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Recommendations and metaanalyses

Recommendations of the French Society of Rheumatology for the management in current practice of patients with polymyalgia rheumatica

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ABSTRACT

Objective. – To develop recommendations for the routine management of patients with polymyalgia rheumatica (PMR).
Methods. – Following standard procedures, a systematic review of the literature by five supervised junior rheumatologists, based on the questions selected by the steering committee (5 senior rheumatologists), was used as the basis for working meetings, followed by a one-day plenary meeting with the working group (15 members), leading to the development of the wording and determination of the strength of the recommendations and the level of agreement of the experts.
Results. – Five general principles and 19 recommendations were drawn up. Three recommendations relate to diagnosis and the use of imaging, and five to the assessment of the disease, its activity and

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General corticosteroid therapy
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comorbidities. Non-pharmacological therapies are the subject of one recommendation. Three recommendations concern initial treatment based on general corticosteroid therapy, five concern the reduction of corticosteroid therapy and follow-up, and two concern corticosteroid dependence and steroid-sparing treatments (anti-IL-6).

Conclusion. – These recommendations take account of current data on PMR, with the aim of reducing exposure to corticosteroid therapy and its side effects in a fragile population. They are intended to be practical, to help practitioners in the day-to-day management of patients with PMR.

1. Introduction

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease manifested by arthromyalgia of the limbs and a biological inflammatory syndrome [in particular C-reactive protein (CRP)] in people over 50 years of age [1]. It is a common disease, with an estimated prevalence of 0.7% and an incidence of 0.6/100 person-years over 50 in the USA [2,3], with the incidence increasing between ages 50 and 80 years. The pathophysiology of this disease is not fully understood, but the involvement of immunosenescence on the one hand, and certain cytokines, notably interleukin 6, on the other, are among the elements recently implicated [4–6]. In the absence of currently validated diagnostic criteria, diagnosis is based on a combination of clinical, biological and imaging evidence. Diagnosis can be difficult in atypical forms, hence the importance of assessing the many differential diagnoses [1]. Classification criteria were proposed in 2012 [7], and may help with diagnosis. The value of ultrasound imaging and, more recently, positron emission tomography has also been highlighted, although the use of these techniques is not currently standardized or codified [8–10]. PMR is frequently associated with giant cell arteritis (GCA) (approximately 25% of cases), and these two conditions are part of the same disease spectrum [4,11,12].

Treatment is classically based on systemic corticosteroid therapy, tapered over 12 to 18 months until weaning, according to 2015 international recommendations [13], with more recent recommendations for a "treat to target" strategy [14]. Nearly half of patients with PMR develop one or more relapses during the tapering of corticosteroid therapy [14], and, at 2 and 5 years, the percentage of patients still on systemic corticosteroid therapy is 51% and 25%, respectively [15]. This prolonged exposure increases the risk of toxicity from general corticosteroid therapy, which is estimated to affect 85% of patients [14], especially as the frequency of comorbidities in patients with PMR is higher than in the general population [16,17], thereby further increasing the risk of side-effects from corticosteroid therapy in this population.

Recent events have drawn attention to the particular circumstances in which PMR may occur, particularly during treatment with immune checkpoint inhibitors [18], and also to new therapeutic approaches, in particular corticosteroid-sparing therapies [19,20].

All these factors have led the French Society of Rheumatology (SFR) to draw up recommendations for the management of patients with PMR in everyday practice.

These recommendations are aimed at doctors and all healthcare professionals involved in the management of patients with PMR. These recommendations will not concern the forms of GCA initially associated with PMR.

2. Methods

A group of French experts with two project leaders appointed by the SFR (DW, VDP) was created.

The recommendations were based on EULAR practices, which were used in the latest SFR recommendations [21]. A steering committee of five rheumatologists (DW, VDP, ED, EM, AS) was set up, responsible for identifying the main current issues.

An expert group of 15 rheumatologists and other specialists with expertise in the management of PMR was formed by the steering committee.

The literature review was carried out by five young university hospital rheumatologists, under the supervision of a member of the steering committee, using BIBOT [22] software and a methodology based on analysis of the Pubmed-Medline, Cochrane, Embase and Databases literature using identified keywords.

Smaller groups of experts (3 experts) were responsible for one or two major questions. Meetings were organized in the presence of all the groups to present the results of the literature review and the proposals of the sub-groups, and then to draw up the initial recommendations by all the experts divided into working groups. Finally, discussions on reformulations, cancellations and additions, based on published data and the literature review, were held between experts at a collegial face-to-face meeting, with at least 75% agreement recommended.

Remotely, the text of the recommendations was submitted to the same experts for validation and scoring of the degree of agreement (visual scale from 0 to 10, where 0 = no agreement at all, and 10 = complete agreement).

3. Results

The steering committee selected nine groups of questions, which were the subject of a literature review and recommendations based on the answers provided:

- Q1: What additional tests should be suggested when diagnosing PMR?
- Q2: What use should be made of complementary tests, in particular ultrasound, PET-CT and MRI?
- Q3: What assessment should be made of disease activity and prognostic factors for response?
- Q4: What is the strategy for initiating corticosteroid therapy?
- Q5: What is the strategy for reducing corticosteroid therapy/defining corticosteroid dependence?
- Q6: What treatments allow either control of the activity of PMR or overall corticosteroid sparing?
- Q7: What is the strategy for using these treatments?
- Q8: How are complications of PMR and/or treatments monitored (what are the complications of corticosteroid therapy? How can they be prevented? What are the prognostic criteria?)?
- Q9: What are the procedures for monitoring a patient suffering from PMR?

The final result comprises five general principles and 19 groups of recommendations.

Table 1
Differential diagnosis.

Other chronic inflammatory rheumatic diseases	• Microcrystalline rheumatism, particularly CPPD • Rheumatoid arthritis in the elderly • Edematous polyarthritis in the elderly (RS3PE) • Spondyloarthritis of the elderly (LOPS)
Other inflammatory diseases	• Myositis • Connective tissue diseases • Cancers, myeloma, lymphoma • Infections (endocarditis)
Non-inflammatory diseases	• Parkinson disease • Dysthyroidism • Osteomalacia, hyperparathyroidism • Iatrogenic (statins, beta-blockers, immunological checkpoint inhibitors, etc.)
Mechanical conditions	• Rotator cuff • Osteoarthritis • Capsular retraction

The strength (based on the level of evidence) and degree of agreement of the experts (see above) are indicated for each recommendation. For memory, A corresponds to level 1 evidence (meta-analysis based on randomized controlled trials or at least one randomized controlled trial); B: level 2 evidence (at least one non-randomized controlled trial or quasi-experimental study) or extrapolated from level 1 evidence; C: level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence; and D: level 4 evidence (expert opinion) or recommendation extrapolated from level 1, 2 or 3 evidence.

3.1. General principles

A. Polymyalgia rheumatica (PMR) is a non-destructive inflammatory arthromyalgia of the limbs, with elevated CRP, affecting patients over 50 years of age, and which may be associated with giant cell arteritis (GCA) throughout its course.

This principle is an introduction to a classic general fact [1,4,12]. The potential association to GCA is recalled, with a range of incidence of two to 78 cases of GCA presenting after PMR per 1000 person-years [1,4].

B. It is essential to rule out differential diagnoses.

In fact, 25% to 45% of initial diagnoses of PMR appear to be erroneous and are not confirmed at one year [23,24]. This process should also be carried out in the event of a new evaluation in the absence of a therapeutic response to corticosteroids. The classic differential diagnoses are summarized in Table 1 [1].

C. PMR is a potentially curable disease requiring personalized, multidisciplinary pharmacological and non-pharmacological management, taking into account comorbidities and the risks of treatment side effects.

This principle underlines the interest and broad outlines of early and comprehensive management of the disease.

D. Rheumatological expertise is essential, both for early diagnosis and for the organization of treatment in close collaboration with the general practitioner.

Recent studies have emphasized the benefits of rapid referral to a rheumatologist, improving diagnostic performance, with lower initial doses of corticosteroids and a lower rate of hospitalizations [25,26]. Rapid referral has been the subject of recent international recommendations [27]. This task force recommends a referral within one week in case of suspected PMR with severe symptoms [27]. The rheumatological expertise is also requested during the follow-up.

E. Treatment is based on corticosteroid therapy. No corticosteroid-sparing treatment currently has marketing authorization in France. The prescription of targeted treatments should only be considered after a collegiate decision has been taken and is intended to allow corticosteroid sparing.

The panel felt that these last two general principles were essential for organizing the practical management of patients with PMR.

3.2. Recommendations

Recommendation 1
The diagnosis of PMR is based on the presence of inflammatory pain in the girdles, an elevated CRP in a patient over 50 years old and the exclusion of differential diagnoses (D).

There are no diagnostic criteria for PMR; this wording follows the classic presentation in current practice, leading to the diagnosis being discussed. The classification criteria [7] can provide diagnostic assistance. The exclusion of differential diagnoses (Table 1) [1,27] is an important step in the approach, already indicated in the general principles. It may require the use of additional investigations depending on the situation (Table 2, Fig. 1). The classical presentation associates stiffness and inflammatory aching of shoulder and pelvic girdle and in the neck, systemic manifestations (weight loss, fever, fatigue, depression, etc.) in up to 40% of the cases, and distal musculoskeletal manifestations in about 50% of patients (pain and swelling of wrists and/or knees, less frequently metacarpophalangeal involvement and distal extremity swelling, carpal tunnel syndrome). CRP is elevated in 99% of the cases of untreated patients at diagnosis [1].

Recommendation 2
In case of typical presentation, except for radiographs of affected sites, no systematic imaging examination is required for diagnosis (D).

The diagnosis is based on clinical elements; standard imaging is part of the classic rheumatological work-up, useful in particular

Table 2
Initial assessment.

	Examination	Indication Diagnosis	Possible pre-therapeutic assessment
Biology	CRP	X	X
	Blood count	X	X
	Alkaline phosphtases, transaminases	X	X
	Vitamin/phosphocalcic assessment	X	X
	ACPA/RF	X	X
	CPK	X	
	TSH	X	
	ANA	X	
	Protein electrophoresis	X	
	Serologies HIV, HBV, HCV, quantiferon		
	Fasting blood glucose (HbA1c)		
	Lipid profile		
	BU		
Imaging	X-rays of the shoulders and pelvis ± joint	X	
	ultrasounds	X	

CRP: C-reactive protein; ACPA/RF: anti-citrullinated peptide antibodies/rheumatoid factor; CPK: creatine phosphokinase; TSH: thyroid stimulating hormone; ANA: anti-nuclear antibodies; BU: urine strip deepstick.

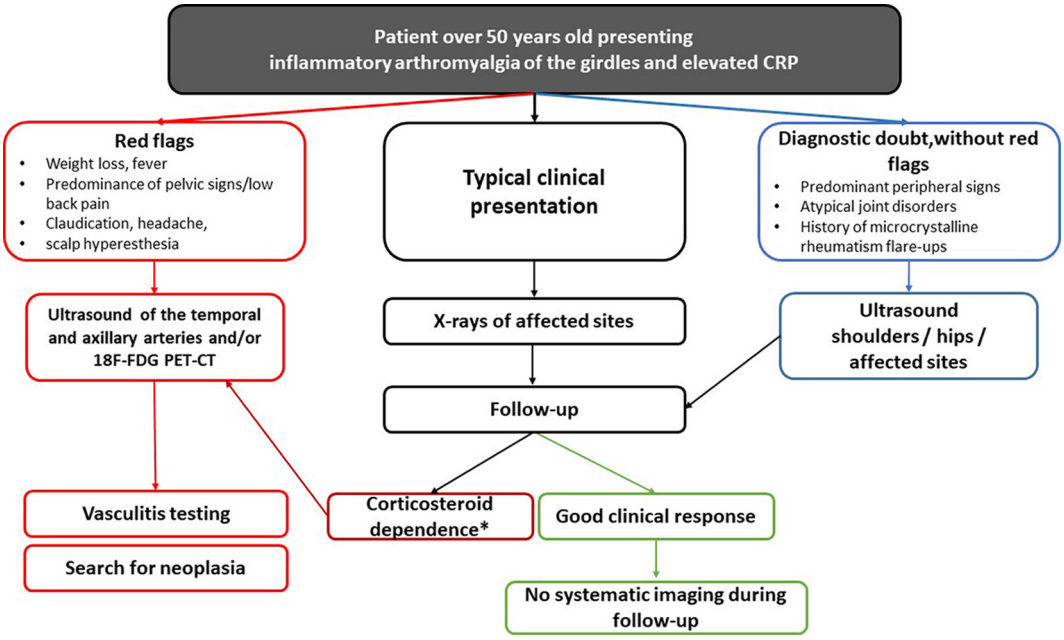

Fig. 1. Use of imaging in PMR. *see recommendation 17 for definition.

for differential diagnosis (rotator cuff tear, calcium pyrophosphate deposition disease).

Recommendation 3

- In case of diagnostic doubt and/or atypical clinical presentation, ultrasound of the joints or vessels, 18F-FDG PET-CT or MRI may be indicated (C).
- In the event of clinical manifestations suggesting large vessel vasculitis or a neoplastic lesion, ultrasound of the vessels or 18F-FDG PET-CT should be offered (C).

This recommendation concerns the use and place of imaging examinations (Fig. 1).

3.2.1. Ultrasound mode B and Doppler of the affected joints

The ultrasound abnormalities most frequently visualized during the diagnosis of PMR are subacromiodeltoid bursitis and tenosynovitis of the long biceps, while trochanteric bursitis, glenohumeral synovitis and coxofemoral synovitis are less frequently detected [28]. The good diagnostic performance of ultrasound, with on average a sensitivity of 66% (36% to 87%) and a specificity of 89% (66% to 97%) for bilateral subacromial bursitis, its accessibility and daily use for many rheumatologists, make it a test of choice [29]. In addition, ultrasound signs have been integrated into the ACR/EULAR classification criteria for PMR [7] and this integration seems to improve the specificity of the clinical criteria. Ultrasound also represents an interesting examination to rule out certain differential diagnoses. Thus, several studies have shown the benefit of ultrasound in cases of diagnostic doubt. Calcium pyrophosphate deposition disease

Table 3
Clinical signs to look for GCA during PMR (red flags).

General signs	Symptoms	Abnormalities on physical examination
• Alteration of general condition (anorexia, asthenia, weight loss) • Fever • Night sweats	• Temporal or occipital headaches • Sign of the comb, the pillow • Scalp hyperesthesia • Jaw claudication • Visual disturbances - Amaurosis transitory - Diplopia - Visual blur • Otalgia • Cough • Arterial claudication of upper/lower limbs	• Anomaly of the temporal arteries - Induration - Pulse not felt - Pain • Peripheral pulse abnormalities (decrease or absence) • Arterial murmur • Aortic insufficiency murmur • Blood pressure asymmetry

should be suspected in cases of glenohumeral erosion and involvement of the acromioclavicular joint and rheumatoid arthritis seems more likely in cases of wrist involvement [30].

3.2.2. Positron emission tomography-computed tomography (PET-CT) with 18F-fluorodeoxyglucose (FDG)

This additional examination allows the simultaneous visualization of different sites of interest, particularly at the spinal and muscular level. In the literature, the diagnostic performance of this examination is very good (subject to a comparison most often with predominantly oncological populations) with an average sensitivity estimated at 86% at the level of the ischial tuberosities and an average specificity estimated at 81% for interspinous bursitis [31]. In addition, 18F-FDG PET-CT seems to improve the diagnostic performance of clinical criteria and also allows the detection of possible subclinical vasculitis. Indeed, 18F-FDG PET-CT reveals large vessel arteritis in nearly 25% of patients with genuine PMR [12]. The identification of such a feature would modify the initial management with a dose adjustment of corticosteroid therapy and would determine the monitoring of risks specific to vascular inflammation. Cancer is one of the other conditions to be ruled out when treating a patient presenting with PMR; the risk of discovering cancer is rare but increased by 69% during the first 6 months following diagnosis [32]. Some cancers are incidents and not related to the PMR symptoms but others are more related to the manifestations (haematologic neoplasia). However, in a recent study, no significant difference was observed between 18F-FDG PET-CT and chest radiography combined with abdominal ultrasound for the detection of neoplasia [33]; 18F-FDG PET-CT thus seems interesting in certain specific situations and in particular when the initial clinical presentation includes atypical elements suggesting vasculitis or a neoplastic lesion (alteration of general condition, fever, predominance of pelvic signs/low back pain, claudication, headache, hyperesthesia of the scalp) (Table 3) [12].

All of these elements suggest that the use of whole-body 18F-FDG PET-CT is possible when diagnosing PMR. This use cannot be systematic, in particular because of its high cost, and should be limited to cases with warning signals (Fig. 1). If an 18F-FDG PET-CT is performed, this should ideally be performed without corticosteroid therapy or within the first 10 days of treatment (at best within 3 days) in a patient whose blood sugar level ideally does not exceed 7 mmol/L (up to 11 mmol/L tolerated). Performing a 18F-FDG PET-CT seems essential in cases of steroid resistance or steroid dependence to rule out vascular damage or neoplasia. Such imaging procedure is interesting to promote in a fast track procedure of PMR diagnosis based on each patient symptoms.

3.2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a powerful examination during PMR, allowing the identification of articular and extra-articular damage and having good diagnostic performance [34]. However, the visualization of a single anatomical region as well as its reduced availability make this examination less interesting than ultrasound or 18F-FDG PET-CT. MRI can, however, constitute a satisfactory alternative in certain difficult clinical situations but remains limited by accessibility difficulties and its cost.

Recommendation 4
The therapeutic objective must be to achieve remission without treatment, defined by the absence of pain and inflammatory syndrome linked to PMR (D).

This therapeutic objective is common to all inflammatory rheumatic diseases; it is the target of the "treat to target" concept [14]. The pragmatic definition proposed can be supplemented by the evaluation of an activity score (PMR-AS < 10) (see below, Recommendation 8) and absence of GCA symptoms.

Recommendation 5
At diagnosis and throughout PMR monitoring, it is imperative to look for clinical signs of arterial damage (GCA) (B).

Already mentioned in the general principles, this possibility is recalled in the form of a recommendation, subclinical arterial damage can be associated with PMR in nearly 25% of cases [4,11,12]. Certain clinical clues can point the way (Table 3). In the event of arterial damage, it is a GCA, requiring specific treatment [35–38].

There is currently no scientific data to prove that the incidental discovery of subclinical GCA, particularly in 18F-FDG PET-CT, requires a dose adaptation of corticosteroid therapy. However, the group of experts recommends this attitude in particular when discovering hypermetabolism of large vessels.

Recommendation 6
In case of PMR, the patient's comorbidities, risk factors for side effects of corticosteroid therapy and the frailty syndrome must be assessed and management proposed according to current recommendations (B).

Comorbidities are common in populations over 50 years of age, with a higher prevalence in patients with PMR compared to the general population and increasing under treatment [16,17]. These elements must be evaluated at diagnosis and during treatment (Box 1), with, alongside the classic factors, the frailty syndrome [39] (Table 4), concerning nearly one in five patients with PMR [40].

The side effects (SE) of corticosteroid therapy, even at small doses, are classic and must be prevented. A systematic review [41] quantified the risk of SE of corticosteroids at low to medium doses (equivalent to 30 mg of prednisolone) for more than a month in chronic inflammatory diseases including PMR. In patients with PMR (4 studies, 167 patients), the rate of SEs was 80/100 patient years (95% CI 15 to 146) and the most commonly reported SEs were gastro-intestinal, endocrine and metabolic, cardiovascular, infectious and psychiatric [41].

3.2.4. Cardiovascular risks

A systematic review [42] of observational studies was carried out to compare cardiovascular risk (coronary risk) in patients with

Box 1
Comorbidities and risk factors for side effects of corticosteroid therapy
Research and management of comorbidities or risk factors is recommended in particular if:

- Psychiatric disorders: history of psychiatric illness or psychiatric disorders during previous corticosteroid therapy
- Identification of osteoporosis risk factors and pre-existing fractures
- Hypertension, diabetes, glucose intolerance, cardiovascular diseases, dyslipidemia, ulcer, complicated diverticulosis
- Presence (or risk factors) of cataract or glaucoma
- Presence of chronic or recurrent infections
- Frailty syndrome

Table 4
Definition of frailty syndrome in the elderly according to Fried.

Criteria	Description
Unintentional weight loss	Unintentional loss of > 4.5 kg in the last 12 months
Fatigue	The person feels that everything they do requires effort, or that they can no longer do what they used to do; and this often, frequently or most of the time. Subjective fatigue, originally assessed from two questions included in the CES-D depression questionnaire
Low level of physical activity	Very low energy expenditure, estimated on the basis of a questionnaire[a] Corresponds to a very sedentary person, who does not do any regular physical activity
Muscular weakness	Defined by a very low grip test force, measured with a dynamometer (in the lower 20th percentile). Threshold values adjusted according to sex and BMI: between 17 and 21 kg in women, between 29 and 32 kg in men
Slow walking speed	> 7 seconds to cover 4.5 m, at your usual walking speed, or > 6 seconds, if height > 159 cm for women, > 173 cm for men
0 criteria met: Robust elderly person 1 or 2 criteria met: Pre-frail elderly person 3 or more criteria met: Frail elderly person	

[a] In the bottom 20th percentile, by age, of the Minnesota Leisure Time Activity Questionnaire (MLTAQ).

PMR (out of 34,569 patients) compared to subjects without PMR. The adjusted combined hazard ratio for coronary artery disease in PMR patients was 1.72 (95% CI 1.21–2.45).

3.2.5. Metabolic risks

In a meta-analysis [43], the frequency of diabetes occurring during treatment with corticosteroids was 6% (95% CI 3% to 9%) in patients with RA and 13% (95% CI 9% to 17%) in patients with GCA/PMR, raising the interest in screening for corticosteroid-induced diabetes, in particular by measuring HbA1c. The data from the studies are quite heterogeneous but there seems to be an increased risk of metabolic syndrome and cardiovascular diseases in PMR taking corticosteroids.

3.2.6. Infectious risks

A primary care study of a retrospective cohort conducted in England confirms the excess risk of infection (all infections combined) with an incidence of 160.7 (95% CI 159.3–162.2) per 1000 patients/year [42,44]. The cumulative risk of infection increases with the higher daily dose of corticosteroids. The most frequently diagnosed types of infections were lower respiratory tract infections (27.3%), conjunctivitis (8.6%), and shingles (7.4%). The most common causes of infection related death were pneumonia (52.6%), urinary tract infections (3.0%).

3.2.7. Psychiatric risk and poor tolerance

We must not ignore the well-known but poorly quantified psychiatric risk, to be looked for in the history. Patients sometimes describe significant symptoms of intolerance (nervousness, sleep problems, etc.), which should not be underestimated and impact compliance [45].

Recommendation 7
Screening and systematic prevention of osteoporosis must be carried out from diagnosis, including measurement of bone mineral density (BMD) (A).

Due to age and exposure to systemic corticosteroid therapy, osteoporosis represents a major risk during PMR. A national Italian multicenter cross-sectional and longitudinal observational study (The Glucocorticoid Induced OsTeoporosis TOol, GIOTTO Study) included 553 patients under chronic corticosteroid treatment and suffering from rheumatoid arthritis (RA), PMR or connective tissue disease (CTD). This study shows a prevalence of a history of clinical fractures before any treatment with corticosteroids, in 12%, 37% and 17% of patients suffering from CTD, PMR or RA respectively. During corticosteroid treatment, new clinical fractures were reported in 12%, 10% and 23% of patients suffering from CTD, PMR and RA, respectively [46].

It is therefore appropriate to implement the national recommendations published on this subject [47], and in most cases to treat patients to avoid corticosteroid-induced osteoporosis.

Recommendation 8
Assessment of disease activity must be carried out at each visit using a validated tool (PMR-AS) (A).

The PMR Activity Score (PMR-AS) (Fig. 2) is a score, which has shown a good correlation with the clinical and biological parameters of PMR [48,49]. It is calculated as follows: CRP (mg/dl) + VAS pain by the patient (0–10) + VAS activity by the doctor (0–10) + DMS (min) × 0.1 + EMS (0–3) (DMS: duration of morning stiffness and EMS: elevation of the upper limbs) [48].

This score makes it possible to classify disease activity into low (score < 7), intermediate (between 7 and 17) and high (> 17) [48]. Remission is defined as a score < 1.5 [50]. The definition of relapse has been shown to have good sensitivity and specificity if the score > 9.35 or if there is an increase in the score ≥ 6.6 between two assessments [51]. It also helps guide the prescription of corticosteroid therapy in a prospective study carried out by private and hospital rheumatologists [52]. It has been demonstrated that the PMR-AS can be used by general practitioners with good agreement with rheumatologists on the study of clinical vignettes [53].

It has been proposed to simplify this score as follows: low activity < 10, intermediate between 10 and 20, high activity > 20. Studies have shown that these thresholds make it possible to guide

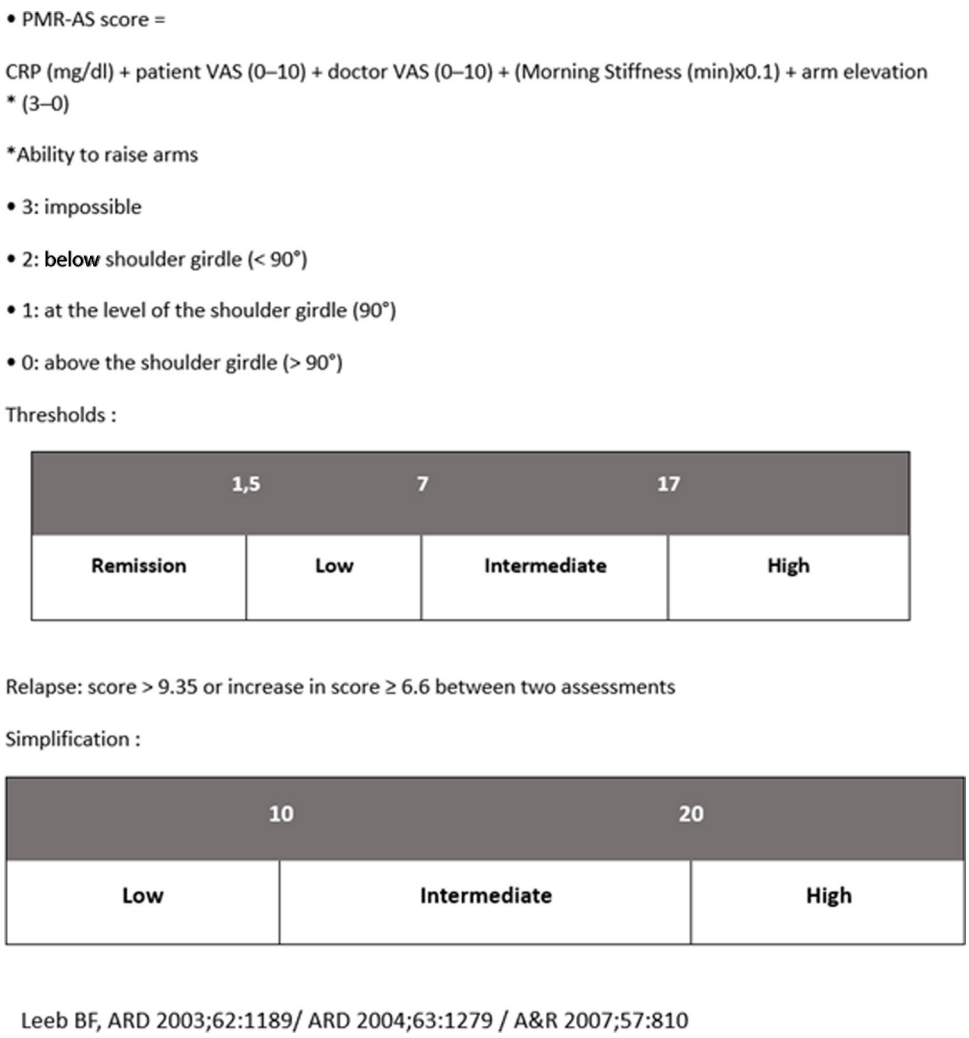

Fig. 2. Activity and therapeutic response criterion: PMR-AS.

the management of corticosteroid therapy in daily practice and allow diagnosing a relapse [51,52]. Furthermore, in a national prospective study, few patients had a PMR-AS value between 7 and 10 or between 17 and 20 [52].

Recommendation 9

Non-pharmacological therapy must be associated from the diagnosis (education/information, physical activity, individualized exercises, hygiene and diet rules, fight against sarcopenia and prevention of falls) (D).

These non-pharmacological means are important for monitoring treatment and preventing complications of corticosteroid therapy. They are to be applied throughout the disease as part of overall care [54,55]. Sarcopenia is observed in 26% of patients diagnosed with PMR, within 12 months of diagnosis and treated with corticosteroids [38]. Therapeutic education will remind people of the need not to abruptly interrupt corticosteroid treatment without medical advice, and what to do if side effects appear. It will also provide information on the potential risk of adrenal insufficiency during the decline and especially after stopping general corticosteroid therapy.

Recommendation 10

Pharmacological treatment is based on general corticosteroid therapy, with a recommended initial dose of 0.2 to 0.3 mg/kg/day of prednisone, adapted to comorbidities and disease activity (C).

This statement recommends low doses of prednisone at the initiation of treatment for isolated PMR, in accordance with previous recommendations suggesting an initial dosage between 12.5 and 25 mg/day [13]. The group wanted to favor a dosage based on weight to be closer to practice and to emphasize the difference with the management of GCA for which the initial doses are higher. Lower doses reduce the risk of SEs from corticosteroid therapy [56]. On the other hand, it has been suggested that higher initial doses are associated with a greater risk of subsequent relapses when tapering [57], with each 5 mg increase in initial dose being associated with a 7% increase of the subsequent risk of relapse. Prednisone is the molecule favored by the group due to its manageability and effectiveness (expert opinion). In a study including 60 PMR treated with an initial dose of 12.5 mg/day of prednisone, 78% of patients responded after a mean interval of 6.6 days (standard deviation 5.5 days). The mean daily dose of prednisone per kg in responders was

0.19 ± 0.03 mg and 0.16 ± 0.03 mg in non-responders ($P = 0.007$) [58].

Recommendation 11
At PMR diagnosis, tocilizumab can be used if rapid withdrawal (3 months) of corticosteroids is necessary, or exceptionally as monotherapy if it is necessary to avoid corticosteroid therapy, after collegial discussion. Failing that, methotrexate is an alternative (B).

This recommendation is based on published study data.

Tocilizumab is an anti interleukin-6 receptor (IL-6R) monoclonal antibody. The PMR-SPARE study, a randomized, placebo-controlled trial including 36 patients, demonstrated the effectiveness of tocilizumab (162 mg per week subcutaneously) [59]. The primary endpoint, remission (absence of stiffness linked to PMR) without corticosteroids at week 16, was obtained for 63.2% of patients on tocilizumab and 11.8% of patients on placebo ($P = 0.002$). At 24 weeks, the cumulative dose of corticosteroids was 781 mg in the tocilizumab group and 1290 mg in the placebo group ($P = 0.001$). In the PMR-SPARE study, corticosteroids were weaned within 12 weeks. In an open phase 2a study, tocilizumab (8 mg/kg/month intravenously) made it possible to obtain corticosteroid withdrawal in 4 months and remission without relapse at 6 months in nine out of ten patients included (the 10th having stopped the study after 2 months) [60].

The effectiveness of methotrexate as a corticosteroid-sparing treatment in early polymyalgia rheumatica is demonstrated, although modest, in the two randomized, blinded, placebo-controlled studies [61,62] and in one randomized trial without placebo [63]. An effect on corticosteroid sparing was observed from 12 to 16 months [62]. Early cessation of corticosteroid therapy (less than 6 months of treatment) through the use of methotrexate has not been demonstrated. Stopping methotrexate after one year does not allow long-term remission to be maintained [64]. A meta-analysis of two controlled trials supports the effectiveness of methotrexate for remission [65]. Tolerance was good, at low doses (7.5–10 mg per week), in PMR.

The use of tocilizumab alone (8 mg/kg per month, intravenously), without the use of corticosteroids, in recent PMR has only been evaluated in open studies [66,67]. In the first study (TENOR), 20 of the 20 patients included obtained a PMR-AS less than or equal to 10 after 12 weeks of treatment (primary endpoint) [66], with a very low number of relapses upon stopping the treatment with tocilizumab, and substantial corticosteroid sparing (70%). In the second study, four of the 13 patients included obtained a PMR-AS less than 1.5 after 12 weeks of treatment (primary endpoint) [67]. However, ten of the 13 patients had a PMR-AS less than 10 at week 12 and only two patients had to receive corticosteroids due to ineffectiveness of tocilizumab.

No therapeutic trial has compared a strategy using methotrexate versus an anti-IL-6 receptor monoclonal antibody. There are no specific data in populations of very elderly patients or those suffering from a frailty syndrome. The infectious risk inherent to immunosuppressants must be taken into account. The contraindications of these targeted treatments should be followed and the cost of these treatments should be taken into account, particularly in comparison to methotrexate.

Recommendation 12
The lack of response to initial corticosteroid therapy must lead to a reassessment of a) the dose administered; b) compliance; c) the diagnosis of PMR (D).

Table 5
Tapering profile of corticosteroid therapy over 6 months depending on the initial dose.

W0	W2	W4	W6	W8	W12	W16	W20	W24
30	25	20	15	10	9	8	7	6
25	20	15	12.5	10	9	8	7	6
20	15	12.5	10	9	8	7	6	5
17.5	15	12.5	10	9	8	7	6	5
15	12.5	10	9	8	7	6	5	4
12.5	10	9	8	7	6	5	4	3
10	9	8	7	6	5	4	3	2

After week 24: decrease of 1 mg every month.

The good clinicobiological response to well-conducted corticosteroid therapy is a classic constant, often considered as confirmation of the diagnosis. True corticosteroid resistance (absence of improvement after sufficient follow-up, with correct compliance and appropriate dosage) requires reconsideration of the diagnosis.

Recommendation 13
The cumulative dose of corticosteroids must be as low as possible in order to avoid iatrogenic complications by using a strategy of adaptation of treatments according to the activity criteria of PMR and the comorbidities of the patient (B).

This recommendation highlights the notion of cumulative dose, often used to assess the risks of side effects, and in studies to analyze the corticosteroid-sparing effect of certain treatments. It underlines, at this stage of the treatment process, the group's constant concern to reduce overall exposure to corticosteroid therapy throughout this illness.

Recommendation 14
The duration of corticosteroid therapy is 12 months (with an initial dose not exceeding 0.3 mg/kg/d). The dose of 10 mg should be reached between 4 and 8 weeks, followed by a monthly decrease of 1 mg until complete cessation (B).

The ideal expected duration is 12 months. In this formulation, the group proposes to mark the decrease in general corticosteroid therapy [68], taking up the 2015 international recommendations [13] while proposing target stages with a re-evaluation by the rheumatologist and a concrete decrease plan usable in practice and detailed in Table 5. Short exposure and low doses reduce the risk of side effects and adrenal insufficiency.

Recommendation 15
Reassessments should be planned, within the first 4 weeks following the start of treatment, then every 4 to 12 weeks until remission without treatment is achieved (D).

Monitoring patients with PMR is fundamental, particularly under treatment, to assess its effectiveness and tolerance and adapt the tapering schedule. Poor tolerance may impair therapeutic observance. The practical modalities of this re-evaluation follow-up must take into account the contingencies of current medical activity (appointment times, accessibility, geographical distance, etc.) and can be optimized by close collaboration between the general practitioner and the rheumatologist, but also through simplified options such as telephone contact or teleconsultation. An initial

re-evaluation in the first 4 weeks of treatment is particularly important to validate/authenticate the clinical and biological response (with a PMR-AS < 10) and initiate and explain the prednisone-tapering program. The following steps make it possible to check whether the response is maintained during the decline, adapt the treatment according to relapses/flares and tolerance. Follow-up after the end of corticosteroid therapy may be considered, in particular with regard to the theoretical risk of post-steroid therapy adrenal insufficiency. The latter is little studied in PMR, with a prevalence estimated at 11% based on biological assays [69].

Recommendation 16
In the event of a first flare-up during corticosteroid therapy tapering, it is recommended to return to the previous dose on which the patient was asymptomatic (D).

This expert opinion (with the aim of reducing exposure to corticosteroid therapy) was proposed as a recommendation due to the observation, too frequent in practice, of too significant re-escalation (or even a resumption of the initial dose) of the dose of prednisone in the event of reappearance of symptoms during of the decrease.

Recommendation 17
In the case of corticosteroid dependence, defined by the appearance of more than one flare-up/relapse of PMR (clinical and biological), preventing a decrease below the threshold of 5 mg/day, a corticosteroid-sparing strategy must be considered after collegial discussion (C).

Such a situation, characterized by the inability to decrease corticosteroids following good practice guidelines, is not exceptional and reflects the observation of the high number of patients still on corticosteroid therapy after 2 or even 5 years of treatment [14]. This recommendation proposes a pragmatic definition of corticosteroid dependence in PMR. The dose of 5 mg/day represents the threshold beyond which the complications of long-term corticosteroid therapy are significantly increased [70].

Recommendation 18
In PMR, in cases of corticosteroid dependence/inability to decrease corticosteroids, tocilizumab or sarilumab after collegial discussion (A), or failing that, methotrexate (C), can be used for 6 to 12 months to achieve corticosteroid withdrawal.

In the event of failure to wean corticosteroids according to a decreasing rate respecting the recommendations, the therapeutic strategy must be adapted.

The randomized, placebo-controlled SEMAPHORE trial [20] demonstrated the effectiveness of tocilizumab (8 mg/kg per month, intravenously) in corticosteroid-dependent PMR. The study included 100 patients. The main endpoint, based on clinical activity (PMR-AS less than or equal to 10 after 24 weeks of treatment) and corticosteroid sparing (withdrawal or significant reduction in the daily dose), was obtained for 67.3% of patients in the tocilizumab group and 31.4% of patients in the placebo group ($P < 0.001$). There is currently no marketing authorization for tocilizumab in PMR.

The SAPHYR randomized, placebo-controlled trial demonstrated the effectiveness of sarilumab, another anti IL-6R monoclonal antibody (200 mg every 2 weeks, subcutaneously), in active or corticosteroid-resistant PMR. This study was terminated prematurely due to the COVID-19 pandemic. The study included 118 patients out of the 280 planned and 78 patients received complete treatment. The main endpoint, remission at 3 months, maintained at one year, with compliance with the corticosteroid taper protocol, was achieved in 28.3% of cases in the sarilumab group and 10.3% in the placebo group ($P = 0.019$) [71]. Sarilumab has marketing authorization in PMR relapsing on corticosteroids in the United States.

Data concerning the effectiveness of methotrexate in relapsed or corticosteroid-dependent polymyalgia rheumatica come from observational studies [72,73]. No therapeutic trial has compared a strategy using methotrexate versus an anti-IL-6 receptor monoclonal antibody.

There are no specific data in populations of very elderly patients (> 85 years) or those suffering from a frailty syndrome. The infectious risk inherent to immunosuppressants must be taken into account, as well as the economic impact.

Based on these elements, experts consider that tocilizumab or sarilumab are effective in achieving corticosteroid withdrawal in corticosteroid-dependent or relapsed PMR. Despite the absence of a prospective controlled trial, experts consider that methotrexate can be offered as an alternative, based on the data available in early PMR. Experts consider that the use of a corticosteroid-sparing treatment should allow an ambitious goal of weaning off corticosteroids in 3 to 6 months. Despite the limited clinical data available, experts suggest that stopping corticosteroid-sparing treatment should be considered between 6 and 12 months in recent PMR (TENOR) [66] and after 12 months in corticosteroid-dependent PMR [19], remembering that the negativation of CRP under anti IL-6 receptor will interfere with biological monitoring and therefore the evaluation of disease activity and with the notion of relapse. The methods for stopping these corticosteroid-sparing treatments remain to be defined in the absence of data from studies. In retrospective analysis, reducing doses or spacing injections seems to result in fewer subsequent relapses than abrupt cessation of the anti IL-6 R [19]. In all cases, the balance between benefit and SEs must be evaluated.

Recommendation 19
Systematic monitoring by imaging is not indicated (B).

Concerning follow-up, ultrasound does not seem to correlate with clinical improvement and repeating the examination is not recommended [74]. The use of 18F-FDG PET-CT is not recommended during follow-up in the event of a satisfactory clinical response, as studies show no correlation between clinical and iconographic improvement [75]. On the other hand, in a situation of corticoresistance or corticodependence, 18F-FDG PET-CT must be considered (Fig. 1).

4. Discussion

This manuscript reports the results of the development of the first recommendations of the French Society of Rheumatology for the management of patients with PMR, summarized in Table 6. These recommendations take into account all stages of the management of a patient suffering from PMR, with the initial process of confirming the diagnosis and evaluating the disease and the situation (comorbidities).

Table 6
Summary of the general principles and recommendations.

	Wording	Level of evidence	Degree of agreement. Average (SD)
General principles			
A	PMR is a non-destructive inflammatory arthromyalgia of the limbs, with elevated CRP, affecting patients over 50 years of age, and which may be associated with GCA throughout its course		9.6 (1.0)
B	It is essential to rule out differential diagnoses		9.4 (1.0)
C	PMR is a potentially curable disease requiring personalized, multidisciplinary pharmacological and non-pharmacological management, taking into account comorbidities and the risks of treatment SEs		9.6 (0.6)
D	Rheumatological expertise is essential, both for early diagnosis and for the organization of treatment in close collaboration with the general practitioner		9.6 (1.1)
E	Treatment is based on corticosteroid therapy. No corticosteroid-sparing treatment currently has marketing authorization in France. The prescription of targeted treatments should only be considered after a collegiate decision has been taken and is intended to allow corticosteroid sparing		9.5 (0.6)
Recommendations			9.6 (0.6)
1	The diagnosis of PMR is based on the presence of inflammatory pain in the girdles, an elevated CRP in a patient over 50 years old and the exclusion of differential diagnoses	D	9.6 (0.6)
2	In case of typical presentation, except for radiographs of affected sites, no systematic imaging examination is required for diagnosis	D	9.1 (1.4)
3	In case of diagnostic doubt and/or atypical clinical presentation, ultrasound of the joints or vessels, 18F-FDG PET-CT or MRI may be indicated. In the event of clinical manifestations suggesting large vessel vasculitis or a neoplastic lesion, ultrasound of the vessels or 18F-FDG PET-CT should be offered	C	9.3 (1.4)
4	The therapeutic objective must be to achieve remission without treatment, defined by the absence of pain and inflammatory syndrome linked to PMR	D	9.6 (0.7)
5	At diagnosis and throughout PMR monitoring, it is imperative to look for clinical signs of arterial damage (GCA)	B	9.7 (0.4)
6	In case of PMR, the patient's comorbidities, risk factors for SEs of corticosteroid therapy and the frailty syndrome must be assessed and management proposed according to current recommendations	B	9.8 (0.3)
7	Screening and systematic prevention of osteoporosis must be carried out from diagnosis, including measurement of BMD	A	9.7 (0.5)
8	Assessment of disease activity must be carried out at each visit using a validated tool (PMR-AS)	A	9 (1.1)
9	Non-pharmacological therapy must be associated from the diagnosis (education/information, physical activity, individualized exercises, hygiene and diet rules, fight against sarcopenia and prevention of falls)	D	9.6 (0.6)
10	Pharmacological treatment is based on general corticosteroid therapy, with a recommended initial dose of 0.2 to 0.3 mg/kg/day of prednisone, adapted to comorbidities and disease activity	C	9.7 (0.4)
11	At PMR diagnosis, tocilizumab can be used if rapid withdrawal (3 months) of corticosteroids is necessary, or exceptionally as monotherapy if it is necessary to avoid corticosteroid therapy, after collegial discussion. Failing that, methotrexate is an alternative	B	8.9 (1.5)
12	The lack of response to initial corticosteroid therapy must lead to a reassessment of: a) the dose administered; b) compliance; c) the diagnosis of PMR	D	9.5 (1.0)
13	The cumulative dose of corticosteroids must be as low as possible in order to avoid iatrogenic complications by using a strategy of adaptation of treatments according to the activity criteria of PMR and the comorbidities of the patient	B	9.7 (0.5)
14	The duration of corticosteroid therapy is 12 months (with an initial dose not exceeding 0.3 mg/kg/d). The dose of 10 mg should be reached between 4 and 8 weeks, followed by a monthly decrease of 1 mg until complete cessation	B	8.8 (1.4)
15	Reassessments should be planned, within the first 4 weeks following the start of treatment, then every 4 to 12 weeks until remission without treatment is achieved	D	9.1 (0.9)
16	In the event of a first flare-up during corticosteroid therapy tapering, it is recommended to return to the previous dose on which the patient was asymptomatic	D	9.6 (0.5)
17	In the case of corticosteroid dependence, defined by the appearance of more than one flare-up/relapse of PMR (clinical and biological), preventing a decrease below the threshold of 5 mg/day, a corticosteroid-sparing strategy must be considered after collegial discussion	C	9.5 (0.6)
18	In PMR, in cases of corticosteroid dependence/inability to decrease corticosteroids, tocilizumab or sarilumab after collegial discussion (A), or failing that, methotrexate (C), can be used for 6 to 12 months to achieve corticosteroid withdrawal	A C	9.3 (1.1)
19	Systematic monitoring by imaging is not indicated	B	9.8 (0.3)

BMD: bone mineral density; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; SD: standard deviation; SE: side effect.

The objective of treatment is clear, with remission and corticosteroid withdrawal, in a deliberate approach to reducing exposure to corticosteroid therapy in patients with particularly fragile conditions. This management is based on non-pharmacological means, to be applied throughout the course, and pharmacological means to be adapted according to the therapeutic response and tolerance to treatment. The entire process is summarized in the algorithm in Fig. 3. These recommendations take into account recent therapeutic developments and are intended to be practical to be implemented by as many people as possible. Some questions do not currently have documented answers; they appear on the research agenda (Box 2).

These first recommendations will be refined/updated based on the results of the work in progress, particularly in the therapeutic area. Alternatives or options for sparing corticosteroid therapy are being evaluated [76]. Results were observed during controlled proof-of-concept studies in recent PMR with rituximab (anti-CD20) in combination with corticosteroid therapy [77,78], and with abatacept (CTLA4-Ig) as monotherapy (abatacept versus placebo for 12 weeks in 34 randomized patients): PMR-AS $\leq$ 10 at week 12:

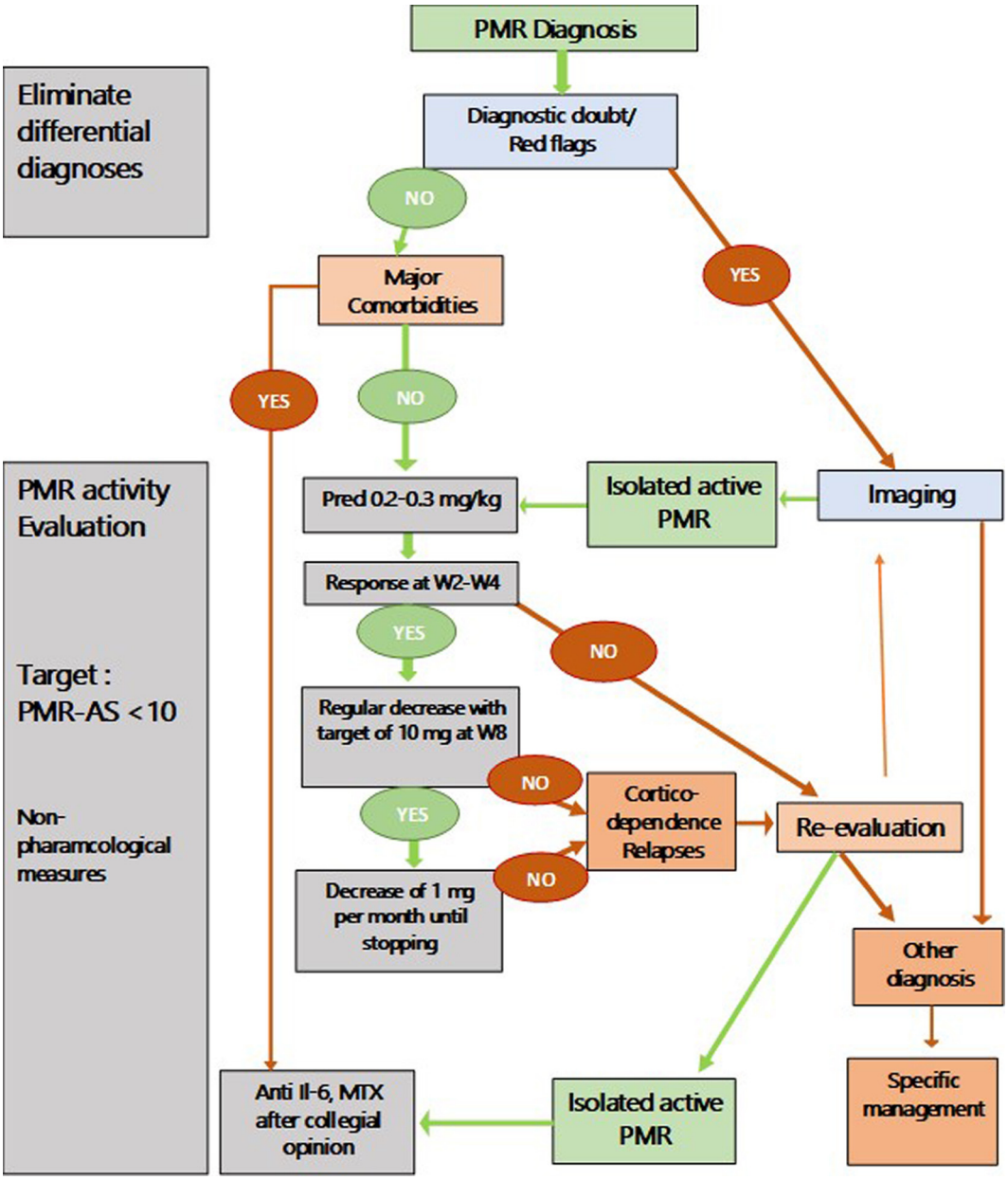

Fig. 3. Algorithm for the management of PMR.

Box 2
Research agenda:

- Comparison of corticosteroid-sparing molecules with each other
- Strategies for stopping targeted treatments (excluding corticosteroids)
- Comparison of short corticosteroid therapy versus no corticosteroid in combination with DMARD
- Biological tools for monitoring disease activity under DMARD (in particular anti-IL-6 receptor)
- Assessment of the reality of the risk of adrenal insufficiency when decreasing/stopping corticosteroid therapy
- Medical economic evaluation of the use of targeted treatments (anti-IL-6R in particular) versus methotrexate and versus isolated corticosteroid therapy

50% of patients in the abatacept group and 22% of patients in the placebo group (adjusted $P = 0.07$) (ALORS study) [79]. Studies are underway with rituximab in recent forms [80], and in forms with relapses [81]. The same is true with secukinumab (anti-IL-17A) in patients taking corticosteroids with relapses [82]. JAK inhibitors are also in the news, with an open randomized trial showing an equivalent response between tofacitinib and corticosteroids in treatment-naive patients [83], and an ongoing study comparing, in recent PMR, baricitinib versus placebo without corticosteroids for 12 weeks [84].

We see that this current work is exploring new and original therapeutic strategies, using targeted induction therapies, without corticosteroid therapy, illustrating this concern to minimize exposure to general corticosteroid therapy. The results of these ongoing studies are likely to reshuffle the cards and completely modify the pharmacological treatment algorithm. However, in practice, it will be necessary to take into account the medicoeconomic impact of these new treatments compared to corticosteroid therapy, and also

the potential limitations of their use (in particular JAK inhibitors) in elderly people with comorbidities [85].

These recommendations are planned to be updated according to new data concerning tolerance and therapeutical options in PMR.

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