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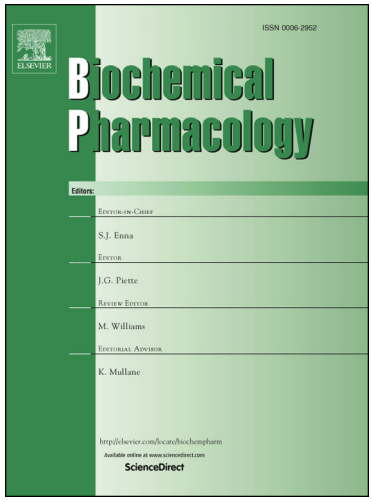

Review

Treatment of polymyalgia rheumatica

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Abstract

Polymyalgia rheumatica (PMR) is an inflammatory disease characterized by bilateral pain involving predominantly the shoulders and proximal aspects of the arms and less commonly the neck and the pelvic girdle. This review discusses briefly the main epidemiological data and clinical features of this condition. Especial attention is paid in the management of the disease. For this reason, both the classic management and the impact of new therapies are discussed in depth. In general, patients with PMR experience a rapid response to 12.5-25 mg/prednisone/day in less than a week. Patients with poor response to glucocorticoids or with relapsing disease require other therapies aimed mainly to spare glucocorticoids. Among them, methotrexate is the most commonly used. Nevertheless, different studies indicate that this agent yields only a modest effect. Biologic therapies against the main cytokines involved in the pathogenesis of the disease have been used in refractory patients. However, randomized controlled trials do not support the use of anti-tumor necrosis factor agents in PMR. In contrast, several case series and retrospective studies highlight the efficacy of the anti-interleukin-6 receptor tocilizumab in PMR. Nonetheless, controlled trials are needed to fully establish the beneficial effect of this agent. The potential favorable effect of the Janus-kinase inhibitors and new anti-interleukin-6 antagonists remains to be determined.

Keywords: Polymyalgia rheumatica, glucocorticoids, methotrexate, DMARD, biologic therapies, anti-interleukin-6 receptor tocilizumab

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1. Introduction

Polymyalgia rheumatica (PMR) is a common inflammatory disease of unknown etiology affecting especially elderly people from Western countries, characterized by severe pain and stiffness involving the shoulders, proximal aspects of the arms, neck, pelvic girdle and proximal aspects of the thighs. Patients with PMR have morning stiffness lasting typically more than 45 minutes as well as non-specific symptoms such as fatigue and malaise **(1,2)**. Typically, patients with PMR have elevation of acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) **(1,3)**.

PMR is rarely observed in individuals younger than 50 years **(2)**. Women are affected two to three times more often than men. The incidence rate increases progressively with age in both sexes until the age of 80 years **(4)**. The highest incidence is in people older than 65 years, particularly between ages 70 and 80 **(2)**.

PMR is more common in Scandinavian countries and in people of Northern European descent **(5,6)**. The annual incidence of PMR for individuals older than 50 years in the period 1985-1997 in Göteborg (Sweden) was 50/100,000 **(7)**. Similarly, data from the Olmsted County (Minnesota, USA) showed an annual incidence of 63.9/100,000 inhabitants aged 50 years and older **(4)**. By contrast, a lower incidence of PMR has been observed in Southern Europe countries **(8,9)**. In this way, the annual incidence of PMR in Italy and Spain was reported as 12.7/100,000 and 18.7/100,000 population aged 50 years and older, respectively **(8,9)**.

The prevalence of PMR is also higher in Northern European populations. Recent data from Olmsted County have shown that the overall age and sex adjusted prevalence rate of PMR was 701/100,000 people (870 in women and 508 in men /100,000 people) **(10)**,

while the prevalence of PMR in UK was 910/100,000 inhabitants (1040 in women and 780 in men/100,000 people) **(11)**.

The susceptibility for suffering PMR is a result of the interaction between genetics and unknown environmental factors **(12)**. In fact, a possible association with different infections such as mycoplasma pneumoniae, parvovirus B19 and chlamydia pneumonia has been described **(6)**. Regular fluctuations and seasonal variations in the incidence of disease throughout the year supports this hypothesis **(13,14)**.

PMR is frequently associated with giant cell arteritis (GCA), the most common vasculitis in elderly people in Western countries, that mainly involves the large and medium arteries, especially the branches of the proximal aorta **(1,3,15)**. Furthermore, both entities respond well and quickly to glucocorticoids (GCs).

2. Pathophysiology

PMR as a disease mainly involving extra-articular synovial structures at shoulders and hips. Although both joints and periarticular tissues can be involved in patients with PMR, arthritis is usually mild and typically non-erosive, explaining only partially the symptomatology of these patients **(16)**. By contrast, a clear inflammation of peri-articular tissue and synovial bursae such as the subacromial/subdeltoid (SAD) bursa, usually associated with tenosynovitis of the biceps (**Figure 1**), the trochanteric and iliopsoas bursae, and the cervical or lumbar interspinous bursae, has been demonstrated using different imaging techniques such as ultrasonography (US), scintigraphy, magnetic resonance imaging (MRI) and positron emission tomography integrated with computed tomography (PET/CT) **(17,18)**. This soft-tissue inflammation would explain much better many of the musculoskeletal manifestations and the pain that PMR have at

proximal level of the extremities **(18)**. In fact, some authors have suggested that PMR may be a disorder predominantly involving the extra-articular synovial structures **(19)**. Arthroscopic studies have also shown the presence of mild synovitis in the proximal joints of patients with PMR. The inflammatory infiltrate found in the shoulder synovial membranes and other involved joints was composed mainly of macrophages and CD4 T lymphocytes **(20)**.

Interestingly, evidence of subclinical arterial inflammation, including activated dendritic cells, interleukin (IL)-1 and IL-6, can also be detected in the temporal arteries of some patients with PMR without evidence of GCA **(21)**. However, unlike GCA, interferon gamma (INF-ϒ)-producing T cells are not prominent in PMR. On the contrary, proinflammatory cytokines may have an important role in PMR. Increased interstitial concentrations of IL-1α/β, IL-1 receptor antagonist, IL-6, IL-8, tumor necrosis factor α (TNF-α), and monocyte chemoattractant protein 1 have been detected in symptomatic muscles of patients with PMR when compared with controls **(22)**.

At the cellular level, a decrease in the regulatory T (Treg) cells and marked shift in the Th17 cell/Treg cell balance towards an increased Th17 cell response occurs in PMR **(23)**. In newly diagnosed PMR patients, there is an inverse correlation between the number of lymphocyte B cell and the ESR, CRP and serum B-cell activating factor (BAFF) levels **(24)**. In addition, patients recently diagnosed with GCA or PMR exhibit decreased numbers of circulating B cells compared to healthy controls **(24)**.

3. Clinical manifestations

Patients with PMR are generally older than 50 years and they present with pain and stiffness in the shoulders as well as in the proximal aspects of the arms, neck, pelvic girdle and thighs, usually bilateral. The disease has a rapid onset, generally in a few

days. Morning stiffness last typically > 45 minutes in the involved areas, improves progressively over the day and worsens after rest **(1,25,26)**. Constitutional symptoms such as asthenia, anorexia and weigh loss along with low-grade fever are frequent **(1)**. Painful restriction of active movement is also often observed. Other findings include muscle tenderness, peripheral non-erosive arthritis predominantly involving the knees and wrists, carpal tunnel syndrome, distal extremity swelling with pitting edema and distal tenosynovitis **(16)**. In some cases, the clinical picture may be similar to that observed in patients with remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome **(27,28)**. **Table 1** summarizes the main clinical features observed in patients with PMR.

Patients with PMR typically have increase of acute phase reactants. Indeed, ESR and CRP are generally greater than 40 mm/1st hour and 6 mg/L, respectively **(1,26)**. However, some patients may present with low ESR and CRP **(29)**, and in these cases other conditions mimicking PMR should be excluded **(1,26)**. Other nonspecific laboratory abnormalities such as increased levels of α-2 globulin proteins, anemia, thrombocytosis and hypoalbuminemia can also be found **(30)**. On the contrary, anti-cyclic citrullinated peptide antibodies (anti-CCP), rheumatoid factor (RF), antinuclear antibodies and anti-neutrophil cytoplasmic antibodies are generally negative **(1)**.

4. Diagnosis of PMR

The diagnosis of PMR is supported by a clinical history, physical examination and the assessment of routine laboratory markers of inflammation **(15,31-33)**. New onset headache, scalp tenderness or visual manifestations may indicate that PMR is associated with GCA. In fact, PMR may be the initial manifestation in patients with GCA. Indeed, most studies indicate that the frequency of patients with PMR who have associated

GCA is around 15-20% **(15,34,35)**. Nonetheless, in some series of GCA patients in whom the diagnosis was confirmed by a positive temporal artery biopsy, the frequency of PMR was up to 40%-50% of the cases **(36)**. Patients with isolated PMR have in general lower values of ESR and less frequently anemia and thrombocytosis than those with PMR associated with GCA **(37).**

However, and although the diagnosis of PMR in typical cases is not difficult, there are no specific tests to make a diagnosis of PMR nowadays. Because of that, the diagnosis is usually based on classification criteria **(1)**. In 2012, the European League Against Rheumatism (EULAR) together with the American College of Rheumatology (ACR) established a new classification criteria, remarking the relevance of polymyalgia hip involvement, the absence of pain in other joints as well as negative results for anti-CCP antibodies and RF **(38)**. These criteria also include for first time the use of US to detect bilateral SAD bursitis and/or trochanteric bursitis **(38)**. Other authors have included a rapid response to glucocorticoids (GCs) as an important criterion for the diagnosis of PMR, although this is nonspecific and it has not been incorporated in the 2012 EULAR/ACR criteria.

In atypical cases, the clinician must establish the differential diagnosis with other systemic diseases and/or malignancy, particularly in patients who do not respond to GCs **(1,26,39)**.

5. Imaging studies in PMR

Ultrasonography, MRI and PET/CT have been used in PMR to detect synovitis in proximal joints and extra-articular structures and may help with the diagnosis of the disease. Indeed, US and MRI are useful and equally effective to confirm the presence of bursitis in patients with PMR **(40-42) (Figure 1)**.

^{18}F-fluorodeoxyglucose (FDG) PET/CT have observed FDG accumulation at the level of spinous processes at cervical and lumbar spine in around one-half of PMR patients **(43)**. In general, FDG uptake is associated with interspinous bursitis and it is more commonly observed in the lumbar spine than in the cervical region.

Finally, PET/CT has revealed to be especially useful to disclose the presence of vascular involvement associated with PMR. Blockmans et al. showed that about one third of 35 patients with isolated PMR had increased vascular FDG uptake, typically in the subclavian arteries. Nevertheless, uptake intensity was less than that seen in GCA **(44)**.

6. Treatment of PMR

6.1. Glucocorticoids: the cornerstone in the treatment of PMR

The main goals of the treatment of PMR are to control the disease and prevent relapses. To achieve these goals, oral prednisone/prednisolone constitutes the keystone of the treatment in PMR **(39,45,46)**. The reasons for the successful effect of GCs in PMR are multiple and are based on their strong antiinflammatory and immunosuppressive properties. In particular, GCs exert their main anti-inflammatory/immunosuppressive effects primarily on leucocytes and secondary immune cells, where their functions as well as their distribution are affected. More specifically, GCs exert their main effects through genomic and non-genomic mechanisms, resulting in their typical therapeutic effects and contributing to its final anti-inflammatory efficacy.

The initial dose of prednisone/prednisolone recommended by the EULAR/ACR guidelines ranges between 12.5-25 mg/day **(45,47)**. However, this dose must be individualized to every case. Thus, patients with diabetes or osteoporosis would start with a dose between 12.5-15 mg/day **(1)** while very symptomatic people without these risk factors could receive a starting dose of 20-25 mg/day. The EULAR/ACR

recommendations for the management of PMR suggest using a single dose of GCs **(45,47)**. Nevertheless, in our experience a divided dose of prednisone at the onset of treatment may help to a quicker improvement of the symptoms, especially in patients with in patients with very active clinic **(1)**. With this strategy, patients usually experience improvement in a 1-2 weeks, commonly within the first 72 hours **(46,48)**. In general, the clinical improvement is associated with a normalization of acute phase reactants, normally within 2-4 weeks after the onset of therapy **(25,46)**.

Regarding GC tapering **(49)** there is not a standardized approach on how they should be removed in patients with PMR in remission **(50)**. In our experience, we maintain the initial prednisone dose for 3-4 weeks and then we taper it progressively whenever the response has been favorable. In those in whom we start treatment with a prednisone dose of 15 mg/day, our tapering scheme is 12.5 mg daily for 2-4 weeks, 10 mg daily for 4-6 weeks and then we reduce the dose by 1-1.25 mg/month or 2.5 mg every 2-3 months **(1) (Table 2)**.

Although experts support the use of prednisone or prednisolone for the treatment of PMR, some studies assessed the role of deflazacort in the management of these patients **(51,52)**. However, deflazacort was found to be less potent than prednisone/prednisolone when used at equivalent doses **(51,52)**. By contrast, modified-release prednisone has shown greater percentages of complete responders than for immediate-release prednisone (53.8% vs. 40.9% respectively) in early PMR at 4 weeks of treatment **(53)**. The use of intramuscular (IM) methylprednisolone acetate (120 mg every 2 weeks for 12 weeks followed by monthly injections with dose reductions of 20 mg every 3 months) was less effective than an initial dose of 15 mg/oral prednisolone/day and led to lower rates of discontinuation of the therapy **(54)**.

Table 3 shows the main adverse effects of the chronic use of corticosteroids.

Non-steroidal anti-inflammatory drugs are of little value in the management of PMR, and increase the risk of gastrointestinal or renal complications.

6.2. Glucocorticoid-sparing agents

Either conventional immunosuppressive drugs or biologic agents have be used in patients with PMR requiring prolonged GC therapy due to refractory or relapsing disease with the objective of stopping GCs at some point in the evolution and avoid the appearance of adverse effects.

Methotrexate (MTX) either oral or parenteral (subcutaneous/intramuscular) is the most used drug in the PMR as a GC-saving agent. MTX is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. It acts intra-cellular by irreversibly binding to and inhibiting dihydrofolate reductase, inhibiting the formation of reduced folates, and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis. MTX yields reduced monocytic cell activation, decreased IL-1 and IL-6 secretion, inhibition of cyclo-oxygenases synthesis, neutrophil chemotaxis and adhesion molecules expression **(55)**. These effects may explain the antiinflammatory role of MTX in PMR. The initial dose of MTX generally ranges between 10 to 15 mg/week **(46,48)**. Some studies have shown no benefit whereas others indicate that MTX may be useful to reach clinical remission and decrease the number of relapses **(56-58)**. Van der Veen et al. carried out a randomized double blind, placebo-controlled study in 40 patients with PMR, six of them with clinical features of GCA **(56)**. The study did not show any additional benefit of the association of oral MTX to prednisone after 2 years of follow-up (time to and duration of remissions, number of relapses, or cumulative prednisone doses). However, the MTX dose in this study was very low (7.5 mg/week orally) **(56)**. It is possible that higher doses of MTX given subcutaneously, would have been more appropriate to assess if MTX is useful as a GC-sparing agent in PMR. In

another study, Caporali et al. assessed the efficacy and safety of prednisone in combination with oral MTX versus prednisone alone in patients with newly diagnosed PMR **(57)**. Specifically, these authors evaluated the percentage of PMR patients no longer taking prednisone, the number of relapses, and the cumulative prednisone dose after 76 weeks of treatment. The study protocol recommended reducing the dose from 25 mg/day up to 0 at 24 weeks of treatment. Oral MTX (10 mg/week) or placebo were given weekly for 48 weeks. Remarkably, 87.5% of the patients from the MTX group (28 of 32 patients) had stopped of taking prednisone at 76 weeks. The median cumulative prednisone dose in PMR patients treated with MTX was 2.1 g vs. 3.0 g for patients taking prednisone alone **(57)**. In addition, patients undergoing MTX therapy had a significant reduction in the number of relapses when compared to those receiving prednisone plus placebo. These results supported the use of oral MTX (10 mg/week) in the management of PMR **(57)**.

Another prospective study performed by Ferraccioli et al. evaluated the potential beneficial effect of IM MTX in patients with PMR **(58)**. In this study, 24 patients recently diagnosed of PMR were randomized to receive 10 mg/week of IM-MTX plus prednisone, or prednisone alone. At month 12 all patients were in clinical remission in both arms of the study **(58)**. However, the cumulative prednisone dose was significantly lower in the MTX treated group than in the placebo group. Unlike those from the MTX group, patients receiving placebo showed a reduction in the bone mineral density **(58)**. Therefore, although the efficacy of MTX in the management of PMR is still controversial**,** the 2015 EULAR/ACR recommendations for the management of PMR support the use of this drug in patients with inadequate response to GCs, in those with relapses and in patients experiencing GC- related adverse events **(47) (Table 3)**.

The use of other conventional DMARDs is more anecdotal. De Silva et al. conducted a double-blind randomized placebo-controlled study to assess the efficacy of azathioprine (AZA) as a GC-sparing agent in 31 patients with PMR, GCA or both conditions **(59)**. In fact, patients treated with AZA had a lower GC requirement. However, the number of patients included in this study was relatively small and almost a third from them met definitions for GCA **(59)**. Moreover, the relatively high frequency of side effects observed in the study does not support the use of AZA for this indication. Likewise, hydroxychloroquine was not found useful in PMR patients when compared to GCs alone **(60)**. Regarding the use of leflunomide, a small series of difficult-to-treat patients with GCA (n=11) and PMR (n=12) were retrospectively assessed by Diamantopoulos et al. **(61)**. Leflunomide-treated patients with PMR had CRP reduction of 6 mg/dL and showed 3.7 mg reduction in prednisolone dose **(61)**. Although these results suggest that leflunomide may be useful in PMR therapy, further information is needed to support its use as a GC sparing agent in PMR. Furthermore, potential hepatotoxicity of leflunomide in elderly may be a concern, as this drug has a black box warning for liver injury, especially in arthritis patients or ageing people with pre-existing liver disease, elevated liver enzymes or patients who are taking other drugs that can cause liver injury (https://www.fda.gov/Drugs/DrugSafety/ucm218679.htm).

6.3. Biologic therapies in PMR

Studies of biologic treatment in isolated PMR are scarce, and most of them are carried out in PMR associated with GCA. TNF-α antagonists were the first biologic agents used in both GCA and PMR, either as monotherapy (in PMR) or in combination with GCs (in PMR plus GCA). Initial studies based on single cases or small series revealed encouraging results **(62)**, particularly in patients with diabetes mellitus and osteoporosis **(63)**. However, data from more rigorous studies, including randomized control trials, did

not support the initial results **(64-68)**. In this regard, the only randomized clinical trial on the efficacy of infliximab in PMR did not disclose additional benefit in newly diagnosed patients with PMR **(69)**. Another randomized control trial with etanercept in monotherapy *versus* placebo in patients with PMR did not meet primary or secondary end points either **(70)**. Based on these poor results, the 2015 EULAR/ACR recommendations did not support the use of anti-TNF drugs for the management of isolated PMR **(47)**.

IL-6 is a pleiotropic pro-inflammatory cytokine produced by a number of cells including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in different physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of hemopoiesis. IL-6 has been implicated in the pathogenesis of a broad spectrum of diseases including inflammatory diseases, and also in the pathogenesis of PMR **(71,72)**. In fact, since the decrease of IL-6 in serum was associated with a reduction in disease activity, the blockade of IL-6 has been considered as a plausible therapeutic option in PMR, similarly that it has happened with the GCA **(73)**. Tocilizumab (TCZ) is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor. The inhibition of the entire receptor complex prevents IL-6 signal transduction to inflammatory mediators that convene B and T cells **(74)**.

Retrospective studies **(75,76)** and prospective clinical trials **(77,78)** indicate that the anit-IL-6 receptor TCZ is useful in GCA. In addition, many of the patients with GCA included in these studies also had PMR manifestations that improved quickly following the use of this biologic agent. Furthermore, preliminary data in PMR patients with poor response or unacceptable GC-induced adverse effects indicate that TCZ may be effective in these patients **(79,80) (Table 3)**. A prospective open-label study including

20 patients with active recent-onset PMR who received three TCZ infusions at 4-week intervals showed clinical improvement of PMR symptoms at 12 weeks of follow-up **(81)**. In another study, 10 patients with recently diagnosed PMR were included in a prospective open-label phase IIa trial with TCZ **(82)**. In this study, patients were given intravenous TCZ (8 mg/kg/month) for 1 year, getting a rapid tapering of GCs according to a standardized protocol. Patients with PMR who declined to receive TCZ or who did not fulfill the inclusion criteria were used as a control group. Interestingly, in 9 of the 10 TCZ-treated patients, relapse-free remission without GCs was achieved at 6 months **(82)**. Furthermore, patients were able to discontinue GCs within 4 months of study entry. Persistent remission was also obtained in these patients throughout the entire 15-month study. On the contrary, none of the PMR patients used as controls reached GC-free remission at 6 or 12 months. Besides, 60% of the PMR patients from the control group suffered relapses **(82)**. In addition, the mean cumulative prednisone dose was twice lower in TCZ-treated (1,085 mg) than in the control group (2,562 mg) **(82)**. These results support the use of TCZ as GC-sparing agent in patients with active PMR. Interestingly, TCZ has recently been approved by the US FDA for treating GCA, a condition that is often associated with PMR (https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm559791.htm). However, TCZ has not been approved for the treatment of patients with isolated PMR yet.

TCZ was also effective in patients with aortitis, some of them presenting as isolated PMR, refractory to prednisone and in most cases to conventional DMARDs **(83)**. **Table 2** and **Figure 2** summarize the main therapeutic steps in the treatment of PMR.

Experience on the use of other biologic agents in patients with PMR is very limited.

IL-1 and IL-17 are two important proinflammatory cytokines involved in the pathogenesis of this disease **(23,71)**. In this line, secukinumab and canakinumab, two antagonists of these pathways have been proved, in a two-week single-blind, randomized 3-arm proof of concept study, in patients with PMR **(84)**. Secukinumab is a human IgG1 monoclonal antibody binding interleukin-17A, while canakinumab is a human monoclonal antibody targeted at interleukin-1β. In that study, a rapid improvement of pain was observed in the GC-treated patients. However, only moderate improvement of movement was found in those PMR patients treated with secukinumab or canakinumab **(84)**. Therefore, the use of these agents in patients with isolated PMR requires further research (**Figure 2**).

Abatacept, a dimeric fusion protein that inhibits the interaction of CD80/CD86 molecules with CD28 leading to a decrease of T cell activation, has been used in GCA **(85)**, but data about its use in PMR have not been published up to date.

Currently, a trial in phase III on sarilumab, another IL-6R antagonist, is being carried out. Primary results obtained with this agent will be presented on April 2021 (NCT03600818).

6.4. Small molecules: JAK/STAT inhibitors

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is a path strongly implicated in the cellular regulation in humans. In this stage, a broad spectrum of cytokines that are implicated in the pathogenesis of autoimmune diseases use this pathway to transduce intracellular signals **(86,87)**. As well, several polymorphisms of JAK and STAT genes have been associated with different autoimmune diseases **(86)**. In addition, high concentrations of interferon-gamma (IFN-γ) mRNA have been found in the temporal arteries of patients with GCA with severe ischemic complications **(86)**. The JAK/STAT-inhibitor tofacitinib, a kinase inhibitor for

JAK3 and JAK1, prevented T cell accumulation in the vessel wall and suppressed IFN-γ production and signaling by this pathway **(87)**. Tofacitinib also yielded a marked reduction of the blood levels of IFN-γ in an experimental model of vasculitis in mice **(88)**. Unfortunately, unlike GCA, there are no animal models of PMR to date that allow us to corroborate these data. Currently, there are one phase 2 trial and another phase 3 evaluating the effect of baricitinib (ClinicalTrials.gov Identifier NCT03026504) and upadacitinib (ClinicalTrials.gov Identifier NCT03725202) in patients with relapsing GCA whose results are promising. Based on the close association between GCA and PMR, it is possible that JAK inhibition might also have a role in the treatment of patients with PMR in the future **(87) (Figure 2)**.

6.5. Future perspectives in PMR therapy

Optimizing the benefit/risk ratio of GCs to minimize adverse events while achieving sustained remission is an ongoing challenge **(71,89,90)**. Therefore, the development of innovative GC preparations and/or glucocorticoid receptor ligands might increase the benefit/risk ratio of GCs. In this line, selective GC receptor agonists and modulators (SEGRMs) may be promising drugs aimed to enhance anti-inflammatory cellular pathways selectively. In consequence, these drugs would avoid the activation of mechanisms associated with adverse effects related to these agents **(91)**.

Also, GCs can be selectively delivered in inflamed tissues using very-small, nanometre-sized liposomes **(92)**. Liposomes have been studied as drug delivery systems in the therapy of RA. Its applicability to other inflammatory conditions such as PMR may be possible in a near future. Finally, modified-release prednisone was shown to permit optimal chronotherapy with bedtime administration and the release of prednisone at the optimal time for suppression of pro-inflammatory cytokines (that is, around 2 a.m.).

This kind of formulation has already been proved in new-onset GCA with excellent results in comparison with immediate-release prednisone **(93)**.

Because of several case series have shown some potential benefit of leflunomide in patients with refractory PMR **(61,94)**, we think that prospective evaluation of this agent in randomized controlled trials would be stimulating.

6.6. Polymyalgia and immunotherapy

Immune checkpoint inhibitors (ICI) are a family of agents highly effective in different types of tumors such as melanoma, lung cancer, metastatic renal cancer or malignant hematologic disorders. However, these agents also produce frequent undesirable side effects. In particular, it has been observed that anti CTLA-4 (ipilimumab) and anti PD-1 (nivolumab or pembrolizumab) antibodies often produce immune-related adverse effects (IRAEs) or triggers flares of previous rheumatic diseases already known **(95,96)**. Indeed, a broad spectrum of immune toxicities has been reported up to now such as sarcoidosis, polyarthritis, lupus, celiac disease, dermatomyositis, and also PMR and GCA **(96)**. As well, new cases of PMR-type conditions have also been reported by other authors in patients under these therapies **(97-99)**. Though, in a recent retrospective review performed to identify all patients who received ICI therapy at Mayo Clinic between 2011 and 2016, only 16 patients (five with PMR) experienced a flare of their preexisting rheumatic disease over around 700 patients treated **(100)**. In general, cases of PMR and other IRAEs respond well to treatment with GCs and DMARDs.

Conclusions

PMR is a common inflammatory disease in people older than 50 years from Western countries. Glucocorticoids are the first line of therapy for PMR. However and due to the frequent occurrence of adverse events, GC-sparing agents are habitually required. Among them, MTX is the most commonly used conventional DMARD (**Table 2**).

Nonetheless, its effect to prevent relapses of the disease and to reduce the cumulative prednisone dose is often modest. Biologic agents have been used in patients with refractory disease or in those in whom GCs have to be discontinued due to adverse events. Randomized controlled trials do not support the use of anti-TNF agents in the management of PMR. In contrast, several case series and retrospective studies have highlighted the efficacy of the anti-IL-6R TCZ in PMR, although controlled trials including large series of patients to evaluate the efficacy of this agent in refractory PMR are needed. The potential positive effect of the JAK inhibitors in isolated PMR remains to be determined. The **graphic abstract** summarizes the main etiopathogenic, clinical and therapeutic aspects of polymyalgia rheumatica.

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Conflicts of interest

None declared.

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FIGURE LEGENDS

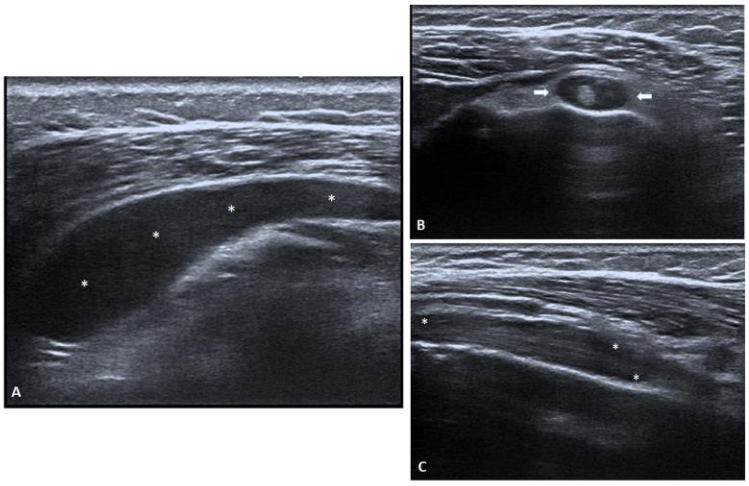
Figure 1. **Ultrasonography of the left shoulder in a patient with polymyalgia rheumatica**. Ultrasonographic images showing typical findings at periarticular soft tissues of the left shoulder. A. Longitudinal view of the subacromial/subdeltoid bursa. White asterisks represent the virtual cavity of the bursa filled with synovial fluid. B. Transverse view of biceps tendon with signs of inflammation and fluid around the tendon (white small arrows). C. Longitudinal view of biceps tendon showing signs of tenosynovitis (white asterisks inside the tendon sheath). Images obtained in our Outpatient Clinic.

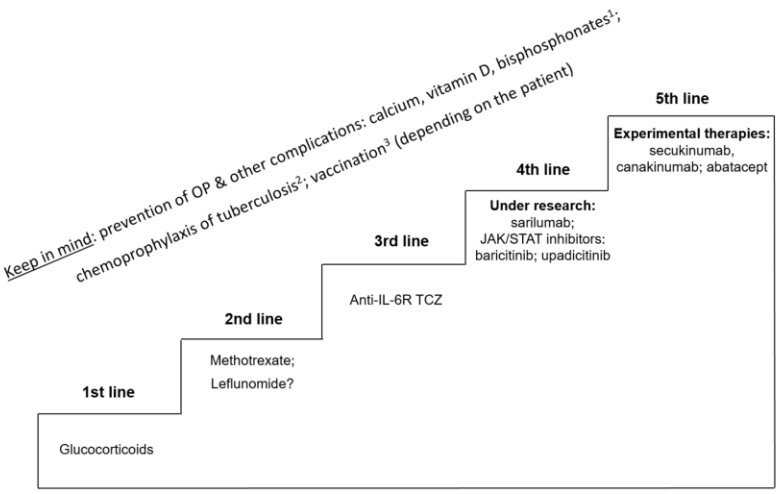
Figure 2. **Schematic view for a stepped treatment of polymyalgia rheumatica**.

Footnotes: IL-6R: interleukin 6 receptor; JAK/STAT: Janus kinase/signal transducers and activators of transcription; OP: osteoporosis; TCZ: tocilizumab.

GRAPHICAL ABSTRACT. **Relationship of PMR with GCA and other related inflammatory diseases in the elderly**.

Footnotes: DMARDs: disease-modifying anti-rheumatic drugs; EORA: elderly-onset rheumatoid arthritis; IL: interleukins (1, 6, 8); MCP-1: monocyte chemoattractant protein 1; NSAIDs: non-steroidal anti-inflammatory drugs; PMR: polymyalgia rheumatica; RS3PE: remitting seronegative symmetrical synovitis with pitting oedema syndrome; TNF-α: tumor necrosis factor alpha; Th: T-helper (Th1, Th17) lymphocytes; Treg: regulatory T lymphocytes. The two images at the center bottom show a subacromial bursitis and tenosynovitis of the biceps in a patient with PMR. The one on the right at the middle exemplifies the “halo sign” in a temporal artery of a patient with giant cell arteritis.





[1] In case of osteoporosis or high risk fracture; [2] If positive contact history, positive Mantoux or chest X-ray suggestive of past tuberculosis; [3] Before biologic therapy

Table 1. Symptoms, clinical features and imaging findings of PMR.

A) Inflammatory pain and stiffness in shoulders, hips or neck and[¶]:
- Age older than 50 years
- Pain in upper arms and/or thighs
- Morning stiffness > 45 minutes
- Rapid onset of manifestations[a]
- Symptoms are usually bilateral[b]
- Restricted range of motion[c]
- Muscle tenderness in affected muscles
- Difficulty for basic activities of daily life[d]
- Peripheral non-erosive arthritis[e]
- Distal swelling and/or edema of hands

B) Non-specific manifestations without evidence of infectious or neoplastic disease:
- Low-grade fever
- Anorexia
- Weight loss (40-50% of cases)
- Fatigue/malaise

C) Unexplained anemia and elevated acute phase reactants, CRP and/or ESR:
- ESR ≥ 40 mm/first hour[f]
- CRP > 6 mg/L

D) Other non-specific laboratory findings:
- Thrombocytosis
- Increased levels of α-2 globulin
- Hypoalbuminemia
- Absence of RF and anti-CCP antibodies[g]

E) Imaging findings by US, MRI or PET/CT:
- Subacromial/subdeltoid bursitis
- Tenosynovitis of the biceps
- Glenohumeral synovitis
- Trochanteric or iliopsoas bursitis
- Cervical/lumbar interspinous bursitis
- Mild synovitis in peripheral joints
- Occult large vessel involvement[h] by PET/CT

Abbreviations: PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; US: ultrasonography; MRI: magnetic resonance imaging; PET/CT: positron emission tomography integrated with computed tomography

[¶] In addition to one or several of the items included in this section.
[a] The onset of symptoms is often rapid, generally over a few days and in some cases overnight.
[b] Although symptoms can start alone on one side, clinical manifestations are later bilateral.
[c] In all joints affected and near regions.
[d] Such as dressing, washing, brushing hair, getting out of bed or rising from a chair.

[e] Typically, arthritis of patients with PMR is most commonly asymmetrical, mild, non-erosive and affects peripheral joints, particularly knees and wrists, appearing in 23-39% of the cases.
[f] The initial erythrocyte sedimentation rate can be <40 mm/h in up to 20% of patients with PMR.
[g] The presence of RF or anti-CCP antibodies forces to discard rheumatoid arthritis.
[h] In around a third of patients with PMR without symptoms or signs of giant cell arteritis.

Table 2. Main drugs used or in progress in the management of polymyalgia rheumatica.

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1. *Glucocorticoids* (gold standard therapy):

- Most commonly prednisone/prednisolone oral: initial dose 12.5-25 mg/day.

- In patients of low weight or with complications such as diabetes or osteoporosis start with 12.5-15 mg/day.

- In obese or very symptomatic people without risk factors, start with 20-25 mg/day.

- Intramuscular methylprednisolone acetate (120 mg eow for 12 weeks followed by monthly injections with dose reductions of 20 mg every 3 months) is effective but less than standard regimen of oral prednisolone.

- Bilateral shoulder injections of 6-methylprednisolone every 4 wks in special cases*.

2. *Glucocorticoid-sparing agent* (moderate efficacy)[#]:

- Methotrexate has only a modest effect as a steroid saver.

- The recommended dose of methotrexate is at least 10-15 mg preferably via parenteral.

- Leflunomide 10-20 mg/day has shown promising results in patients refractory to glucocorticoids.

3. *Biological agents*:

- Anti-IL-6R tocilizumab[#] is the only biological agent that has shown utility to treat PMR, especially in relapsing patients.

4. *Therapies in research*:

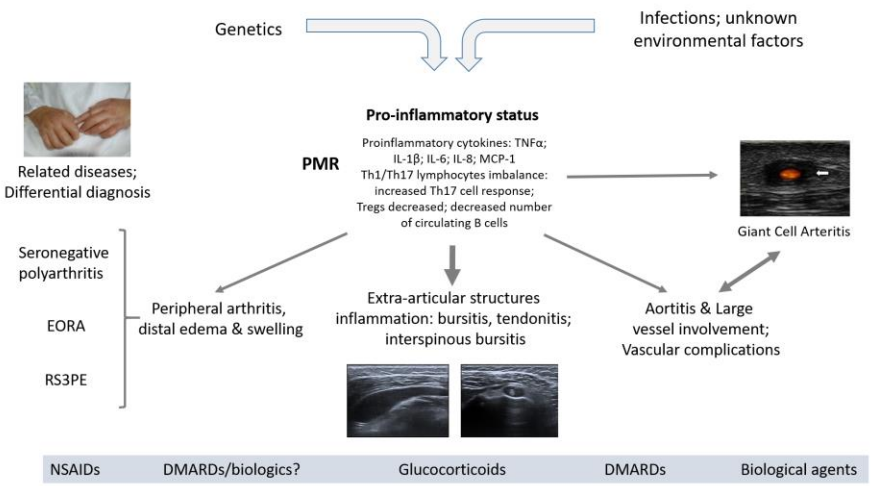
- Janus kinase inhibitors; other IL-6R antagonists

Abbreviations: PMR: polymyalgia rheumatica; IL-6R: interleukin 6 receptor; eow: every other week.
*Especially in patients with severe subacromial/subdeltoid bursitis only as an adjuvant therapy at specific moments.
#None of them currently approved for the treatment of PMR.

Table 3. Main adverse effects of prolonged use of glucocorticoids.

A) Musculoskeletal:
Osteoporosis
Steroid myopathy
Osteonecrosis[a]
B) Metabolic/hormonal effects:
Diabetes and glucose intolerance
Body morphology disturbances
Adrenal suppression
Libido decrease
Hirsutism
C) Cardiovascular system:
Hypertension
Dyslipidemia
Atherosclerosis and ischemic heart disease
D) Immune system (infections):
Increased risk of general infections
Increased risk of opportunistic infection and herpes zoster
E) Psychological:
Mood disturbances and psychosis
Insomnia
F) Dermatological:
Acne, alopecia, capillary fragility
Skin atrophy
G) Ocular:
Cataract, glaucoma
H) Gastrointestinal:
Gastritis, peptic ulcer disease

[a]Mainly involving hips, knees, shoulders and elbows.


Genetics
Infections; unknown environmental factors
Related diseases; Differential diagnosis
Pro-inflammatory status
PMR
Proinflammatory cytokines: TNFα; IL-1β; IL-6; IL-8; MCP-1
Th1/Th17 lymphocytes imbalance: increased Th17 cell response;
Tregs decreased; decreased number of circulating B cells
Giant Cell Arteritis
Seronegative polyarthritis
EORA
RS3PE
Peripheral arthritis, distal edema & swelling
Extra-articular structures inflammation: bursitis, tendonitis; interspinous bursitis
Aortitis & Large vessel involvement; Vascular complications
NSAIDs
DMARDs/biologics?
Glucocorticoids
DMARDs
Biological agents