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The future of polymyalgia rheumatica research: what can we learn from rheumatoid arthritis?

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In an American study, the lifetime risk of polymyalgia rheumatica (PMR), when compared to that of rheumatoid arthritis (RA), was similar in men and about one third lower in women [1]. In contrast, despite the rising trend in number of publications per year there are 41 times more articles about RA in PubMed compared to PMR (147.249 articles about RA and 3589 articles about PMR from inception till October 12, 2022). This immense difference in scientific interest pertains both to mechanistic and preclinical studies as well as to clinical studies, on which we will focus. There are several possible explanations for this attention gap (Figure 1). First, the diagnosis of isolated PMR (this is without accompanying giant cell arteritis) is primarily based on clinical symptoms in combination with raised inflammatory markers. Although this is sometimes supplemented by ultrasound, MRI or PET imaging with a good diagnostic accuracy of composite PET scores [2], there are no fully specific markers for PMR. Conversely, even though RA remains a clinical diagnosis, biomarkers like rheumatoid factor and anti-citrullinated peptide antibodies and radiographic erosions contribute to clinicians' confidence in their assessment. Second, in contrast to RA, PMR is not a destructive disease, which might attenuate the urge for further research. However, like RA, PMR has a considerable impact on the quality of life of affected patients [3]. A third possible reason for this large difference in scientific interest is the age of onset of the disease. Since patients with RA are generally younger, the number of years patients are affected by RA is higher and the socio-economic impact is greater, encouraging governments and pharmaceutical industry to invest in scientific research in RA. Fourth, in PMR, treatment with glucocorticoids usually results in rapid resolution of the symptoms and inflammation. In contrast to RA, a treatment of 6 to 15 months is sufficient for permanent remission in about half of patients [4]. However, the other half of patients experience relapse during steroid tapering, prolonging the required duration of treatment with glucocorticoids. In a meta-analysis of observational studies, 25% of patients with PMR were still taking glucocorticoids 5 years after diagnosis [4]. So, in a considerable proportion of cases, PMR is a chronic relapsing-remitting disease, not unlike RA. Finally, patients with RA or PMR associated with GCA are promptly referred to a specialist. In contrast, patients with isolated PMR are frequently managed by general practitioners and are only referred in case of multiple relapses and difficulties with weaning off glucocorticoids, which hampers scientific research.

In RA, a treat-to-target strategy is widely accepted with clinical remission as the main therapeutic target [5]. Several composite disease activity measures are available, including disease activity score (DAS)-28, simplified disease activity index (SDAI) and clinical disease activity index (CDAI), all of which have been extensively validated. By contrast, in PMR, valid, well-tested disease activity measures are lacking. There is a great variability in definitions of remission and relapse, using clinical symptoms, inflammatory markers and/or response to treatment changes. In 2004, Leeb and Bird developed a composite score for measurement of disease activity in PMR, called the polymyalgia rheumatica activity score (PMR-AS) [6]. It consists of 5 domains: morning stiffness time, ability to elevate the upper limbs, physician's global assessment, pain and C-reactive protein level. However, high-quality evidence on the measurement properties is lacking and there is still no consensus on the optimal cut-off point. OMERACT has defined a core domain set of outcome measures for PMR, but these are not yet routinely used [7,8]. This lack of reliable, valid, and sensitive outcome measures impedes the reproducible evaluation of the disease activity of PMR and the assessment and comparison of the efficacy of glucocorticoid-sparing agents for this disease.

In addition to the crucial differences between PMR and RA in terms of disease activity measures, similar discrepancies exist for patient-reported outcomes. In RA, it has long been established that a treat-to-target strategy improves patient's quality of life through better control of symptoms, prevention of structural damage and improvement of physical and social functioning [9]. However, a substantial number of patients with well-controlled disease activity still report residual symptoms, such as pain, fatigue, functional disability and impairment in mental health [10]. This is all the more relevant because perceptions on the impact of the disease often differ between patients and physicians, usually in the form of higher disease activity when scored by patients [11]. To obtain a more comprehensive overview of the disease status, it thus appears important to consider patients' perceptions of the disease burden in addition to clinical and laboratory assessment [11]. Some authors have even suggested to consider patient-reported outcomes as a separate treatment target, distinct from the clinical one, as part of a dual-target approach with personalized, multidisciplinary interventions besides pharmacological treatment adaptations [12]. In contrast, patient-reported outcomes are insufficiently studied and lack consistency in PMR. For instance, little is known about their evolution during the disease course and their relationship with disease activity. To improve the care and quality of life of patients with PMR, future studies should therefore aim to incorporate the patient's perspective in their assessment.

Arguably, the biggest difference between PMR and RA are the available treatment options. The 2022 EULAR treatment guideline for RA recommends the combination of short-term glucocorticoids and methotrexate as initial therapy [5]. In case of insufficient disease control, several other well-established treatment options exist, including conventional synthetic disease modifying antirheumatic drugs (DMARDs), such as leflunomide and sulfasalazine, biological DMARDs, such as TNF-inhibitors, IL6-inhibitors, abatacept and rituximab, and targeted synthetic DMARDs, such as JAK-inhibitors [5]. This wide range of treatment options stands in stark contrast with the situation in PMR, where glucocorticoids in monotherapy remain the cornerstone. The 2015 EULAR/ACR collaborative initiative recommends the use of methotrexate in addition to glucocorticoids in case of relapse, as a first line treatment in patients with a high risk of relapse and/or prolonged therapy and as first line treatment in patients with a high risk of glucocorticoid-related adverse events [13]. However, the scientific underpinning of this recommendation is rather loose, with supportive as well as non-supportive old studies in recently diagnosed PMR [14–16] and no randomized controlled trials in patients with relapsing PMR. Two recent randomized controlled trials and several non-randomized and observational trials showed promising results for tocilizumab, but this needs to be confirmed in larger trials with longer follow-up [17–19]. In a meta-analysis of observational studies, 77% of the patients were still taking glucocorticoids at year 1, 51% at year 2 and 25% at year 5 after diagnosis [4]. Stated differently, one year of treatment with glucocorticoids does not suffice in a sizable group of PMR patients. As in RA, long-term therapy is often needed to achieve acceptable disease control. Since long-term glucocorticoid treatment causes a high risk of side effects [20], trials examining glucocorticoid-sparing agents in PMR are urgently needed. Several clinical trials are currently ongoing (rituximab, leflunomide, abatacept, JAK-inhibitors, an anti-TNF glucocorticoid receptor modulator antibody drug conjugate, low dose interleukin 2).
In conclusion, there is a striking difference in scientific interest between RA and PMR. In RA, a treat-to-target strategy with the early introduction of DMARDs is highly recommended. Both composite disease activity measures and patient-reported outcomes are well-studied and

commonly used in daily clinical practice. In PMR, further studies examining disease activity measures, patient-reported outcomes and glucocorticoid-sparing agents are urgently required to improve effectiveness of the therapeutic approach and to increase the quality of life of patients with this condition. The introduction of fast-track clinics could probably aid in the improvement and harmonization of PMR research.

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Figure 1: Overview of the reasons for the lack of scientific research in polymyalgia rheumatica

Abbreviations: GP, general practitioner; PRO, patient-reported outcomes