Title

An international survey of current management practices for polymyalgia rheumatica by general practitioners and rheumatologists

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Abstract

Objectives. To explore current management practices for polymyalgia rheumatica (PMR) by general practitioners and rheumatologists including implications for clinical trial recruitment.

Methods. An English language questionnaire was constructed by a working group of rheumatologists and general practitioners (GPs) from 6 countries. The questionnaire focused on: 1: Respondent characteristics, 2: Referral practices, 3: Treatment with glucocorticoids, 4: Diagnostics, 5: Comorbidities, and 6: Barriers to research. The questionnaire was distributed to rheumatologists and GPs worldwide via members of the International PMR/giant cell arteritis Study Group.

Results. In total, 394 GPs and 937 rheumatologists responded to the survey. GPs referred a median of 25% of their suspected PMR patients for diagnosis and 50% of these were returned to their GP for management. In general, 39% of rheumatologists evaluated patients with suspected PMR more than 2 weeks after referral, and a median of 50% of patients had started prednisolone before rheumatologist evaluation. Direct comparison of initial treatment showed that the percentage prescribing more than 25 mg prednisolone daily for patients was 30% for GPs and 12% for rheumatologists. Diagnostic imaging was rarely used. More than half (56%) of rheumatologists experienced difficulties recruiting people with PMR to clinical trials.

Conclusion. This large international survey indicates that a large proportion of people with PMR are not referred for diagnosis and the proportion of treatment naïve patients declined with increasing time from referral to assessment~~there was a delay between referral and first rheumatology clinic visit and a large proportion of patients seen by rheumatologists were not treatment naïve~~. Strategies are needed to change current referral and management of people with PMR, to improve clinical practice and facilitate recruitment of patients to clinical trials.

Keywords
Polymyalgia rheumatica, guideline, glucocorticoid, diagnostic, treatment, research

Key messages.

- ~~Delay between referral and rheumatologist evaluation was seen for people with new PMR.~~
- Only 25% of people with new PMR was referred for diagnosis limiting recruitment to trials.~~Half of people with new PMR referred to rheumatologists were not treatment naïve.~~
- The proportion of treatment naïve patients declined with increasing time from referral to evaluation
- A significant number of people with new PMR received prednisolone doses higher than recommended.

Introduction

Polymyalgia rheumatica (PMR) is the most common systemic rheumatic disease of older adults and largely treated with glucocorticoids. The European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) treatment guideline recommends initial prednisolone doses from 12.5 to 25 mg and continuation of treatment for at least one year, but it is unknown if the guideline is followed [1]. A large variation in clinical practice among both general practitioners (GPs) and rheumatologists has been reported in studies from the United Kingdom [2, 3]. In addition, high quality evidence is lacking to support routine concomitant glucocorticoid sparing treatment with methotrexate, and given the limitations to use this drug in older adults with restricted renal function, new treatment options are needed for people with PMR. With the current expansion in PMR research, there is an increasing need for recruitment to PMR trials.

PMR is often managed entirely in primary care settings, whereas clinical trials are usually conducted in institutions of specialist care [4, 5]. Another barrier to research could be the time to~~delays in~~ rheumatology evaluation and initiation of glucocorticoid treatment prior to initial rheumatologist evaluation [6]. It is unknown how widespread these challenges are worldwide.

Diagnostic uncertainty in PMR exists. Existing classification criteria for PMR are intended for capturing patients with this disease, but do incorporate the key elements of diagnosis [7]. It is well-known that misdiagnosis is common even in rheumatological practice [8]. Moreover, studies from the United Kingdom indicate that GPs as well as rheumatologists do not always rule out differential diagnoses [3, 9]. However, this issue has not been studied systematically.

The increased risk of comorbidities such as osteoporosis, cardiovascular disease and diabetes in PMR may be related to use of glucocorticoids, but possibly also to inflammation caused by the disease itself [10-13]. Comorbidities should be screened for and managed accordingly [1, 14]. However, studies from the United Kingdom indicated that systematic screening for comorbidities are not performed [2-4]. It is unknown if this is a worldwide problem in people with PMR.

In this study, we investigated current management practices for PMR by general practitioners and rheumatologists including implications for clinical trial recruitment.

Methods

Study Design

A working group from the International PMR/giant cell arteritis (GCA) Study Group, consisting of rheumatologists and GPs from Denmark, the Netherlands, the United Kingdom, Austria, Australia, and Colombia drafted an English language questionnaire [15]. The survey was refined using iterative feedback via email and during online meetings in June, August, and October 2021. The questionnaire included 78 questions for rheumatologists and 71 questions for GPs focusing on 6 main areas: 1: Respondent characteristics, 2: Referrals of people with PMR, 3: Treatment with prednisolone, 4: Diagnostics used to confirm the diagnosis and investigate differential diagnosis, 5: Management of comorbidities, and 6: Barriers to research (see Supplementary data 1 and 2 for full questionnaire). The questions were mainly multiple-choice format, but single-choice format was also used (Supplementary questionnaires).

To be eligible for the study, respondents had to be medical doctors managing people with PMR, and GPs should also attend patients with any medical problem (generalist). The questionnaires were distributed to rheumatologists and GPs worldwide via members of the International PMR/GCA Study Group, using the snowball principle. Answers were collected anonymously via an online survey tool (REDcap), from 2nd of November 2021 to 27th of January 2022 [16]. Eight reminders including update about the overall number of respondents were sent to involved members of the PMR/GCA Study Group during this period.

Ethical considerations

The questionnaire for rheumatologists and GPs was anonymous, and therefore no ethical approval was necessary according to local institutional protocols. Since all

data were collected anonymously, data protection agency registration was not necessary according to the General Data Protection Regulation.

Statistics

Analysis used descriptive statistics. Data are presented as number (percentages) for categorical variables and median (interquartile range (IQR)) for continuous variables. Countries were grouped by income and geographical region based on the World Bank classifications for the rheumatologist data. This was not performed on GP data due to the lower number of countries with GP respondents [17]. Data from countries with more than 15 respondents are shown separately, data from countries with less than 15 respondents were pooled into a single category ("other countries"). Data from countries with more than 15 respondents from both rheumatologist and GP were compared directly.

Results

In total, 394 GPs and 937 rheumatologists responded to the questionnaire. Eleven and 27 countries had more than 15 respondents for GPs and rheumatologists, respectively. Countries with less than 15 respondents are presented in Supplementary Table S1-2. Nine countries (Austria, Canada, Colombia, Denmark, Italy, the Netherlands, Romania, Switzerland, and the United Kingdom) had more than 15 respondents for both GPs (264 respondents) and rheumatologists (297 respondents).

Respondent characteristics

Respondent characteristics are summarized in Supplementary Table S3-4. Median age (IQR) of respondents was 46 (39-55) years for GPs and 44 (36-53) years for rheumatologists. Most GPs were working in urban areas (70%) and rheumatologists in university hospitals (55%). GPs reported seeing a median of 3 people with new onset PMR yearly and rheumatologists a median of 10 people with new onset PMR yearly. A national or local PMR guideline was available for 56% of GPs and 52% of rheumatologists and almost all respondents stated that they adhered to the guideline.

Referrals

GPs referred a median of 25 (IQR 5-90)% of people with suspected PMR for diagnosis, and 50 (1-100)% of these patients were subsequently discharged to their GP for treatment (Table 1). Most frequently GPs referred people with suspected new PMR to departments of rheumatology at the hospital (72%), followed by rheumatologists working in private practice (35%) (Supplementary Table S5). The major reasons for referral were uncertainty of diagnosis (64%), risk of glucocorticoid related adverse events (25%), and patient's requests (34%). During the disease course, 20 (10-50)% of patients with established PMR were referred by their GP (Table 1)

Overall, 64% of GPs could discuss patients with a rheumatologist before referring and all referred patients were seen by a rheumatologist (Table 2 and

Supplementary Table 6-10). In general, 39% of rheumatologists evaluated people with suspected new onset PMR more than 2 weeks, and 19% more than 4 weeks, from referral by GP. However, 61% were evaluated within 2 weeks. ~~During the disease course, 20 (10-50)% of patients were referred by their GP (Table 2).~~ The referral diagnosis was changed upon evaluation by rheumatologist in 15 (5-30)% of patients with an already established PMR diagnosis.

Treatment with prednisolone

Overall, a median of 50 (IQR 15-75)% of patients newly diagnosed with PMR had started treatment before rheumatologic evaluation (Table 2 and Supplementary 6-10). As reported by rheumatologists, patients seen within 14 days, compared to those seen more than 14 days from the initial referral, were less frequently started on prednisolone (median 40 (IQR 10-60)% vs. median 50 (IQR 25-80)%), and in patients seen by a rheumatologist within 28 days compared to those seen more than 28 days from referral (50 (10-63)% vs. 70 (30-90)%).

Direct comparison between GP and rheumatologist data in 9 countries with more than 15 respondents showed a median prednisolone /equivalent starting dose of 20 (IQR 15-30) mg for GPs and 15 (15-20) mg for rheumatologists. The percentage of patients receiving more than 25 mg daily was 30% for GPs and 12% for rheumatologists. Overall, duration of prednisolone treatment was shorter if patients were managed by a GP than by a rheumatologist (median 9 months (IQR 4-12) vs. 12 months (11-18). The percentage of respondents prescribing treatment for less than 6 months was 27% for GPs and 5% for rheumatologists. Data from all countries are shown in Table 1-2 and Supplementary 6-10.

Diagnostics

Diagnostic workup to confirm PMR is illustrated in Figure 1 for comparison between GPs and rheumatologists in 9 countries with more than 15 responders. In general, diagnostic workup to confirm PMR was more frequently performed by rheumatologists than GPs. Clinical examination was always performed by 97% of rheumatologists and 90% of GPs and C-reactive protein was always performed by 97% of rheumatologists and 88% of GPs to confirm PMR. Imaging to confirm the

diagnosis was not routinely performed. All data for GPs and rheumatologists are shown in supplementary Figure S1.

Diagnostic procedures applied by rheumatologists to investigate for GCA in people with PMR without cranial symptoms are detailed in Figure 2. Vascular ultrasound was the most utilized diagnostic imaging technique, and 16% of respondents stated to use vascular ultrasound in all new PMR patients.

In the 9 compared countries, rheumatologists more often utilized laboratory tests than GPs to investigate differential diagnoses other than GCA (Supplementary Figure S2). In general, imaging (e.g. X-ray of the chest) to investigate differential diagnoses other than GCA was rarely performed by either GPs or rheumatologists (Figure 3). All data for GPs and rheumatologists are presented in Supplementary Figure S2.

Assessment and management of comorbidities

Direct comparison between GPs and rheumatologists in 9 countries demonstrated that screening for comorbidities at diagnosis and follow up was not routinely performed by neither GPs nor rheumatologists (Figure 4). Notably dual energy X-ray absorptiometry was always performed by only 41% of rheumatologists and 23% of GPs at diagnosis, but 55% of GPs vs. 45% of rheumatologists always performed diabetes screening at diagnosis. All data for GPs and rheumatologists are demonstrated in Supplementary Figure S3.

Direct comparison between GPs and rheumatologists in 9 countries showed that treatment with vitamin D and calcium, proton pump inhibitors, and bisphosphonates were always prescribed by 50% vs. 87%, 30% vs. 28%, and 9% vs. 27%, respectively (Figure 4). All data for GPs and rheumatologists are shown in Supplementary Figure S3.

Barriers to research

Fifteen percent of the responding rheumatologists (n=129) performed research in PMR, of which 64/129 (52%) had participated in clinical trials. Of these, 36/64 (56%) had experienced difficulties with recruitment to trials. Finally, 19/36 (52%) answered that not enough patients were referred, 27/36 (75%) that patients had received

prednisolone prior to rheumatologic evaluation, 17/36 (47%) that patients did not want to participate, and 14/36 (39%) that diagnosis were uncertain due to prednisolone treatment.

Discussion

This is the first international study exploring current management practices for PMR by general practitioners and rheumatologists including implications for clinical trial recruitment. Our results show that only a minority of people with PMR was referred to rheumatologists. Time from referral to actual visit was long and many received prednisolone before rheumatologist evaluation. Finally, initial prednisolone dose was often above the guideline recommendation for PMR. Many of these factors were also major barriers to clinical trial recruitment.

Clinical Management

PMR is a challenging clinical diagnosis with many differential diagnoses, and a high risk of misdiagnosis [8, 18]. In addition, people with PMR may be diagnosed with GCA or rheumatoid arthritis during the disease course [19]. Hence, it is interesting that only a minority of people with PMR were actually referred to rheumatologists for diagnosis or second opinion during follow-up. Earlier findings from the United Kingdom and United States of America also demonstrated that only 44% and 60% of people with PMR were referred for rheumatologist evaluation at some point during the disease course [4, 5]. Current EULAR/ACR guidelines on PMR do not specify which patients should be managed in general practice or by rheumatologists, and local variations in referral policy may influence referral practices [1]. In addition, the main reason for referral for diagnosis~~during follow-up~~ was diagnostic uncertainty in most countries, which indicates that referred patients represent a subgroup of people with PMR. Clinical recommendations that more clearly describe when GP's should refer patients with uncertainty related to PMR diagnosis to a rheumatologist could help standardize referral pattern. In patients with diagnostic uncertainty we used the term "suspected PMR", but in the future it should be defined if the term polymyalgic syndrome, referring to the symptomatology (even though ill defined in literature) or the term "suspected PMR", referring to the disease would be more appropriate to use.

This study demonstrated that a large proportion of people with suspected new onset PMR were evaluated a long time after referral and had received prednisolone prior to evaluation by rheumatologist. Interestingly, we also found a relationship between the percentage of patients starting prednisolone prior to rheumatologic evaluation and the time from referral to evaluation. The often disabling symptoms associated with PMR, may compel GPs to start glucocorticoids if the waiting time for rheumatologist is too long. The time lag to rheumatologist evaluation may therefore be an obstacles for improvement of clinical practice and recruitment to trials in PMR. Recently introduced fast-track setups, typically offering GPs an opportunity to refer people with suspected new PMR for rheumatologist evaluation within one week, may be part of the solution and reduce waiting time for evaluation by rheumatologist [6]. Previously, Fast track strategies for GCA has improved the diagnostic process in this disease and reduced permanent visual impairment [20].

This study demonstrated that higher initial doses of prednisolone and shorter treatment durations than recommended by existing guidelines were more commonly employed by GPs than by rheumatologists [1]. A higher initial dose of prednisolone increases the risk of comorbidities [21]. Therefore, future initiatives should focus on how prednisolone starting dose could be reduced among GPs. The short treatment duration seen in general practice and in some parts of the world, raises questions regarding the level of diagnostic certainty in these settings as rapid prednisolone tapers in PMR increase the risk of relapse [22]. However, people with PMR solely seen in general practice may also represent a subgroup with milder or more typical disease and a smaller proportion of patients with concurrent GCA than the 22%, usually reported [23]. Further studies are needed to determine the correct treatment duration in different subsets of PMR.

Diagnostic imaging was not widely used to confirm PMR. This may reflect that no diagnostic imaging has currently been validated for the diagnosis of PMR but may also indicate a lack of available expertise or resources for this investigation. Ultrasound may have a role in the diagnosis of PMR [7]. In addition, positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) may have a future role in the diagnosis of a PMR sub-population, but

have not been validated yet. It is recognized that these are expensive and currently not widely available internationally outside of large specialist centers. More studies are needed to evaluate if PMR sub-populations should be evaluated with these modalities [24, 25].

While cancer and chronic infections are important differential diagnoses to consider, imaging was rarely used, and no guidelines support the routine use of imaging to investigate differential diagnoses in people with suspected new onset PMR. Previous studies have shown that PMR symptoms may be related to cancer for up to 2 years after diagnosis [26, 27]. Although not presently supported by guidelines, there could be a rationale to screen people with PMR without cranial symptoms for GCA with vascular ultrasound in the future. GCA in patients with PMR is common, but future studies should focus on evaluating GCA in different subsets of PMR [23].

Considering the potential high prednisolone dose applied by many rheumatologists and GPs, screening frequency for osteoporosis and diabetes both at diagnosis and during the disease course was surprisingly low. In addition, both diseases commonly occur after the diagnosis and are often attributed to prednisolone treatment [10, 13]. Management guidelines recommend screening for comorbidities and initiation of treatment when needed [1, 14, 28]. In addition, this international study and previous studies from the UK demonstrated that not all patients received drugs for bone prophylaxis [4]. Further initiatives should focus on improving the adherence to existing guidelines and treatment schemes.

Barriers to research

In the last few years, research in PMR has expanded considerably. The first few randomized controlled trials with biologics have recently been published and several are ongoing [29, 30]. To perform larger trials, it is essential that researchers can recruit treatment naïve patients, but the extent of difficulties with recruitment has not previously been evaluated. In this study we demonstrate that more than half of researchers performing clinical trials in PMR experienced difficulties with recruitment. The biggest obstacle for recruitment was that patients had received prednisolone prior to rheumatologic evaluation, followed by not enough patients

being referred. This may be attributed to the widespread handling of PMR in primary care and the long duration between referral and evaluation by a rheumatologist also demonstrated in this study as well as previous studies from the UK and Denmark [4, 6, 31].

The major strength of this study is the large number of respondents from many countries worldwide. Study limitations include first, the decentralized recruitment process and unknown actual survey response rates. This may result in response bias, possibly overestimating the adherence to guidelines, since rheumatologists and GPs with an interest in the field may potentially be more likely to answer the questionnaire. Second, a high percentage of rheumatologists participating in the survey was from university hospitals and most GPs were based in urban areas, where clinical practice might differ from that of non-university hospitals and rural areas, for example due to better availability of imaging tests or research interest in PMR in the former places. Third, GP respondents primarily came from Europe, and the direct comparison of 9 countries between GPs and rheumatologists therefore especially reflects clinical practice in Europe. Fourth, we cannot exclude misinterpretation of questions in some countries because of lacking language skills. Answers from GPs in Russia were notably uniform rising this suspicion. However, we were unable to check this because all responses were anonymous. Lastly, the structure of primary health care shows global variation which may be reflected in the differences in referral patterns between countries [32, 33].

In conclusion, this study shows that a large proportion of people with PMR are not referred for diagnosis and the proportion of treatment naïve patients declined with increasing time from referral to assessment~~that a large proportion of people with PMR are not treatment naïve before rheumatologist evaluation, and this proportion increases with time from referral to assessment.delays between referral and rheumatologic assessment of patients with PMR and identified that a large proportion of people with PMR are not treatment naïve before rheumatologist evaluation.~~ Strategies are needed to improve current referral processes and care of people with PMR. This would improve clinical practice and could facilitate more opportunity for trial recruitment.

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Data availability statement

The data underlying this study are available from the corresponding author upon reasonable request.

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