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## **The Pathophysiology of Polymyalgia Rheumatica, Small Pieces of a Big Puzzle**

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**Keywords:** Polymyalgia rheumatica, HLA-DR, T cell, B cell, Interleukin-6, aging.

### **Take Home Messages:**

- Most of the findings about PMR pathophysiology come from blood sample analysis. Few synovial biopsy studies are available and suggest different implications for immune system actors.
- Lymphocyte subsets are modified in PMR patients, but their role in its pathophysiology is not fully understood. These modifications might be secondary to chronic inflammation.
- Inflammatory cytokines such as IL-6, TNF $\alpha$  and IL-1 are increased in muscle and synovial fluid, but only IL-6 is increased in serum.

- Aging of the immune system might play a role in PMR pathophysiology, but little data are available thus far.

**Abstract:**

Polymyalgia rheumatica (PMR) is a frequent rheumatic condition among people over 50 years of age. Despite its frequent association with giant cell arteritis (GCA), PMR can be isolated. Its pathophysiology is poorly understood. Nevertheless, many studies are ongoing; 98 studies are currently referenced in ClinicalTrials.org involving several conventional and targeted therapies. In this review, we synthesize the current knowledge about PMR pathophysiology according to genetic and immunogenetic, immunologic, antibody and aging data. Immunogenetic data are mainly related to the HLA system and the association between the HLA-DRB1 and PMR. Few studies are also about immunogenetics of proinflammatory interleukins (i.e. IL-6). The decrease of CD8<sup>+</sup>Tcells and the strong increase of IL-6 were the main elements of PMR's pathophysiology until the recent years. The disturbance of B cell homeostasis, the search for IL-6 secretion by the innate immune system, the role of aging, are new elements revealed by recent studies. Aging might be a key element to consider as PMR occurs in patients over 50 years of age. Aging may act by the increased susceptibility to infections, by immunological modifications or hormonal disturbances. The role of the cellular infiltration around the joints remains a crucial question. Only a handful of studies described this infiltration. Finally, this review reveals the gaps in available data and suggests new leads and in-depth studies for further research on PMR pathophysiology.

## **1. Introduction**

Polymyalgia rheumatica (PMR) was first reported by Forestier and Certonciny in 1954 in the Italian journal “Reumatismo” as “rhizomelic pseudopolyarthritis” [1]. Stuart Barber, in 1957, used the term “polymyalgia rheumatica” for the first in *Annals of Rheumatic Diseases* [2]. In the 1960s, connections were established between polymyalgia rheumatica and giant cell arteritis (GCA) thanks to temporal artery biopsies and arteriography [3,4]. Polymyalgia rheumatica is observed in 40 to 60% of patients with GCA, and GCA affects 16 to 21% of patients with PMR [5–9]. Pathophysiology of GCA has been more studied than PMR [7,10,11]. However, isolated PMR remains difficult to classify. Should we refer to PMR as vasculitis, an autoimmune disease or an inflammatory disease? [12] PMR occurs in patients over 50 years of age, with a peak incidence at approximately 75 years of age, suggesting that aging plays a role in its pathophysiology. PMR is characterized by inflammatory pain in the shoulder and pelvic girdle that may wake patients during the night and is responsible for important morning stiffness that often lasts more than one hour. A strong increase in acute phase reactants is common in PMR patients. C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) are critical indicators for diagnosis. Because of such inflammation and the absence of specific autoantibodies, some authors have suggested classifying PMR as an autoinflammatory disease [12]. However, PMR can also be a syndrome of elderly-onset rheumatoid arthritis, a typical autoimmune disease, and differential diagnosis may be difficult. Currently, no pathognomonic biological or imaging tests exist for PMR diagnosis, and the diagnostic workup aims to rule out differential diagnoses. Corticosteroids remain the basis of PMR treatment, and several studies have evaluated methotrexate as a steroid-sparing agent [13–15]. Recently, tocilizumab has been demonstrated to decrease the cumulative dose of corticosteroids needed to achieve low disease activity in early PMR patients and appears to work even without corticosteroids [16–18]. Phase 3 studies to evaluate anti-interleukin-6

therapies as steroid-sparing agents in steroid-dependent PMR are ongoing. The lack of a targeted therapy underlines the poor understanding of PMR pathophysiology, and without a doubt, a deep understanding of the inflammatory and immune mechanisms underlying disease activity will enable great advances in PMR treatment. The objective of this review is to summarize the current knowledge about PMR pathophysiology to form new ideas for further investigations.

## **2.1 What does immunogenetics tell us about PMR?**

The first descriptions of the association between alleles or polymorphisms and PMR were revealed in the 1990s, and the first family of genes studied was, as in several autoimmune diseases, the human leukocyte antigen (HLA) family. First, HLA-DR and especially DR4Dw13 were reported to be associated with PMR in patients [19]. The association of HLA-DRB1 with PMR and GCA was then described [20–23]. This association specifically concerns the second hypervariable region of HLA-DRB1, whereas it is the polymorphism in the third hypervariable region of HLA-DRB1 that is associated with rheumatoid arthritis. Several additional studies confirmed the association between HLA-DRB1 and PMR/GCA [24], limiting this association to the HLA-DRB1\*0401 and HLA-DRB1\*0404 alleles [25] or distinguishing between HLA-DRB1\*01 in PMR and rheumatoid arthritis patients versus HLA-DRB1\*04 in rheumatoid arthritis patients only [26]. The association between HLA alleles and PMR might fluctuate depending on the studied population [27], probably explaining some inconsistencies observed among different studies. Indeed, different studies have been conducted in several parts of the world, and because of different genetic backgrounds, the associations might have been different. Some authors have tried to link this genetic association with immunological findings, such as CD8<sup>+</sup> depletion, in early PMR [28]. A difference between patients with isolated PMR and GCA was also suggested based on an HLA class II difference, but this result has not yet been confirmed in independent cohorts

[29]. Moreover, in PMR patients, HLA-DRB1 subtypes have been described as predisposing factors for vascular complications [30], and a polymorphism of NOS3 has also been associated with vascular dysfunction [31], even in PMR patients without vascular manifestations. These elements might suggest a *continuum* between PMR and vasculitis. However, for now, additional factors are needed to translate these results into clinical practice.

Other polymorphisms associated with PMR have been described. ICAM is an adhesion protein and has been described as strongly expressed in the synovial tissues of patients with PMR. The G/R 241 polymorphism has been reported to be associated with PMR in an Italian population [32] and in subsequent studies [33]. Polymorphisms have also been reported for RANTES [34], TNFa2 [35,36], TNFb3 [35] and IL-1RN\*2 [36,37]. The CCR5 delta 32 allele was not found to be associated with PMR, PMR severity or PMR susceptibility [38]. In patients with GCA who do not carry the HLA-DRB1\*04 allele, a polymorphism in the promoter region of the interleukin (IL)-6 gene (at position -174) was found to be associated with PMR symptoms in some cohorts but not in others [39,40], highlighting the only partially understood role of IL-6 in PMR pathophysiology. Finally, several polymorphisms, for instance, IFN $\gamma$ , have been studied in GCA patients and have been reported to be associated with disease manifestation severity but not PMR [41]. The alleles and polymorphisms that have been studied in the context of PMR and associated or not with PMR are reported in Table 1.

These results suggest the role of genetic predisposition to immune system activation and the production of inflammatory cytokines, as has been described in autoimmune disease (rheumatoid arthritis) or vasculitis (GCA) patients. Several actors might be involved in processes such as immune system stimulation by antigen presence (through HLA), cytokine production (IL-6, TNFa, IL-1) and cell adhesion and recruitment (RANTES, ICAM-1).

Nevertheless, polymorphisms of other actors that might seem important (IL-10, IFN $\gamma$ , CCR5) were not associated with PMR, although IL-10 and IFN $\gamma$  polymorphisms have been discussed in GCA. Finally, the cumulative effect of alleles and polymorphisms has never been studied to date.

## **2.2 Early explorations of the immune system**

In the seventies, in the early days of cytometry, few immune cells were characterized and analyzable. The first population described in PMR patients was immunoblasts. At that time, immunoblasts were described as increased in patients, such as rheumatoid arthritis patients, compared to controls, and the increase in immunoblasts was associated with an increased erythrocyte sedimentation rate and increased disease activity [42]. Immunological mechanisms were also suspected to be responsible for PMR and GCA when a Mayo Clinic team described the increase in immune complexes in the serum of patients with active disease and increasing levels in patients in remission before relapse [43,44].

In the eighties, lymphocyte subsets were analyzed in PMR patients, and T cell (OKT3<sup>+</sup>) and CD8<sup>+</sup> (OKT8<sup>+</sup>) T cells were reported to be lower than those in the controls, whereas CD4<sup>+</sup> (OKT4<sup>+</sup>) T cells were not altered [45–48]. This decrease in CD8<sup>+</sup> T cells was described to be associated with increased activation of these cells, and with treatment, these changes were restored, but only after 24 months of corticosteroid therapy [49]. A decrease in CD8<sup>+</sup> T cells was also reported in subsequent studies and was associated with a decrease in CD3<sup>+</sup>CD16<sup>+</sup> or CD56<sup>+</sup> cells [50]. After 6 months of corticosteroid treatment, the percentage and absolute number of CD8<sup>+</sup> T cells increased, but the percentage and absolute number of CD3<sup>+</sup>CD16/56<sup>+</sup> cells remained the same. The authors suggested that despite clinical control of the disease, immunological abnormalities were not totally corrected by corticosteroid treatment. Some authors even suggested the usefulness of CD8<sup>+</sup> counts for the diagnosis of PMR [51–54]. The persistence of a decrease in CD8<sup>+</sup> T cells despite corticosteroids was also suggested to be

correlated with severe disease and prolonged corticosteroid treatment [55]. However, this decrease in CD8<sup>+</sup> T cells in patients with early PMR and no treatment was contested, as several studies did not observe such a decrease [56–59]. The impact of the methodology used was questioned to explain such variations in the observations. Moreover, soluble CD8 was also described as increased in PMR patients [60]. To reinforce the possible implication of CD8<sup>+</sup> T cells in PMR pathophysiology, it has been suggested that age-related modifications in the CD8<sup>+</sup> population of T cells might influence the development of PMR [61]. The T cell receptor repertoire was characterized in PMR patients, and most changes seemed to be related to the age of patients, as healthy controls matched for age presented the same modifications [62]. Only a few beta-chain variable families were decreased in PMR patients. Compared to adult-onset rheumatoid arthritis, similar alterations in T cell subpopulations were found in those with PMR and elderly-onset rheumatoid arthritis [63]. After many controversies, the use of CD8<sup>+</sup> T cells for diagnosis or prognosis is no longer a matter of interest. However, the rapid development of flow cytometry has enabled the precise characterization of lymphocyte subsets.

### **2.3 Recent data about immune system cells**

In the past ten years, with the improvement of flow cytometry techniques, several studies have also evaluated the distribution and characterization of lymphocyte subsets in PMR (Table 2). At the end of 2008, in line with previous studies on CD8<sup>+</sup> T cells, Shimojima et al. suggested that CD8<sup>+</sup>CD25<sup>+</sup> activated T cells were decreased and that CD4<sup>+</sup>IFN $\gamma$ <sup>+</sup>IL-4<sup>-</sup>, CD8<sup>+</sup>IFN $\gamma$ <sup>+</sup>IL-4<sup>-</sup> and CD4<sup>+</sup>TNF $\alpha$ <sup>+</sup> populations were increased in PMR patients compared to early rheumatoid arthritis patients [64]. Memory/effector CD3<sup>+</sup>CD4<sup>+</sup>CD28<sup>-</sup> T cells have been reported to be increased in the peripheral blood of PMR patients compared to healthy controls [65]. Naïve CD8<sup>+</sup> T cells were decreased and effector/memory CD8<sup>+</sup> T cells were increased in PMR patients compared to healthy controls. Together, these studies suggest that



effector/memory T cells are increased in patients' peripheral blood, but activated T cells should be studied in more detail to conclude an increase or a decrease. This can validate the results of past studies with inconsistent results.

In 2012, for the first time, a decrease in the CD4<sup>+</sup>CD25<sup>high</sup>Foxp3<sup>+</sup> regulatory T cell subset was described in patients with PMR and GCA and associated with an increase in pro-inflammatory T cell subsets, such as Th1 and Th17, suggesting a potential role in the pathophysiology of PMR and GCA [66]. Once again, this suggested that analysis of the inflammatory potential of T cells was more useful than conventional phenotyping. Considering the potential implication of Th17 T cells, ustekinumab has been tested in GCA patients in a prospective open-label trial, enabling a decrease in glucocorticoids, but ustekinumab has not yet been tested in PMR patients [67,68]. In 2013, senescent T cells were reported to be increased in PMR and GCA patients, with an increase in NKG2D – a marker of immunosenescence – expressing T cells [69]. Ligands to NKG2D are expressed in temporal arteries; this may activate T cells in temporal arteries and contribute to inflammation in GCA. On the other hand, the role of these cells in PMR is still unknown, but the link between aging and immunological modifications is of great interest.

After the description of T cell subsets, B cells were analyzed by a Dutch team [70]. The distribution was altered in PMR and GCA patients and was restored after corticosteroid therapy. B cells were decreased, but only some B cell subsets were impacted. Mature naïve, IgM-only memory, switched memory, double negative and plasmablasts were decreased in PMR patients, whereas transitional and unswitched memory were not. A link between the perturbation of B cell homeostasis and increased IL-6 production was also suggested. These results were then sustained by the strong association between the increase in BAFF and the increase in IL-6 – both in the serum of patients – with disease activity [71]. Perturbation of B cell subset homeostasis has been confirmed by our team, with no modification of CD4<sup>+</sup> or

CD8<sup>+</sup> T cells [72]. The absence of modification of T cells is fully explained by the limited markers used for T cell characterization. The previously described decrease in CD8<sup>+</sup> T cells was not found, but this might be explained by the small sample of patients and fluctuations in this observation, as reported in prior studies and discussed previously.

A question that remains unresolved despite these different studies is the link between inflammation and lymphocyte subset distribution. One can easily imagine that inflammation has an impact on lymphocyte subsets and modifies their distribution. Thus, the modification observed after treatment might be related to a decrease in inflammation or to direct treatment action, restoring lymphocyte subset distribution, leading to disease improvement. The main results of the studies described above are summarized in Table 2.

#### **2.4 Autoantibodies: “the chicken and the egg” question**

Several autoantibodies associated with PMR have been described, but none have been recognized as a diagnostic tool [73–81]. Antineutrophil cytoplasmic antibodies have been described in patients with PMR and GCA, but they have been identified with only indirect immunofluorescence staining without specificity for MPO or PR-3 antigen [82]. Supporting the hypothesis of a virus-triggered disease, antibodies directed against respiratory viruses (such as adenovirus and respiratory syncytial virus) have been reported [83]. Moreover, the question of the cause or the consequence of inflammation has already been asked. For example, the presence of autoantibodies directed against intermediate filaments was found to evolve with treatment of PMR to reach a prevalence close to that in healthy controls in patients in remission who received corticosteroid treatment [84]. This suggests that some immunological manifestations might be secondary to the high level of inflammation in PMR and might resolve with proper treatment of inflammation. Anticardiolipin antibodies have also been widely studied in PMR and GCA, with several studies suggesting a role in disease pathophysiology [77–79]. Nevertheless, recent data suggest that anti-cardiolipin antibodies

might be the consequence of vascular lesions rather than a *primum movens* mechanism involved in PMR and GCA pathophysiology [85]. To date, no autoantibody has been recognized as directly involved in PMR pathophysiology or has been suggested to be useful for PMR diagnosis.

## **2.5 Cytokines, the messengers of inflammation**

In 1993, Cornelia Weyand et al. of the Mayo Clinic reported an increase in IL-6 levels in the serum of patients with PMR and GCA but no increase in TNF $\alpha$  levels [86]. A decrease after corticosteroid treatment was reported, but the mechanism underpinning IL-6 production was supposed to still be active because the interruption of the treatment resulted in an early increase in IL-6 serum level and the worsening of disease symptoms. The duration of corticosteroid treatment should be discussed. In this study, corticosteroids were quickly stopped, and a prolonged treatment duration may have prevented such a relapse. According to the authors, the production of IL-6 was mainly due to a population of CD14<sup>+</sup> cells (monocytes) among peripheral blood mononuclear cells. Other cytokines were studied in the serum of patients with PMR, but apart from IL-6, no other cytokine, such as sIL-2R [87,88], IL-1 $\beta$  [88,89], TNF $\alpha$  [89], was found to be increased or useful in diagnosis or follow-up. IL-6 was also studied in patients with relapsing PMR and was increased in patients with relapse, while CRP or ESR was not modified [90]. IL-6 was also reported to be higher in patients with PMR than in patients with elderly-onset rheumatoid arthritis [91]. Measurement of the serum IL-6 receptor has been suggested to be useful for the diagnosis of PMR relapse; this finding also supports the use of IL-6 receptor blockade therapy [92]. Since tocilizumab has been used in PMR patients and is still being investigated as a steroid-sparing agent [16], the evolution of IL-6 under tocilizumab therapy might be of great interest; we have already reported and described the evolution of IL-6 under tocilizumab therapy. Despite an increase in IL-6 in early untreated PMR patients, the level of IL-6 did not change with tocilizumab treatment.

However, it appears that patients could be divided into two groups. In the first group, patients had high levels of IL-6 before tocilizumab therapy, and the level of IL-6 significantly decreased after treatment. In the other group, IL-6 was not very high compared to the controls, and the level of IL-6 did not change (or slightly increased) after tocilizumab therapy [72]. Despite these discrepancies in IL-6 levels in the serum, all patients had a PMR diagnosis and fulfilled Chuang's criteria. Moreover, during follow-up, the diagnosis was not questioned. Interleukin serum levels vary over the course of a day with the circadian production of cortisol: this might explain the very characteristic inflammatory symptoms of PMR patients. However, only serum circadian variation has been studied [93]. The origin of this increase in IL-6 production has not been clearly elucidated. No evidence has been found to suggest that monocytes from peripheral blood produce more IL-6 in PMR patients, but this increase in production might be located in inflamed tissues [94].

## **2.6 Muscles and synovial fluid, from Plato to PMR pathophysiology**

Synovial thickening and inflammation according to arthroscopy have been described [95], and this finding is of major importance because, as in rheumatoid arthritis with synovial thickening, the modifications observed in peripheral blood might be very different from the modifications in involved tissues; thus, the conclusions formed on the basis of peripheral blood alone might not be fully relevant to understand PMR pathophysiology. Indeed, as the shadows of Plato's cave allegory, in peripheral blood, we might be observing very indirect consequences of inflammatory mechanisms hidden in the muscles and synovial tissue. However, unlike the prisoners of Plato's cave, we might be able to break our chains and to partially understand what is taking place in these important tissues. Few studies have focused on cellular infiltration and cytokine expression in tissue and synovial fluid. An increase in IL-6 in the synovial fluid of a patient with PMR was previously described [96]. Vascular infiltration in patients with PMR and GCA was also studied and revealed the infiltration of T

cells producing inflammatory cytokines (IL-1, IL-6 and TNF $\alpha$ ) in both groups of patients [97]. The production of IFN $\gamma$  differed in patients with GCA and PMR and might be implicated in the progression from PMR to GCA, suggesting that PMR is a predisposing condition to vasculitis. In 2010, Kreiner et al. reported an increase in the interstitial level of proinflammatory cytokines, including IL-6 as well as IL-1 $\alpha$  and  $\beta$ , IL-8, and TNF $\alpha$ , compared to healthy controls, whereas cytokine serum levels in PMR patients were not always different from those in healthy controls [98]. These interesting results emphasize the idea of a periarticular mechanism that is poorly reflected by peripheral blood analysis. Specific pain mechanisms might play an important role in the muscles of patients with PMR [99].

Several elements suggest a role of immune cell infiltration in the muscles and periarticular regions, explaining the clinical symptoms of PMR. Immune complexes were observed in the muscle of patients with PMR and GCA [100,101]. Synovitis was reported in PMR [102–104]. Biopsies of the deltoid muscles of patients with PMR contained more microvascularization compared to those of healthy controls. Synovitis of the shoulder was also studied using arthroscopic biopsies, and infiltration of macrophages and T cells but not B cells, NK cells or  $\gamma/\delta$  T cells was observed [105]. Strong expression of adhesion molecules, such as VCAM and ICAM, was described in PMR patients with synovitis and might contribute to the recruitment of many immune system actors involved in PMR synovial infiltration [106]. Vasoactive intestinal peptide (VIP) was reported to be expressed in PMR synovial cells and at significantly higher levels in PMR than in osteoarthritis and rheumatoid arthritis [107]. Nevertheless, the meaning of this increase remains to be determined. High levels of monocyte chemoattractant protein 1 (MCP-1) were reported in early-, untreated PMR and GCA patients, but the levels did not differ between these two groups of patients [108]. Even if monocytes do not produce increased amounts of IL-6, a pathological role has been suggested in GCA [109]. Vascular endothelial growth factor (VEGF) was studied in the serum of PMR patients and in

synovial biopsies. VEGF was higher in untreated PMR patients than in healthy controls. The level of VEGF in the patient's serum decreased after 6 months of corticosteroid treatment [110]. VEGF staining was observed in the synovial tissue of active, untreated PMR patients but was not observed in most of the treated patients.

All of these elements clearly underline the need for additional analyses of synovial fluid and tissue, including muscle tissue samples. However, research should not harm patients, and strict control by the ethics committee is mandatory to enable such studies.

### **2.7 The role of an aging immune system:**

Despite a peak in incidence after 50 years of age, very few studies have specifically investigated the role of the modification of the immune system with aging and its implication in PMR pathophysiology. More GCA studies than PMR studies about the aging of immune system cells and its link with oxidative stress are available [111–114]. Regarding PMR, we previously cited an increase in senescent T cells with an increase in NKG2D [69] expression and modification of the CD8+ population with aging [61]. However, few studies about hormonal modifications with age and their implications in PMR are available. Cortisol and DHEAS production is reduced in patients with untreated, early PMR [115]. The decreased response to adrenal stimulation by ACTH observed in PMR patients might explain this reduced production, and adrenal hypofunction has been confirmed in other studies [116,117]. Finally, homocysteine, as a reflection of vascular aging and inflammation, has been studied and has been found to be higher in patients with PMR and GCA than in healthy controls [118].

Aging may increase susceptibility to viral infections. The viral hypothesis has been discussed in PMR and GCA, with many studies involving both populations. A cyclic pattern has been

described in epidemiological studies of PMR and GCA [119]. Some studies confirmed a seasonal pattern of PMR and GCA [120–122], while others did not [123–125]. A link has been suggested between human parainfluenza virus and GCA with temporal artery infiltration [123] and possibly between parvovirus B19 and PMR, but no study has confirmed these associations [124,126,127]. To date, no infection has been clearly linked to PMR pathophysiology, and even though a seasonal pattern has been described in some cohorts, no exposure to an infective or environmental agent supports this pattern.

### **2.8 The innate immune system, a missing piece of the puzzle?**

Activation of the innate immune system might be of great importance in PMR pathophysiology. Indeed, IL-6 production, the main cytokine increased in peripheral blood and tissues in PMR patients, is mainly produced by innate immune cells. Monocytes extracted from peripheral blood mononuclear cells of PMR patients and cultured with cellular stimulation have not been found to be responsible for IL-6 [94]. However, this lead should not be ruled out too quickly. IL-6 production has been studied in only monocytes from the peripheral blood and not in cells inside muscles or in synovial fluid or tissue. Little data supports implication of the innate immune system. TLR7 might be activated in active PMR, and this activation might decrease with disease remission [128]. This might be a cause of PMR activation of the immune system and IL-6 production, but this might also be only a consequence of the strong inflammation activity observed in PMR. The role of phagocytosis in PMR has also been questioned, but more studies are needed to fully understand this particular mechanism [129].

Recently, leukocyte dynamics in PMR and GCA patients were reported and showed a large increase in monocytes and neutrophils in early stages of the disease, with a decrease in B cells

and NK cells. High levels of monocytes were still observed in patients in remission who received corticosteroids. The authors concluded that leukocyte distribution shifts to the myeloid lineage due to the heavy inflammation associated with PMR, but these cells might also be responsible for the heavy inflammation. As frequently observed in inflammatory autoimmune diseases, deregulation of the immune system might lead to a vicious cycle in which the immune system maintains its activation and a permanent state of inflammation; however, we might also conceive that chronic inflammation progressively leads to dysregulation of the immune system.

### **3. Discussion/Conclusion:**

The first analysis of studies about PMR pathophysiology suggests that we understand only a small proportion of the mechanisms at play. Most of the findings are summarized in figure 1. The increase in IL-6 has been the subject of most articles, and the first results of the protocols using tocilizumab for PMR underline the importance of this cytokine [16,130–132]. However, we do not understand how this cytokine is produced, which mechanisms result in such an increase and why some patients develop vasculitis and others do not. The second analysis partially explains the difficulties just described. We might be focusing on the wrong material, and the observations from peripheral blood might be only a truncated reflection of the real mechanism at play. In rheumatoid arthritis, several analyses have focused on synovial biopsies. In systemic lupus erythematosus, kidney and skin biopsies are also of great use. A better understanding of GCA pathophysiology is due in part to the many studies that analyzed temporal artery biopsies. Undoubtedly, it is easier to obtain biopsies if they are of great relevance for clinical issues. It is more acceptable to use the remains of biopsies than to perform such biopsies for only research purposes. Nevertheless, a deeper understanding of the immunological mechanisms in muscles and synovial tissue appears important to improve the



understanding of the disease and develop new therapeutic options in the future. It is particularly striking that PMR affects patients over 50 years of age and mainly over 65 years of age. The link between aging and PMR seems clear, but few pathophysiological data actually confirm this link. Aging of the immune system is being increasingly studied, but few studies in GCA patients are available; these studies may reveal leads in PMR pathophysiology. However, specific studies will be mandatory to highlight the mechanisms of PMR. Another striking finding is inflammation status, which is a critical diagnostic indicator of PMR. All the present findings tend to characterize PMR as an inflammatory disease and not as an autoimmune disease. The critical role of inflammation might be related to IL-6 due to the increase in this cytokine. However, some patients do not exhibit such a strong increase. IL-6R-blocking therapies have promising results in PMR, but it is probable that some patients will not respond. Other mechanisms of inflammation might be important in such patients. Moreover, the origin of such high levels of proinflammatory cytokines in some patients has not yet been associated with an increase in secretion by monocytes, lymphocytes or other cells. Finally, this analysis highlights the studies about aging. Even though few studies are available, they demonstrate that the endocrine system is surely an important actor and potentially a regulator of the immune system. An increasing number of studies about the aging of the immune system are becoming available [133], and the strong association between PMR and aging suggests a role of aging in its development. Aging, the role of the innate immune system, analysis of the synovial tissue, of muscles and bursas are new leads and suggestions for PMR pathophysiology research.

**Competing interest:** The authors have no competing interest related to this work.

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**Table 1: Allele and polymorphisms studied in polymyalgia rheumatica**

<b>Alleles and polymorphisms studies and associated with PMR</b>	<b>Alleles and polymorphisms studied but not associated with PMR</b>
HLA-DRB1	CCR5 $\Delta$ 32
ICAM (G/R 241)	IFN $\gamma$ [41]
RANTES	TLR-4 [134]
TNFa2 [35]	IL-13 (rs20541 R130Q) [135]
TNFB3 [35]	IL-10 [136]
IL-1RN*2	
IL-6 (-174 allele C) [39]	

PMR: polymyalgia rheumatica; HLA: human leukocyte antigen; CCR: chemokine-C receptor;

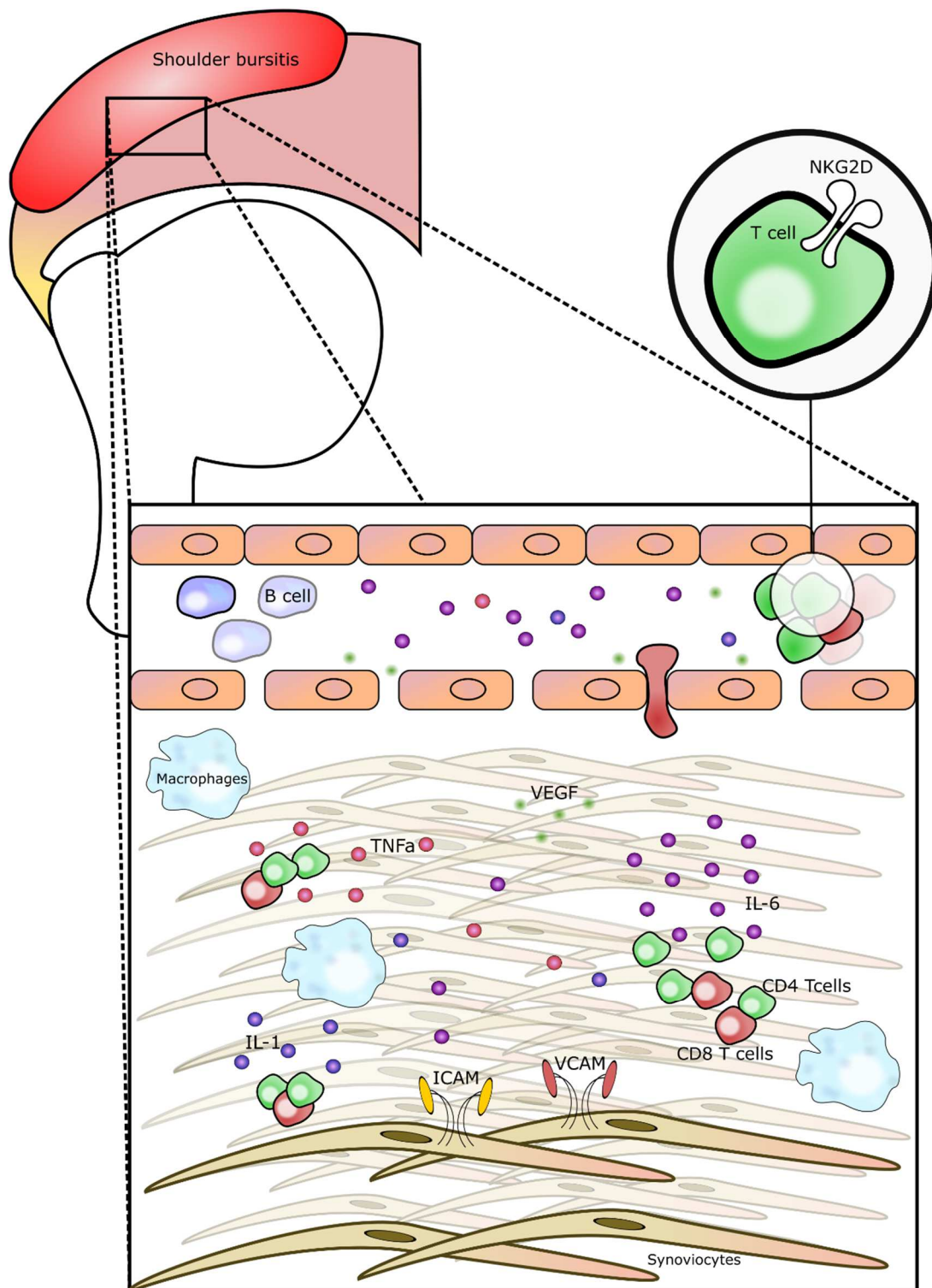
ICAM: intercellular adhesion molecule; IFN: interferon; RANTES: regulated on activation, normal T cell expressed and secreted; TLR: Toll-like receptor; IL: interleukin

**Table 2: Main studies on lymphocyte subsets in polymyalgia rheumatica since 2008**

Year, Main author	Number of patients	Markers	Observations	Population compared
2008, Shimojima et al. [64]	14 PMR	CD4, CD8, CD23, CD25, HLA-DR, CD80, CD86, CD3, CD19, IL-4, IFN $\gamma$	$\downarrow$ CD8 <sup>+</sup> CD25 <sup>+</sup> $\uparrow$ CD4 <sup>+</sup> IFN- $\gamma$ <sup>+</sup> IL-4 <sup>-</sup> $\uparrow$ CD8 <sup>+</sup> IFN- $\gamma$ <sup>+</sup> IL-4 <sup>-</sup> $\uparrow$ CD4 <sup>+</sup> TNF $\alpha$ <sup>+</sup>	Early rheumatoid arthritis patients
2010 Dejacco et al. [65]	38 PMR/GCA	CD3, CD4, CD7, CD8, CD25, CD28, CD45RA, CD45RO	$\uparrow$ CD3 <sup>+</sup> CD4 <sup>+</sup> CD28 <sup>-</sup> $\downarrow$ CD28 <sup>+</sup> CD45RA <sup>+</sup> CD8 <sup>+</sup> $\uparrow$ CD3 <sup>+</sup> CD28 <sup>-</sup> CD4 <sup>+</sup> $\uparrow$ CD3 <sup>+</sup> CD28 <sup>-</sup> CD8 <sup>+</sup>	Healthy controls
2012 Samson et al. [66]	12 PMR	CD4, CD161, Cd45RA, IL-17A, TNF $\alpha$ , CCR6, CD25, FoxP3	$\downarrow$ CD4 <sup>+</sup> CD25 <sup>high</sup> FoxP3 <sup>+</sup> $\uparrow$ CD4 <sup>+</sup> IL-17 <sup>+</sup> IFN $\gamma$ <sup>-</sup> $\uparrow$ CD4 <sup>+</sup> IL-17 <sup>+</sup> IFN $\gamma$ <sup>+</sup> $\downarrow$ CD4 <sup>+</sup> IL-17 <sup>-</sup> IFN $\gamma$ <sup>+</sup>	Healthy controls
2013 Dejacco et al. [69]	78 PMR	CD3, CD4, CD8, CD28, NKG <sub>2</sub> D, TNF $\alpha$ , INF $\gamma$ , IL-4, IL-10	$\uparrow$ CD8 <sup>+</sup> CD28 <sup>-</sup> $\uparrow$ CD4 <sup>+</sup> CD28 <sup>-</sup> $\uparrow$ NKG <sub>2</sub> D expressing T cells	Healthy controls
2014 Van der Geest et al. [70]	18 PMR	CD19, CD24, CD27, CD38, IgD, IgM, Ki-67, Bcl-2	$\downarrow$ CD19 <sup>+</sup> CD38 <sup>low</sup> CD24 <sup>low</sup> $\downarrow$ CD19 <sup>+</sup> CD38 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>+</sup> $\downarrow$ CD19 <sup>+</sup> CD38 <sup>+</sup> CD24 <sup>+</sup> IgM <sup>-</sup> $\downarrow$ CD19 <sup>+</sup> CD27 <sup>-</sup> IgD <sup>-</sup> $\downarrow$ CD19 <sup>+</sup> CD27 <sup>+</sup> CD38 <sup>high</sup> CD24 <sup>-</sup>	Healthy controls
2017 Carvajal Alegria et al. [72]	18PMR	CD3, CD4, CD8, CD19, CD27, IgD, CD24, CD38, CD16, CD56	$\downarrow$ CD19 <sup>+</sup> CD27 <sup>-</sup> IgD <sup>+</sup> $\downarrow$ CD19 <sup>+</sup> CD27 <sup>+</sup> IgD <sup>-</sup> $\downarrow$ CD19 <sup>+</sup> CD24 <sup>low</sup> CD38 <sup>low</sup> $\downarrow$ CD19 <sup>+</sup> CD24 <sup>high</sup> CD38 <sup>high</sup>	Healthy controls

PMR: polymyalgia rheumatic; GCA: giant cell arteritis; CD: cluster of differentiation; TNF:

tumor necrosis factor; IFN: interferon; Ig: immunoglobulin



**Figure 1: Schematic of polymyalgia rheumatica pathophysiology according to findings from blood samples and tissue samples.**