Recommendations for early referral of individuals with suspected polymyalgia rheumatica: An initiative from the international giant cell arteritis and polymyalgia rheumatica study group

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Abstract

Objective To develop international consensus-based recommendations for early referral of individuals with suspected polymyalgia rheumatica (PMR).

Methods A task force including 29 rheumatologists/internists, 4 general practitioners, 4 patients, and a health care professional emerged from the international giant cell arteritis and PMR study group. The task force supplied clinical questions, subsequently transformed into Population, Intervention, Comparator, Outcome (PICO) format. A systematic literature review was conducted followed by online meetings to formulate and vote on final recommendations. Levels of evidence (LOE) (1-5 scale) and agreement (LOA) (0-10 scale) were evaluated.

Results Two overarching principles and five recommendations were developed. LOE was 4-5 and LOA ranged between 8.5 and 9.7. The recommendations suggest that 1) each individual with suspected or recently diagnosed PMR should be considered for specialist evaluation, 2) before referring an individual with suspected PMR to specialist care, a thorough history and clinical examination should be performed and preferably complemented with urgent basic laboratory investigations, 3) individuals with suspected PMR with severe symptoms should be referred for specialist evaluation using rapid access strategies, 4) in individuals with suspected PMR who are referred via rapid access, the commencement of glucocorticoid therapy should be deferred until after specialist evaluation, 5) individuals diagnosed with PMR in specialist care with a good initial response to glucocorticoids and a low risk of glucocorticoid related adverse events can be managed in primary care.

Conclusions These are the first international recommendations for referral of individuals with suspected PMR, which complement the EULAR/ACR management guidelines for established PMR.

Introduction

Classification criteria for polymyalgia rheumatica (PMR) have previously been developed by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR).[1, 2] Subsequently, recommendations for the management of patients with confirmed PMR were developed by EULAR and ACR.[3] In addition, the British Society for Rheumatology (BSR) recommends early referral of patients with PMR in some circumstances, such as normal acute phase reactants.[4] However, consensus on the referral of individuals with suspected PMR to specialist care has not been established.

A recent global survey regarding diagnosis and initial management of suspected PMR in both primary and secondary care demonstrated considerable heterogeneity.[5] In this survey, specialty referral for diagnostic confirmation occurred in only 25% of patients with suspected PMR, a figure comparable to previous studies from the United Kingdom and the United States of America.[6, 7] Of those referred, 50% had already started glucocorticoid treatment prior to specialist evaluation, complicating subsequent diagnostic assessment. Partnership between primary care and specialist care providers is vital for the management of patients with PMR, and consensus on the subpopulation of patients with suspected PMR needing specialist evaluation is long overdue.

Early involvement of specialist care may be particularly important in PMR. First, approximately 20% of individuals with PMR may have concomitant giant cell arteritis (GCA) at diagnosis, which requires urgent evaluation.[8] Recently it has also been pointed out that the two diseases may be different parts of the same diseases spectrum.[9] Second, PMR must be differentiated from common mimickers such as rheumatoid arthritis and osteoarthritis.[10] Finally, primary care providers may not have experience with the use and safety profile of newer targeted therapies for PMR, which are becoming increasingly available.[11] Given these concerns, international consensus on the role of recently described rapid referral strategies for patients with suspected PMR,[12] which are well established in GCA,[13-16] would be useful for both primary care providers and broader health care systems.

The aim of this project was to develop international consensus-based recommendations for the early referral of individuals with suspected PMR and formulate a research agenda to improve the care of this group of patients.

Methods

The task force consisted of 38 participants from the international GCA/PMR study group[17] including 28 rheumatologists, 1 general internist (DB), 4 general practitioners (TH, MG, UC, MF), 4 individuals with lived experience of PMR (EB, LN, EH, AV), and a health care professional (AdT). The task force members came from 16 countries (Australia, Austria, Belgium, Brazil, Colombia, Denmark, France, Germany, Italy, Netherlands, Peru, Portugal, Spain, Switzerland, United Kingdom, and United States of America). The steering group included AH, AT, KK, AWN, CBM, CD, EBr, SES, SM and WAS, and the scientific committee additionally included ABD, EMH, LN, TD, and TH. The tasks assigned to the groups are described in detail below. The convenors (KK and CD) and the methodologist (CBM) led the task force following the EULAR standard operating procedures.[18] Preceding the initial online scientific committee assembly in October 2022, two virtual meetings of the steering group were held to define the project. Subsequently, all members of the task force were invited to submit topics by e-mail to be addressed in the recommendations. This process resulted in 70 different suggestions. At a virtual meeting, the scientific committee selected, rephrased, and summarized the suggestions into a total of 10 clinical questions through a summation of themes. After another round of e-mail inputs by the scientific committee and subsequently the task force, the steering group agreed upon six research questions in an online meeting, and these were later transformed into the Population, Intervention, Comparator, Outcome (PICO) format (Supplementary S1).

The systematic literature review (SLR) was conducted by the two fellows (AWN and AH) under the guidance of CBM and KK. The protocol was registered with the PROSPERO database (registration number: CRD42023391575). Full text papers with cohorts consisting of more than 20 participants with suspected PMR and evaluating at least one of the six PICOs were included. The SLR supporting these recommendations is published elsewhere.[19] The results of the SLR including the risk of bias assessments were discussed by e-mail and during two online meetings of the steering group and one online meeting of the scientific committee. Based on these results, a draft of the recommendations reflecting each PICO question was formulated. The draft recommendations and the results of the SLR were presented to the task force at a virtual meeting in June 2023, where the final consensus on the recommendations was achieved and voted on. Consensus for each

recommendation was accepted if >75% of the members voted in favor of the recommendation in the first round, >67% in the second round, and >50% in the third round.

The level of evidence for each recommendation is indicated by using the Oxford Centre for Evidence Based Medicine levels of evidence (LoE).[20] Levels of agreement (LoA) on the overarching principles and recommendations were obtained through an anonymous e-mail questionnaire (scale 0-10, with 10 denoting complete agreement). A research agenda was drafted based on the knowledge gaps identified by the SLR and the task force members.

Results

General aspects

The subject patient population of these recommendations is individuals with suspected PMR. The management of patients diagnosed with PMR has been covered in existing EULAR/ACR recommendations.[3]

The intended users of these statements are general practitioners and specialists (in rheumatology, geriatrics, and internal medicine) caring for individuals with suspected PMR. They may also be used by other stakeholders (e.g. decision makers) to improve the care of PMR.

The task force defines individuals with suspected PMR as people above the age of 50 years, presenting with symmetrical proximal joint/muscle symptoms (i.e. shoulder and pelvic girdle), and elevated C-reactive protein (CRP). In case of a high clinical suspicion of PMR, CRP can be dispensable. **The possibility to refer patients with suspected PMR when inflammatory markers are negative or not available certainly increases the probability of referring a higher number of patients who turn out not to have PMR. The task force, however, was of the opinion that at the stage of referral sensitivity is more important than specificity, given that patients would be evaluated by a specialist who can consider all information including acute phase reactants.** Ischaemic symptoms of GCA (headache, scalp tenderness, jaw claudication (i.e. difficulty and pain with chewing that improves with rest), double vision or visual loss, or limb claudication) are normally absent as they would indicate the presence of GCA.

Overarching principles

The task force identified two overarching principles judged essential for the management of individuals with suspected PMR (Table 1). These principles are based on consensus and not inferred from the SLR. A third principle concerning screening for comorbidities was omitted after discussion in the final task force meeting, since the task force deemed it only relevant after having established the diagnosis.

Overarching principle 1: Management of individuals with suspected PMR should be based on shared decision between the health care provider and patient and take severity of symptoms into consideration.

The principle of shared decision enshrines the right of the patient to understand what is being offered, why it is offered, what the expected outcome is, and how the treatment could impact their lives and those of their family and caregivers. This especially concerns the decision to start treatment in primary care or referring to secondary care (with or without treatment) depending on the level of clinical suspicion and the management preferences of the patient. It may also include treatment options and examinations prior to referral or establishing a diagnosis.

Overarching principle 2: All individuals with suspected PMR should be informed (preferably written) about the potential overlap with GCA. They should be counselled about the need to seek urgent attention if they develop symptoms of GCA.

Patient education should be tailored as outlined in the respective EULAR recommendations.[21] Patients with PMR may have GCA at the time of diagnosis, and GCA might also develop during the disease course.[8, 22] Therefore, individuals with suspected PMR should be educated about the potential to develop GCA and instructed to monitor for the development of headache, scalp tenderness, jaw claudication, transient visual disturbances, etc., and report this back to the health care provider. The efficacy of different approaches to convey this information has not been studied, but patient representatives stressed the importance of providing written material.

Recommendations

A total of five specific recommendations were included and are listed in Table 1.

Recommendation 1 (PICO 4): Each individual with suspected or recently diagnosed PMR should be considered for specialist evaluation.

Two studies have evaluated shared care in patients with established PMR, demonstrating the use of lower prednisolone doses and a higher frequency of screening for osteoporosis in shared care compared to sole management in general practice.[6, 23] No evidence exists for patients with suspected disease and this recommendation is therefore based on expert opinion.

The risk of misdiagnosis may be as high as 30% for patients with PMR diagnosed by a rheumatologist.[10, 24, 25] This has not been systematically evaluated in general practice, but the proportion of misdiagnosis could be higher, because general practitioners only see an average of 3

new patients with PMR yearly.[5] The task force therefore agreed that referral of a higher proportion of patients with suspected PMR might reduce the proportion of patients treated unnecessarily with glucocorticoids, which are known to frequently cause adverse effects.[26-28] Particularly when alternative diagnoses are suspected, patients should be sent for specialist evaluation (Table 2). In addition, the co-existence of GCA and PMR and new emerging treatment options for PMR also call for routine referral of patients with suspected PMR.[8, 11]

Recommendation 2 (PICO 1): Before referring an individual with suspected PMR to specialist care, a thorough history and clinical examination should be performed and preferably complemented with urgent basic laboratory investigations (Table 3).

Among all studies included in the SLR, clinical diagnosis achieved the best combination of sensitivity and specificity for the diagnosis compared to various classification criteria.[8, 29-31] There are no studies evaluating the importance of specific features of history, clinical examination, and laboratory investigations prior to referral for specialist evaluation. In addition, the concept of pre- and post-test probability, as well as any threshold for a relevant clinical likelihood of the PMR diagnosis, has not been established.

The consensus view of the task force is that a thorough history and clinical examination focusing primarily on typical symptoms of PMR and GCA and supported by basic laboratory investigations as outlined in Table 3 should be performed in all patients with suspected PMR. If the general practitioner suspects an alternative diagnosis to be more likely than PMR after initial evaluation, further investigations should focus on this before referral to a rheumatologist.

The task force agreed that specific rheumatological tests such as rheumatoid factor and anti-citrullinated protein antibodies are not needed prior to referral, mainly to avoid diagnostic delay and potentially unnecessary costs to the health care system. In contrast, the task force agreed that CRP is useful for establishing a diagnosis of PMR and should generally be considered, to avoid further diagnostic delay at specialist evaluation. Testing for erythrocyte sedimentation rate may have additional value in some countries and/or certain clinical situations. To avoid referral delay, the task force recommended that laboratory investigations should be performed urgently. Imaging of any kind is not mandatory before referral given that the waiting time for imaging would delay the referral of individuals with a high suspicion of PMR. However, if cancer or any other

differential diagnosis of PMR is highly suspected, this possibility should be investigated before referral, which usually includes imaging. Little is known about the incidence of cancer in individuals suspected of having PMR, but it might be relatively low.[12] In patients with established PMR, data on the frequency of unidentified cancer are contradictory.[32-34]

Recommendation 3 (PICO 6): Individuals with suspected PMR with severe symptoms should be referred for specialist evaluation using rapid access strategies.

Two retrospective studies have demonstrated that rapid referral pathways for PMR reduced the time to evaluation, hospital admission rate, number of hospital visits, and proportion of patients started on glucocorticoids before specialist evaluation.[12, 35]

The task force defined 'severe symptoms' as the presence of symptoms limiting the individual in activities of daily living (e.g. getting out of bed or getting dressed) but acknowledges that severity may be perceived differently from individual to individual. Based on the existing evidence and experience from clinical practice, the task force recommends that individuals with suspected PMR exhibiting severe symptoms should be referred for specialist evaluation using rapid access strategies when available, preferably within one week after referral. Delay in specialist care evaluation beyond one week may result in a higher proportion of patients being started on glucocorticoids.[5, 12] The task force acknowledged that rapid access strategies for GCA usually offer evaluation within 72 hours. In the absence of GCA symptoms, however, the incidence of sight loss in PMR is low and one week was agreed upon as a realistic compromise. For people with suspected PMR without limitation of activities of daily living, waiting longer than one week for review might be acceptable. In patients with symptoms necessitating prompt glucocorticoid treatment, the primary care provider should contact the specialist to facilitate an evaluation within 1-2 days, to avoid hospital admission.[35]

The best model for a rapid access strategy for suspected PMR has not yet been defined. The task force recommends an outpatient setup with access to supplementary laboratory work and imaging. Given that PMR may be considered as part of a disease spectrum with GCA,[9] rapid acces strategies for both diseases may be run by the same experts even thought that separate protocols are required for the two diseases.

Recommendation 4 (PICO 5): In individuals with suspected PMR who are referred via rapid access, the commencement of glucocorticoid therapy should be deferred until after specialist evaluation.

It is well known that glucocorticoids can improve signs and symptoms of PMR, thereby impacting subsequent diagnostic evaluation. In addition, glucocorticoids may also conceal the symptoms of GCA and important differential diagnoses such as cancer and other rheumatic diseases. Studies evaluating 2-[18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and computed tomography (PET/CT) and ultrasonography have demonstrated a lower diagnostic sensitivity following the administration of glucocorticoids.[36, 37] Therefore, after taking the principles of shared decision making and the disabling symptoms of PMR into consideration, the task force recommends that glucocorticoids should be delayed in patients with suspected PMR referred to specialist care if rapid evaluation is possible. If a rapid access strategy cannot be applied, starting glucocorticoids before specialist evaluation may be justified in the presence of severe symptoms.

Recommendation 5 (PICO 4): Individuals diagnosed with PMR in specialist care with a good initial response to glucocorticoids and a low risk of glucocorticoid related adverse events can be managed in primary care; they should be referred back to specialist care if glucocorticoids can not be tapered or GCA is suspected.

Although this recommendation is not related to suspected but rather diagnosed PMR patients, it deals with referral and referral back to primary care management, and the task force was therefore of the opinion that it should be included. While all people with suspected PMR should be considered for specialist evaluation to establish the diagnosis and decide on initial treatment, not all patients with established PMR may need to be managed in specialist care. In particular, patients with a low risk of glucocorticoid related adverse events as defined by EULAR[38] (e.g. patients without a diagnosis of diabetes or osteoporosis) and an initial good glucocorticoid response, defined as clinical response within one month with initial prednisolone-equivalent daily doses not higher than 25 mg, could be discharged within 1-2 months to primary care. While there are still insufficient data on risk stratification of PMR, the task force was of the opinion that these patients have a relatively low risk of glucocorticoid adverse events. However, the task force acknowledged that management in primary care or at hospital can be subject to local variations.

Patients experiencing glucocorticoid related adverse events, suspicion of concurrent GCA, or glucocorticoid resistant disease, should be referred back to specialist care. It was specifically stated by the task force that suspicion of GCA should result in rapid referral back to specialist care, to prevent ischemic events.

Research agenda

Based on the knowledge gaps demonstrated in this project, a research agenda was developed to provide goals for the future (Table 4).

Discussion

These are the first international recommendations for referral of individuals with suspected PMR and aim to complement the current EULAR/ACR guidelines for management of established PMR. The major novelty is the referral of all patients with suspected PMR using rapid access strategies, and prior to prednisolone initiation.

These recommendations advocate for significant change to the diagnostic and management approaches currently employed in primary care.[5] An important reason is that diagnosing PMR can be challenging due to lack of a specific diagnostic tests, and the risk of misdiagnosis may be as high as 30% for PMR patients diagnosed by a rheumatologist, and potentially higher by primary care providers.[10, 24, 25] Referral of a higher proportion of patients with suspected PMR might therefore reduce the proportion of misdiagnosis and thereby reduce unnecessary treatment with glucocorticoids. Imaging, including ultrasonography of hips and shoulder joints, and particularly FDG-PET/CT, is promising and may improve diagnostic accuracy in the future, but is currently limited by cost, availability and expertise.[39-41] Moreover, the frequent co-existence of GCA and PMR and emerging treatment options for PMR also call for routine referral of patients with suspected PMR.[8, 11, 42, 43]

A subset of individuals with PMR have solely PMR symptoms and concurrent GCA detected on imaging, which has previously been demonstrated in selected cohorts from specialist care.[22, 44] While these recommendations were being drafted, a study found an elevated risk of relapse among patients with PMR who had signs of large vessel vasculitis on imaging, suggesting that imaging may be useful from a prognostic perspective.[45] It has also been postulated that identifying such patients could prevent progression of vascular damage. These potential benefits must be weighed against the following potential harms, which were raised by task force members: 1) Risk of overtreating individuals with solely PMR symptoms and GCA on imaging, who would receive additional glucocorticoids and glucocorticoid-sparing agents without evidence that they required it or would benefit from it, 2) availability of imaging (cost implications for FDG-PET/CT, and expertise for ultrasonography), 3) an unknown pretest likelihood in patients with suspected PMR for subclinical GCA in contrast to established PMR, and 4) the risk of incidental findings on FDG-PET/CT requiring additional procedures, which may harm the patient and delay treatment of PMR. Given these considerations, only 23% of the task force voted in favor of screening for GCA among

patients with suspected PMR and a recommendation for imaging in all patients with suspected PMR was not included.

The result of our SLR demonstrated that referral of patients with suspected PMR for specialist evaluation has been sparsely investigated.[19] The lack of evidence in primary care especially is notably limiting the evidence basis of our recommendations. The current recommendations are therefore the first step in improving clinical practice and the research agenda will set focus for the upcoming years (Table 4).

The task force envisions that these recommendations will help to facilitate the allocation of additional resources for evaluating patients with suspected PMR by rheumatologists, as has previously been the case in rheumatoid arthritis following recognition of the importance of early treatment initiation and the treat to target paradigm.[46, 47] The task force acknowledges that the recommendations cannot be implemented promptly in all countries due to lack of resources in rheumatology and existing challenges in the workforce. In addition, since most studies in PMR concern highly selected patients evaluated in tertiary centers, the real incidence of suspected PMR is unknown and complicates the adaptation of rheumatology services for evaluation of individuals with suspected PMR. Moreover, given the increasing age of the population, it can be expected that the incidence of PMR will rise and this should be considered when planning future care for PMR patients.

The strength of these recommendations is the worldwide task force representing a variety of different health care systems and the stringent methodology applied. Limitations are the low level of evidence as well as the limited number of general practitioners represented in the task force.

In summary, we have developed five recommendations for early referral of individuals with suspected PMR. The task force acknowledges that most of the recommendations are consensus based due to the low level of evidence. However, the level of agreement was high for the final recommendations. Focus for future research is depicted in the research agenda (Table 4). We expect that substantial research progress will take place and the recommendations will be updated accordingly.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

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