C motif chemokine ligand (CXCL)-9, CXCL-10, B cell-activating factor, and GM-CSF are found to be elevated in both PMR and GCA [64,87]. Considering that these disorders are not monolithic and their kinship, understanding the stratification of both PMR and GCA is the key to understanding disease outcomes [64].

PMR, GCA, and RA have a common genetic association with the human leukocyte antigen-DR β 1 gene [68]. Additionally, polymorphism at position −174 in the 5′ promoter region of the IL-6 gene links the immunopathophysiology of PMR, GCA [88], and RA [89].

The shared pathophysiology of PMR, GCA, and RA indicates that these conditions might have common genetic and inflammatory pathways, with IL-6 serving as a key link.

IL-17 also plays a divergent role in the immunopathophysiology of PMR, GCA, and RA. In PMR, Th17 cells may play a role in the peripheral blood; however, no prominent IL-17 response by T cells was observed in the synovial fluid or bursa tissue [57]. There are no available published data demonstrating the efficacy of IL-17 blockers in PMR. In RA, IL-17 contributed to cartilage destruction and bone erosion [90], in the preclinical models [91], with limited benefit seen in clinical trials [92]. This may be due to disease heterogeneity; that is, some patients may have IL-

17-independent disease, failure to inhibit IL-17F by the investigated IL-17A inhibitor, and early vs late involvement of IL-17 in disease pathogenesis [93]. In GCA, IL-17 is produced in the granulomatous lesions and is consistently represented in vasculitic infiltrates [63], with both preclinical [94] and clinical evidence [95] supporting its key role.

Role of immune system in the clinical manifestations of PMR

IL-6 is one of the several factors implicated in the clinical manifestations of PMR including pain, fatigue, sleep disturbances, and mood disorders.

Pain

Both localised and systemic IL-6 activity contribute to pain perception [73]. IL-6 drives peripheral neuronal sensitisation in various rheumatic diseases enhancing nociceptive plasticity and nerve fibre regeneration. Persistent activation can induce central sensitisation, promoting chronic pain [96]. In the central nervous system, neurons and glial cells of the spinal cord and dorsal root ganglia express gp130, making them susceptible to IL-6 trans-signalling [73]. Dorsal root ganglia affected by IL-6 may amplify nociceptive pain. Dysregulated IL-6 heightens ascending pain and suppresses descending inhibitory tracts, increasing pain [96,97]. Overall, IL-6 sensitises pain receptors and neural pathways, intensifying pain perception [73].

Fatigue

Like pain, fatigue is a debilitating symptom of PMR [98], with evolving causes and severity. Key contributors include inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, dysautonomia, and monoamines [99]. IL-6 and other cytokines including TNF-α and IL-1β stimulate the HPA axis prompting cortisol and corticotropin-releasing hormone release. Thus, GCs regulate their own production through negative feedback involving corticotropin-releasing hormone in the hypothalamic paraventricular nucleus and adrenocorticotropic hormone in the anterior pituitary [73,100]. Chronically elevated cytokines like IL-6 desensitise the HPA axis making it unresponsive to acute inflammatory signals. As a result, cortisol production becomes inadequate despite ongoing inflammation [101]. Due to cortisol's role in immunity, inflammation, and stress response, HPA axis dysfunction may contribute to persistent fatigue [100].

Sleep disturbances

IL-6 affects sleep regulation under both physiological and pathological conditions [102]. HPA axis dysfunction alters cortisol production, contributing to sleep disturbances. Under normal conditions, HPA axis promotes arousal by releasing cortisol in the early morning, maintaining wakefulness [103]. However, chronic inflammation and elevated IL-6 can dysregulate this axis, leading to abnormal cortisol secretion patterns, including elevated nighttime cortisol or blunted morning peaks [104]. IL-6 is secreted in a biphasic circadian pattern peaking during the sleep period in healthy individuals or during the wake period in sleep-deprived. Altered IL-6 and sleep disturbances create a positive feedback loop wherein IL-6 impairs sleep, which further leads to elevated IL-6 [105]. Furthermore, elevated IL-6 levels also disrupt sleep architecture by interfering with slow-wave sleep, increasing rapid eye movement sleep latency, and reducing sleep efficiency [106].

Mood disorders

Mood alterations in PMR, presenting as depression and anxiety, are influenced by HPA axis dysfunction [73]. Elevated IL-6 may cause depression through activation of the HPA axis or altered neurotransmitter metabolism [107], including modulation of serotonergic neurotransmission through the STAT3 signalling. IL-6 can also increase dopaminergic and serotonergic turnover in the hippocampus and frontal cortex [108]. Interaction between IL-6 and NF-κB may contribute to depression-associated behaviour by modulating synaptic plasticity [109]. Additionally, elevated IL-6 levels in major depressive disorder are linked to reduced hippocampal volume [108].

Thus, cytokines and FLS play a crucial role in the immunopathophysiological pathways of PMR. Evaluating various targeted biological treatments for PMR is a key research area and has been the focus of several observational and prospective studies.

THE ROAD FROM IMMUNOPATHOPHYSIOLOGY TO THERAPY OF PMR

The main goal in PMR management is achieving clinical improvement [15], and remission [27,110], with minimal GC exposure [15,27], requiring a stepped, safe, and specific approach to diagnosis and a stratified approach to management.

The evolving understanding of the immunopathophysiology of PMR has opened promising avenues for targeted therapeutic interventions beyond conventional GC therapy. The central role of cytokine networks in the immunopathophysiology of PMR provides a strong rationale for cytokine-targeted therapies. Extensive involvement of lymphocytes, myeloid cells, and various proinflammatory cytokines including IL-6 indicates that therapies blocking these pathways might benefit patients with PMR.

Various GC-sparing therapies have been evaluated in clinical trials as listed in Supplementary Table and are elaborated next.

Conventional synthetic immunomodulators

Methotrexate

Methotrexate (MTX) is conditionally recommended as per the 2015 ACR/EULAR recommendations [15], and is suggested as an alternative therapy with moderate/limited evidence as per the 2024 French Recommendations [27]. It has shown mixed results for PMR treatment in different clinical trials (Table 3) [111–129] and real-world evidence (RWE) studies (Table 4) [111–113,130–143]. Studies investigating the effectiveness of oral and intramuscular MTX at 10 mg/wk demonstrated a significant reduction in GC dose when administered as a first-line therapy [111,113]. However, in another study, oral MTX at 7.5 mg/wk did not show any GC-sparing effect when administered as a second-line (prior exposure to GC only) therapy [112]. AEs attributed primarily to GC use were comparable between groups [111,112].

RWE data on MTX in PMR somewhat align with the findings from the clinical trials, showing reduced GC doses and increased disease remission [130–133]. Safety outcomes were also found to be consistent with those reported in clinical trials [131,133].

Leflunomide

To date, there have been no results from randomised controlled trials (RCTs) evaluating the use of leflunomide (LEF) in

Table 3
Clinical trials assessing the efficacy and safety of alternative PMR therapies

Class of therapy	Study design (reference)	Primary endpoint/ outcomes	Efficacy outcome	Safety outcome	Key limitations
csIM	• Multicentre randomised, double-blind, placebo-controlled study • Newly diagnosed patients (N = 72) • MTX + GC (1L) vs placebo + GC (1:1 randomisation) [111]	No GC at 76 weeks	MTX vs comparator: 88% vs 53% patients ([95% CI: 11, 53 percentage points], $P = .03$)	Most common AEs were weight gain, urinary tract infection, and hypertension with almost similar occurrence between groups	• Short follow-up (76 weeks) • High dose of folinic acid • Relatively high starting dose of GC • 10/72 patients (14%) discontinued treatment or were lost to follow-up
	• Randomised double-blind, placebo-controlled study • Untreated patients (N = 40) • MTX + GC (1L) vs placebo + GC [112]	Time to achieve remission Duration of remission Number of relapses Decrease in cumulative GC dose	No statistical significance achieved	Most AEs (weight gain and hypertension) were attributable to GCs	• Small sample size and high drop-out rate • Low MTX dosage (7.5 mg/ weeks)
	• Randomised, prospective study • New-onset patients (N = 24) • MTX + GC (1L) vs GC [113]	Clinical remission Normal APR range No longer on GCs Decrease in cumulative GC dose	All patients in both arms achieved clinical remission All patients in both arms achieved normal APR range MTX vs comparator: 50% vs 0 patients MTX vs comparator: 1.84 g vs 3.2 g, $P < .0001$	Not investigated	• Small sample size
	• Double-blind placebo-controlled study • N = 31 • AZA + GC (2L) vs placebo [114]	Decrease in GC dose at week 52	AZA vs comparator: 1.9 vs 4.2 mg, $P < .05$	Not investigated	• Small sample size • Data may be outdated
IL-6Ri	• Prospective open-label study • New-onset patients (N = 20) • Tocilizumab (1L) [115]	PMR-AS ≤10 at week 12	Median PMR-AS: 4.5 (IQR: 3.2-6.8), $P < .001$	Neutropenia and infections were the most common AEs, consistent with the safety profile of IL-6Ri [115−120]	• Non-randomised design • PMR-AS was the only available AS but it includes the CRP level, which tocilizumab affects directly
	• Prospective, single-centre, open-label pilot study • New-onset patients (N = 13) • Tocilizumab (1L) [119]	Remission at weeks 12 and 52	Remission rate at week 12: 31% Remission rate at week 24: 69%		• Open-label, single-centre design • Small sample size • Infusion schedule of TCZ unavailable
	• Single-centre open-label study • Newly diagnosed patients (N = 9) • Tocilizumab + GC (1L) [120]	Relapse-free remission without GC at 6 months	All patients achieved the primary endpoint		• Open-label study design • Small sample size
	• PMR-SPARE: double-blind, multicentre study • New-onset patients (N = 36) • Tocilizumab + GC (1L) vs placebo + GC (1:1 randomisation) [116]	GC-free remission at week 16	Tocilizumab vs comparator: 63.2% vs 11.8% patients (OR 12.9 [95% CI: 2.2, 73.6], $P = .002$)		• Small sample size • Short follow-up period (16-24 weeks)
	• SEMAPHORE: double-blind, parallel-group, placebo-controlled, randomised controlled study • Patients with disease flare on GC (N = 101) • Tocilizumab + GC (2L) vs placebo + GC (1:1 randomisation) [117]	CRP PMR-AS<10 at week 24	Tocilizumab vs comparator: 67.3% vs 31.4% patients (adjusted relative risk, 2.3 [95% CI: 1.5, 3.6], $P < .001$)		• Only GC-dependent patients included • GC toxicity not measured with a validated tool • Short follow-up period (24 weeks)
	• SAPHYR: multicentre, randomised, double-blind, placebo-controlled study • Patients with disease flare on GC (N = 118) • Sarilumab + GC vs placebo (2L+) + GC (1:1 randomisation) [118]	Sustained remission at week 52	Sarilumab vs comparator: 28% vs 10% patients (difference, 18 percentage points; [95% CI: 4, 32], $P = .02$)		• Trial was prematurely terminated due to the COVID-19 pandemic reducing sample size and statistical power

(*continued*)

Table 3 (*Continued*)

Class of therapy	Study design (reference)	Primary endpoint/ outcomes	Efficacy outcome	Safety outcome	Key limitations
JAKi	• EAST PMR: randomised, monocentre, open-label, controlled, noninferiority study • Treatment-naïve patients (N = 76) • Tofacitinib (1L) vs GC (1:1 randomisation) [121]	PMR-AS<10 at weeks 12 and 24	All patients in both groups achieved the primary endpoint	Herpes zoster infection, hyperlipidaemia [121], and musculoskeletal and connective tissue disorders [122] were the most common AEs, consistent with the safety profile of JAKi	• Single-centre study design • Short observation period (12-24 weeks)
	• Newly diagnosed + relapsing on csDMARDs (N = 14) • Tofacitinib + GC (1L) [123]	PMR-AS<7 with GC≤2.5 mg/days for 4 weeks from week 20	85.7% of patients (95% CI: 57.2%, 98.2%, P = .014)		• Small sample size
	• BACHELOR: randomised, double-blind, placebo-controlled, parallel-group study • GC-naïve patients (N = 34) • Baricitinib (1L) vs placebo [122]	CRP PMR-AS≤10 without oral GC rescue through week 12	Baricitinib vs placebo: 77.8% vs 13.3% (risk ratio [95% CI]: 5.8 [3.2, 10.6], adjusted P < .0001)		• Small sample size
Anti-TNF-α	• Multicentre, double-blind, prospective, randomised, placebo-controlled study • Newly diagnosed patients (N = 51) • Infliximab + GC (1L) vs placebo + GC [124]	No relapse or recurrence at week 52	Infliximab vs comparator: 30% vs 37% of patients (adjusted risk difference, −3 percentage points [95% CI: −31, 24 percentage points], P = .80)	Considerable risk of potential harm (infusion reactions, systemic infection) outweighed the benefits [124,125]	• Small sample size • Short follow-up (52 weeks) • Low dosage of infliximab was used • Rapid GC taper
	• Single-centre, double-blinded, prospective, randomised controlled study • Newly diagnosed patients (N = 40) • Etanercept (1L) vs placebo [125]	Decrease in PMR-AS at day 15	PMR-AS decreased by 24%, P = .011		• Small sample size • Short treatment duration (14 days)
Others	• BRIDGE-PMR: double-blind, randomised, placebo-controlled, proof-of-concept study • Recently diagnosed or relapsed on GC (N = 47) • Rituximab + GC (2L) vs placebo + GC [126]	GC-free remission at 21 weeks	Rituximab vs comparator: 48% vs 21% patients (absolute risk difference [one-sided 95% CI]: 27 [4], P = .049)	Infusion-related reactions and pulmonary embolism were the most common AEs in the rituximab group [126]	• Small sample size • All participants were white, limiting generalisability
	• BRIDGE-PMR extension: double-blind extension of BRIDGE-PMR until 21 weeks • Recently diagnosed or relapsed on GC (N = 47) • Rituximab + GC (2L) vs placebo + GC [127]	Between-group difference in GC-free remission at week 52	Rituximab vs comparator: 52% vs 21% patients (absolute difference [95% CI]: 31 [5,57], P = .04)		• Small sample size • All participants were white, limiting generalisability
	• ALORS: proof-of-concept, randomised, double-blind, placebo-controlled, parallel-group study • Recent-onset patients (N = 34) • Abatacept (1L) vs placebo + GC [128]	CRP PMR-AS≤10 at week 12	Abatacept vs comparator: 50% vs 22% patients, P = .15	Infections and infestations and musculoskeletal and connective tissue disorders were the most common AEs in the abatacept group	• Small sample size • Short duration of assessment (12 weeks)
	• Randomised, double-blind, placebo-controlled, dose-ranging study • GC-dependent patients (N = 181) • ABBV-154 (2L) + GC [129]	Time to flare	ABBV-154 vs Placebo: HRs (95% CI) 40 mg dose: 40.49 (0.27, 0.88), P = .017; 150 mg dose: 0.44 (0.25, 0.79), P = .006; 340 mg dose: 0.20 (0.09, 0.42), P < .001	Incidences of TEAEs were similar between groups, with serious infections (pneumonia and respiratory tract infections) and hypersensitivity reactions being the most common in the ABBV-154 group	• Early voluntary termination of the study, thereby limiting the sample size and the duration of exposure

AE, adverse event; APR, acute-phase reactant; AZA, azathioprine; CI, confidence interval; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; csIM, conventional synthetic immunomodulator; GC, glucocorticoid; HR, hazard ratio; HSD-1, 11β-hydroxysteroid dehydrogenase type 1; IL-6Ri, interleukin-6 receptor inhibitor; JAKi, Janus Kinase inhibitor; MTX, methotrexate; OR, odds ratio; PMR, polymyalgia rheumatica; PMR-AS, PMR-activity score; TEAE, treatment-emergent AE; 1L, first-line (no prior exposure to any therapy); 2L, second-line (prior exposure to GC only); 2L+, second-line plus (second-line with or without prior immunosuppressive therapy apart from GCs).

Table 4
RWE studies assessing the efficacy and safety of alternative PMR therapies

Class of therapy	Intervention	Line of therapy and population [reference]	Comparator	Key endpoint	Efficacy outcome	Safety outcome
csIM	MTX + GC	2L; N = 70 [130]	GC	Reduction in ESR, CRP, and GC dose at 6 months	Significant reduction in ESR (P = .012), CRP (P = .0003), and GC dose (P < .0001)	Not investigated
		2L; N = 100 [131]	GC	Remission with GC suspension at months +12, 24, 36, 48 Number of patients relapsed	No statistical significance achieved P < .0001	Safety findings were consistent with those observed in clinical trials
		2L; N = 454 (new diagnosis or recurrence) [132]	GC	Yearly incidence ratio of flares Yearly flare rate Weighted GC dose ratio	Incidence rate ratio: 0.80 ([95% CI: 0.45, 1.42], P = .45) Incidence ratio: 0.35 (95% CI: 0.23, 0.52) Ratio: 1.37 ([95% CI: 1.04, 1.80], P = .03)	Not investigated
		1L/2L; N = 94 [133]	GC	Relapses GC dose at first relapse Time to remission	P < .001 MTX + GC vs GC: 5.1 vs 3 mg/days, P = .02 MTX + GC vs GC: 22.9 vs 8.7 months, P = .01	Safety findings were consistent with those observed in clinical trials
	LEF + GC	2L; N = 23 (difficulty tapering GCs) [134]	-	Complete response to LEF Median time to achieve response	22/23 patients achieved complete or partial response 2 months (range 2-6)	No new safety concerns were reported
		2L; N = 23 (difficult to treat) [135]	-	Reduction in CRP Reduction in GC dose	6 mg/dL ([95% CI: −10.9, 34.2], P = .05) 3.7 mg ([95% CI: 0.5, 7.0], P = .03)	No serious AEs requiring hospitalisations were reported
		2L; N = 186 [136]	MTX	GC withdrawal Remission	LEF vs MTX: 72% vs 39%, P = .001 More frequent in LEF vs MTX OR = 3.29, 95% CI: 1.46, 7.43, P = .004	Gastrointestinal symptoms were the most common AE and were comparable between LEF and MTX groups
IL-6Ri	Sarilumab/ tocilizumab + GC	2L/3L; N = 415 matched pairs (main cohort) [137]; N = 203 matched pairs (MTX cohort) [137]; N = 89 matched pairs (frail subset) [138]	csIM (MTX, AZA, LEF)	GC discontinuation at 1 year GC discontinuation or minimal GC (≤2 mg/d prednisone equivalent) at 1 year Mean cumulative GC dose over 1 year (mg per person week)	• Il-6Ri vs csIM (main cohort): 47% vs 33%, P < .001 • IL-6Ri vs MTX: 46% vs 36%, P = .026 • IL-6Ri vs csIM (frail subset): 49% vs 21%, P < .001 • IL-6Ri vs csIM (main cohort): 51% vs 36%, P < .001 • IL-6Ri vs MTX: 52% vs 38%, P = .007 • IL-6Ri vs csIM (frail subset): 53% vs 26%, P < .001 • IL-6Ri vs csIM (main cohort): 47.7 vs 51.8, P = .058 • IL-6Ri vs MTX: 48.9 vs 52.8, P = .360 • IL-6Ri vs csIM (frail subset): 48.2 vs 54.9, P = .143	Hospitalised infections were the most common AE and were comparable in both IL-6Ri and csIM groups [139]
	Sarilumab + GC	2L; N = 166 [140]	MTX + GC	Frequency of patients Achieving GC discontinuation Time to GC discontinuation	Sarilumab vs MTX: • ≥6 months follow-up: 61% vs 43%, P = .02 • ≥8 months follow-up: 65% vs 40%, P = .01 • ≥10 months follow-up: 83% vs 57%, P = .02 • aHR: 1.55 (95% CI: 1.13, 2.14), P = .0081	Not investigated
	Tocilizumab + GC	2L; N = 55 [141]	-	PMR-AS Reduction in GC dose	• Significant improvement after tocilizumab initiation (0.51 [IQR: 0.11-3.22] to 0.05 [IQR: 0.02-0.23], P < .001) • Decrease in median GC dose (8.0 mg/days to 0.0 mg/days [IQR: 0.0-2.0], P < .001)	Infections were the most common AE consistent with the safety profile of IL-6Ri [141,142]
		2L; N = 53 (GC-dependent) [142]	-	Proportion of patients tapering to GCs ≤5 mg/d 6 months after the first tocilizumab infusion	• 76.9% (95% CI: 62.2, 88.6) receiving GCs ≤5 mg/d	
JAKi	Tofacitinib + GC	2L; N = 30 [143]	MTX + GC	GC dose at 3 and 6 months	• Month 3: tofacitinib vs DMARDs: 4.08 vs 7.08 mg/days, P < .05 • Month 6: tofacitinib vs DMARDs: 1.84 vs 5.25 mg/days, P < .01	Herpes zoster infection was the most common AE consistent with the safety profile of JAKi

AE, adverse event; aHR, adjusted hazard ratio; AZA, azathioprine; CI, confidence interval; CRP, C-reactive protein; csIM, conventional synthetic immunomodulator; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; IL-6Ri, interleukin-6 receptor inhibitor; IQR, interquartile range; JAKi, Janus Kinase inhibitor; LEF, leflunomide; PMR, polymyalgia rheumatica; PMR-AS, PMR-activity score; MTX, methotrexate; RWE, real-world evidence; 1L, first-line (no prior exposure to any therapy); 2L, second-line (prior exposure to GC/csIM); 3L, third-line (prior exposure to GC and csIM).

PMR treatment, except for a few case series (Table 4) [134,135]. LEF significantly reduced CRP and GC dose and was well-tolerated with no serious AEs requiring hospitalisations, in 23 patients with difficult-to-treat PMR. Limitations of this study included a small sample size, short follow-up, and absence of control group [135]. A retrospective chart review of 186 patients from Argentina found that LEF was more efficacious than MTX in achieving GC withdrawal and clinical remission; however, this study was limited by including a higher ESR/CRP at diagnosis and baseline, higher GC dose at baseline, GC weaning, and MTX dose at baseline [136]. A phase 3 RCT of LEF in newly diagnosed patients with PMR is ongoing in the Netherlands [144,145].

Azathioprine

In an RCT of patients with PMR or GCA or both, patients receiving azathioprine were on a lower GC dose vs placebo (1.9 vs 4.2 mg) by the end of 1 year (Table 3). However, these

data seem outdated, and the study was limited by a small sample size of 31 patients [114].

IL-6 receptor inhibitors

Published data from randomised placebo-controlled trials (Table 3) demonstrated a favourable efficacy and safety profile of IL-6Ri in PMR leading to approval of sarilumab by the US Food and Drug Administration [28], and the European Medicines Agency [29].

Results from the PMR-SPARE including newly diagnosed patients [116], and SEMAPHORE including GC-dependent patients [117], demonstrated that tocilizumab showed better efficacy in achieving GC-free remission [116], and CRP PMR-activity score (PMR-AS)<10 in a higher proportion of patients vs placebo; however, no statistical differences were observed in the QoL scores [117]. Some common limitations associated with both trials were a small sample size and short observational time (16-24 weeks) [116,117].

Results from the SAPHYR study including patients with disease flare during a GC taper showed that sarilumab was associated with a significantly higher proportion of patients achieving sustained remission and reduction in cumulative GC dose vs placebo [118]. Additionally, clinically meaningful improvements in QoL scores were noted with sarilumab, including physical and mental components of Short Form-36, single-unit utility scale of the European Quality of Life 5 Dimensions 3 Level Version, Visual Analog Scale (VAS) scores, Functional Assessment of Chronic Illness Therapy−Fatigue, Health Assessment Questionnaire-Disability Index, pain VAS, and Patient Global Assessment VAS. Results also showed that patients with relapsing PMR have lower QoL parameters at baseline than normative age- and sex-matched controls and the greatest patient-reported outcome response to sarilumab in the most severe (PMR-AS>17) disease [146]. However, the trial was prematurely terminated due to the COVID-19 pandemic, which reduced the sample size and statistical power [118].

Safety profiles of sarilumab and tocilizumab were found to be generally consistent with that of IL-6Ri [116−118].

RWE studies (Table 4) indicate that IL-6Ri exhibit a GC-sparing effect and provides a durable response in PMR, whether used as a second-line (prior exposure to GC only) or third-line (prior exposure to GC and other conventional synthetic immunomodulatory [csIM] therapy) therapy, as evidenced by the US Medicare claims data [137,138]. Rates of serious AEs were comparable in both the IL-6Ri and csIM groups [139]. Another retrospective comparative cohort study from the Komodo HealthMap commercial medical and prescription claims demonstrated that sarilumab appeared to be a more effective GC-sparing agent than MTX as a second-line (prior exposure to GC only) therapy in PMR [140].

JAK inhibitors

Data on the efficacy and safety of JAK inhibitors (JAKi) in PMR are limited. Phase 2 trial data (Table 3) suggest that tofacitinib evaluated as a first-line therapy, showed a reduction in PMR-AS [121,123]. BACHELOR trial demonstrated that oral baricitinib monotherapy at a dose of 4 mg/d for 12 weeks and then 2 mg until week 24 resulted in sustained low disease activity (CRP PMR-AS≤10) at 36 weeks in patients with early PMR without new safety signals [122]. A key limitation of this study was a small sample size of 34 patients. A retrospective study found tofacitinib significantly reduced GC use vs MTX [143] (Table 4). Safety profile was found to be generally consistent with that of JAKi [121,123,143].

Anti-TNF-α

Data on anti-TNF-α therapies in PMR suggest limited therapeutic benefits and potential risks, indicating a minor role of TNF-α in PMR. Trials showed modest effects (Table 3), with infliximab showing nonsignificant results in achieving no relapse/recurrence [124], and etanercept showing a small reduction in PMR-AS [125]. Both studies were limited by a small sample size and a short follow-up [124,125]. Though TNF-α is involved in immunopathophysiology of PMR, the trials with TNF inhibitors elaborated above have shown only modest or no significant clinical benefit in patients with PMR. This may be attributable to the variability in circulating TNF-α levels reported in patients with PMR, with some studies indicating levels comparable to healthy controls, while others demonstrate elevated concentrations. Consequently, TNF-α might be relevant only in a subset of patients or locally at inflammation sites, limiting the efficacy of systemic TNF inhibition [147].

Other treatments

Rituximab

Although the role of B cells in PMR is not fully understood, they have been implicated in its pathogenesis [126]. The BRIDGE-PMR trial showed that rituximab, a B cell-depleting agent, significantly increased GC-free remission rates at 21 weeks vs placebo [126], with consistent results in the 1-year extension study (Table 3) [127]. No new safety concerns were reported [126,127]. Emerging evidence suggests B cells may contribute indirectly to PMR through altered peripheral distribution and IL-6-mediated activation, indicating a more complex role than antibody production [35].

Abatacept

T cell activation is central to immune response in PMR [35]. Abatacept, which blocks CD28-mediated T cell costimulation, was evaluated in the ALORS trial as a first-line monotherapy.

While more patients on abatacept achieved CRP PMR-AS≤10 vs placebo, the difference was not statistically significant (relative risk [95% CI] 2.2 [0.9, 5.5]; adjusted $P = .070$) (Table 3), likely due to the small sample size (n = 34) and trial limitations. No new safety concerns were reported [128]. Despite T cell involvement in PMR, abatacept's mechanism of blocking T cell costimulation may not sufficiently target the dominant inflammatory pathways or the complex immune milieu in PMR. Though successful in RA [148], abatacept has not shown convincing efficacy in PMR, highlighting the distinction between RA's autoimmune [65], and PMR's autoinflammatory nature [30].

Clofutriben (SPI-62)

Clofutriben (SPI-62) is an effective 11β-hydroxysteroid dehydrogenase type 1 inhibitor and when used in combination with GCs, may reduce or prevent some of the side effects of GCs while maintaining the efficacy. Clinical evaluation of clofutriben in patients with PMR is currently underway [149].

ABBV-154

The antibody-drug conjugate ABBV-154 consists of adalimumab (anti-TNF-α) linked to a GC receptor modulator. Phase 2

Table 5
Ongoing clinical trials in PMR

Phase	Intervention [reference]	Mechanism of action	Population	Primary endpoint
1	Secukinumab [150]	Anti-IL-17A	N = 65	$C_{max,SS}$ and $C_{min,SS}$, AUC-time curve, and $C_{avg,SS}$ (time frame: baseline, week 4 and week 8: pre-dose and end-of infusion; weeks 9, 10, 11, 12, 16, and 20: anytime)
2	Clofutriben (SPI-62) [151]	HSD-1 inhibitor	N = 66	ESR, CRP, and fibrinogen at day 28
	Low-dose humanised IL-2 [152]	Treg activation	N = 15	Foxp3 + Treg cells: change in percentage of total lymphocytes at week 12
3	REPLENISH: Secukinumab [153]	Anti-IL-17A	N = 381 (recently relapsed)	Sustained remission at week 52
	REPLENISH-EXT: Secukinumab [154]	Anti-IL-17A	N = 300 (relapsed during the treatment-free follow-up period of the core study and not been on rescue treatment)	Incidences of treatment emergent adverse events and serious adverse events
	REDUCE-PMR-1: Rituximab [155]	Anti-CD20	N = 114 (recently diagnosed)	GC-free remission (PMR-AS<10) at week 52
	REDUCE-PMR-2: Rituximab [156]	Anti-CD20	N = 174 (relapsing)	GC-free remission (PMR-AS<10) at week 52
	ITTGPMR: Tofacitinib [157]	JAKi	N = 98	PMR-AS<10 at week 52
	PMRLEFRCT: LEF [144]	Pyrimidine synthesis inhibitor, DMARDs	N = 94 (newly diagnosed)	PMR relapse within the first 12 months

AUC, area under the curve; $C_{avg,ss}$, average concentration at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; Foxp3 +, forkhead box protein P3-positive; GC, glucocorticoid; HSD-1, 11β-hydroxysteroid dehydrogenase; IL, interleukin; JAKi, Janus Kinase inhibitor; LEF, leflunomide; PMR, polymyalgia rheumatica; PMR-AS, PMR-activity score, Treg, regulatory T cell.

trial in patients with GC-dependent PMR demonstrated longer time to flare in patients receiving ABBV-154 vs placebo, with Kaplan-Meier estimate of 24-week flare-free rate being lower for placebo (Table 3). Safety profile was similar between both groups. However, the study was voluntarily terminated early due to an inadequately differentiated benefit-risk profile vs existing therapies, limiting sample size and drug exposure [129].

Ongoing studies on PMR

Novel targeted therapies are being investigated, which may alter PMR treatment algorithms. Ongoing trials are investigating multiple therapies including biologics, JAKi, csIMs, and clofutriben (Table 5) [144,150–157].

CONCLUSIONS

PMR imposes a substantial clinical burden with GCs offering rapid symptom relief but posing risk of toxicity, AEs, and exacerbation of comorbidities. Minimising GC exposure and achieving remission are the goals of PMR management, highlighting the need for targeted therapies. Understanding the immunopathophysiology of PMR may enable biomarker discovery predicting disease severity, treatment response, and relapse risk, supporting personalised treatment. IL-6 activates FLS which sustain inflammation by releasing more IL-6 and promoting FLS proliferation. IL-6 acts on pain pathways and HPA axis, contributing to PMR symptoms including pain, fatigue, inadequate sleep, and mood disorders. IL-6 blockade has shown clinical benefit in PMR while evidence for MTX, JAKi, anti-TNF-α, rituximab, and abatacept remains limited. Other agents targeting specific pathways are under investigation, and outcomes may fundamentally change the PMR treatment algorithm. These agents may offer new treatment avenues, particularly for GC-resistant or intolerant patients.

Competing interests

All authors report that writing assistance was provided by Sanofi. EHC reports a relationship with AbbVie, Amgen, Bristol Myer Squibb, Celgene, Chugai Pharma, Eli Lilly, Fresenius Kabi, Gilead, Galapagos, Janssen, ObsEva, Regeneron, Sanofi, SynAct Pharma, Tonix, and Viatris that includes: consulting or advisory. EHC reports a relationship with Biogen, BioCancer, Novartis, Novimmune, Pfizer, Roche, and UCB Pharma that includes: consulting or advisory and funding grants. EHC reports a relationship with Fresenius Kabi and Viatris that includes: speaking and lecture fees. SHU reports a relationship with Sanofi, IQVIA, and Harvard Pilgrim Health Care Inc. that includes: consulting or advisory. AFW reports a relationship with AbbVie Inc, Alexion Pharmaceuticals, Amgen Inc, AstraZeneca, Aurinia Pharmaceuticals Inc, Eli Lilly and Company, GSK plc, UCB, and Sanofi that includes: speaking and lecture fees. BD reports a relationship with Roche Chugai, Sanofi, and Novartis that includes: consulting or advisory. BD reports a relationship with AbbVie, Roche Chugai, and Sanofi that includes: funding grants. BD reports a relationship with Cipla, Roche Chugai, and Fresenius Kabi that includes: speaking and lecture fees. FB reports a relationship with AbbVie, Sanofi, Grünenthal, Sparrow, and Horizon Therapeutics (now Amgen) that includes: consulting or advisory. FB reports a relationship with AbbVie, Sanofi, and Horizon Therapeutics (now Amgen) that includes: funding grants. FB reports a relationship with AbbVie, Sanofi, and Pfizer that includes: speaking and lecture fees. YT reports a relationship with AbbVie, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Eisai, Gilead, GlaxoSmithKline, Mitsubishi-Tanabe, and Pfizer that includes: speaking and lecture fees. YT reports a relationship with AbbVie, Asahi-Kasei, Boehringer-Ingelheim, Chugai, Daiichi-Sankyo, Eisai, and Takeda that includes: funding grants.

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Acknowledgements

The authors acknowledge Hubert van Hoogstraten (MD, PhD), from Sanofi (former employee), for critical review of the manuscript. Medical writing assistance for this manuscript was provided by Kritika Dhamija (MS [Pharm]) and Kavita Garg (PhD, CMPP), from Sanofi.

Contributors

All authors were responsible for drafting the article or providing critical revisions and approved the final version to be published. The authors also provided guidance on the content to be incorporated in this manuscript.

Funding

Sanofi and Regeneron Pharmaceuticals, Inc.

Patient consent for publication

Not applicable

Ethics approval

Not applicable

Provenance and peer review

Not commissioned; externally peer reviewed

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.09.005.

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