# Assessment of treatment efficacy in polymyalgia rheumatica

Arends, Suzanne; van der Geest, Kornelis SM; Sandovici, Maria

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among biologics might be subject to a specific form of selection bias called collider bias.[6] Because patients receiving a biologic are clearly different from the remainder of the population, the association between the exposures and outcomes in this subpopulation might not be generalisable to all patients with psoriasis.[9] Therefore, the results cannot not be extrapolated to all patients with psoriasis.

Ongoing studies might help to fill some of these knowledge gaps. First, the ongoing PAMPA randomised trial (NCT05004727) was designed to study the pre-psoriatic arthritis window. Patients with psoriasis with a presumed increased likelihood of progression by virtue of having at least moderate skin disease and asymptomatic joint or entheseal abnormalities on musculoskeletal ultrasound are being randomly assigned to receive either IL-23 inhibitor (guselkumab) or placebo. A third, standard-of-care group has been included for reference. The two co-primary endpoints are improvement in musculoskeletal ultrasound findings at 6 months and the decrease in the proportion of patients who progress to psoriatic arthritis. This trial is the first to address whether treatment of psoriasis with an IL-23 inhibitor can reduce or slow progression to psoriatic arthritis. Additionally, the Accelerating Medicines Partnership Autoimmune and Immune-Mediated Diseases programme, funded by the US National Institutes of Health, will also address pathophysiological changes occurring during the transition from psoriasis to psoriatic arthritis.[10] Furthermore, a planned European study, the Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States (also known as HIPPOCRATES) project, funded by the Innovative Medicines Initiative and EU, is dedicated to understanding this progression and the effect of therapies, gathering data in a prospective manner among 25 000 participants.

Collectively, these innovative prospective strategies that incorporate both therapeutics and biosamples for immunoendotype interrogation should complement efforts to gather observational data. The findings are anticipated to help close the knowledge gap in understanding how and when environmental, immune, and molecular factors modulate (or delay or prevent) the transition from psoriasis to psoriatic arthritis.

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*Alexis Ogdie, Jose U Scher
**ogdiea@pennmedicine.upenn.edu**

Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (AO); Psoriatic Arthritis Center, Division of Rheumatology, New York University Langone Health, New York, NY, USA (JUS); NYU Judith and Stewart Colton Center for Autoimmunity, New York, NY, USA (JUS); Microbiome Center for Rheumatology and Autoimmunity, Division of Rheumatology, NYU Grossman School of Medicine and Langone Orthopedic Hospital, New York, NY, USA (JUS)

1 FitzGerald O, Ogdie A, Chandran V, et al. Psoriatic arthritis. *Nat Rev Dis Primers* 2021; **7:** 59.
2 Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol* 2019; **15:** 153–66.
3 Singla S, Putman M, Liew J, Gordon K. Association between biologic immunotherapy for psoriasis and time to incident inflammatory arthritis: a retrospective cohort study. *Lancet Rheumatol* 2023; published online March 6. https://doi.org/10.1016/S2665-9913(23)00034-6.
4 Ogdie A, Shin DB, Love TJ, Gelfand JM. Body surface area affected by psoriasis and the risk for psoriatic arthritis: a prospective population-based cohort study. *Rheumatology (Oxford)* 2022; **61:** 1877–84.
5 Meer E, Merola JF, Fitzsimmons R, et al. Does biologic therapy impact the development of PsA among patients with psoriasis? *Ann Rheum Dis* 2022; **81:** 80–86.
6 Merola JF, Ogdie A. Does psoriasis treatment affect PsA development? *Nat Rev Rheumatol* 2021; **17:** 708–09.
7 Ogdie A, Rozycki M, Arndt T, Shi C, Kim N, Hur P. Longitudinal analysis of the patient pathways to diagnosis of psoriatic arthritis. *Arthritis Res Ther* 2021; **23:** 252.
8 Gossec L, Siebert S, Bergmans P, et al. Persistence and effectiveness of the IL-12/23 pathway inhibitor ustekinumab or tumour necrosis factor inhibitor treatment in patients with psoriatic arthritis: 1-year results from the real-world PsABio study. *Ann Rheum Dis* 2022; **81:** 823–30.
9 Merola JF, Tian H, Patil D, et al. Incidence and prevalence of psoriatic arthritis in patients with psoriasis stratified by psoriasis disease severity: retrospective analysis of an electronic health records database in the United States. *J Am Acad Dermatol* 2022; **86:** 748–57.
10 Bell S, Merola JF, Webster DE, et al. Aiming for cure and preventive initiatives in psoriatic disease: building synergy at NPF, GRAPPA, and PPACMAN. *Curr Rheumatol Rep* 2020; **22:** 78.

For more on the **HIPPOCRATES project** see https://www.hippocrates-imi.eu/

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The selection of primary study endpoints and inclusion criteria for patients are crucial steps in the design of clinical trials. In patients with immune-mediated inflammatory diseases, the heterogeneity of disease manifestations, including patient symptoms, systemic organ involvement, and laboratory abnormalities, makes these selections more complex. A recent trend aiming to solve this issue is the use of composite


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outcome measures that capture multiple clinically relevant aspects of disease activity. Patients are classified as responders or non-responders on the basis of the combination of their response on different items. Examples of study endpoints are the American College of Rheumatology (ACR) response criteria in rheumatoid arthritis, the Systemic lupus erythematosus Responder Index-4, and the recently developed Composite of Relevant Endpoints for Sjögren's Syndrome and Sjögren's Tool for Assessing Response.[1,2] The selection of patients for study entry can be based on clinical diagnosis, classification criteria, or both, and these criteria are used to facilitate the selection of more homogenous patient groups in research. Furthermore, inclusion is often restricted to the presence of specific clinical manifestations or disease subgroups.

Polymyalgia rheumatica is an inflammatory disease characterised by pain and stiffness, mainly of the shoulder and hip girdle, that affects almost exclusively individuals older than 50 years. The cornerstone of treatment of patients with polymyalgia rheumatica is glucocorticoids, which are gradually tapered over time.[3] However, approximately half of patients will relapse, and long-term use of glucocorticoids can result in severe adverse events with major effects on quality of life.[4] Therefore, there is a need to investigate the glucocorticoid sparing effects of other immunosuppressive treatments in patients with polymyalgia rheumatica.

Laboratory markers of systemic inflammation, pain, stiffness, and physical function are included in The Outcome Measures in Rheumatology core domain set for outcome measures for clinical trials in polymyalgia rheumatica.[5] So far, however, there are no consensus-based criteria for relapse or remission in these patients. The polymyalgia rheumatica activity score (PMR-AS) is a composite score that includes C-reactive protein, visual analogue score (VAS) pain, VAS physician global, duration of morning stiffness, and the ability to elevate the upper limbs.[6] Although this score was proposed almost 20 years ago as a tool for measurement of disease activity, PMR-AS was only recently used as endpoint for response to treatment, owing to the paucity of clinical trials in polymyalgia rheumatica. Fortunately, the advances in immunosuppressive therapy in other inflammatory and autoimmune diseases have catalysed research on glucocorticoid-sparing treatments in polymyalgia rheumatica.

In the BRIDGE-PMR trial, patients with polymyalgia rheumatica were randomly assigned (1:1) to receive a single intravenous infusion of 1000 mg rituximab, a biological B-cell depleting agent, or placebo with 50 mg methylprednisolone, followed by prednisone tapering to 0 mg during 17 weeks.[7] The primary outcome of the trial was glucocorticoid-free remission (defined as PMR-AS <10 without systemic glucocorticoid use) at 21 weeks. In total, 47 patients with polymyalgia rheumatica were included in BRIDGE-PMR; 38 patients with newly diagnosed polymyalgia rheumatica and 9 patients with relapsing disease who were taking 7·5 mg or more of prednisone. At week 21, 11 (48%) of 23 patients in the rituximab group and 5 (21%) of 24 patients in the placebo group were in glucocorticoid-free remission (p=0·049). The next question was whether this difference in glucocorticoid-free remission remains during prolonged follow-up.

In *The Lancet Rheumatology*, Thomas E Bolhuis and colleagues present the results from the extension phase of the BRIDGE-PMR trial, in which patients were followed for 1 year after treatment with rituximab or placebo.[8] The authors should be complimented for this investigator-initiated trial, in which they were able to collect 1-year follow-up data for all patients (ie, no patients were lost to follow-up), and maintain blinding of treating physicians, patients, and data analysts during the extension period. Maintenance of blinding is important since the PMR-AS includes subjective VAS scores. Because several patients did not attend follow-up appointments due to the COVID-19 pandemic, PMR-AS values were imputed for 6 of 47 patients who had a missing score component (4 in the rituximab group and 2 in the placebo group). In the complete case analysis (ie, all patients with complete data), 9 (47%) of 19 patients in the rituximab group and 5 (23%) of 22 patients in the placebo group were in glucocorticoid-free remission at 1 year (absolute difference 25% [95% CI −4 to 53], relative risk (RR) 2·1 [0·8 to 5·2]; p=0·12). In the imputed dataset, 12 (52%) of 23 patients in the rituximab group and 5 (21%) of 24 patients in the placebo group were in glucocorticoid-free remission at 1 year (absolute difference 31% [95% CI 5 to 57], RR 2·5 [1·0 to 6·0]; p=0·04). There were also between-group differences at 1 year in cumulative glucocorticoid dose (median dose: 1595 mg [IQR 1275–2260] for rituximab *vs* 2302 mg [1595–2881] for placebo; p=0·04) and PMR-AS (median

score: 4·2 [2·3–7·2] *vs* 7·2 [3·7–17·5], p=0·046), favouring rituximab. No clear differences were observed in safety-related outcomes or health status (EQ-5D-5L median utility score: 0·71 [0·63–0·77] *vs* 0·71 [0·65–0·77], p=0·87).

The original trial recruited patients with newly diagnosed polymyalgia rheumatica as well as those with relapsing disease—all participants fulfilled the 2012 ACR–European Alliance of Associations for Rheumatology classification criteria (excluding ultrasound) for polymyalgia rheumatica. In patients with newly diagnosed disease, the proportion of patients in glucocorticoid-free remission at 1 year was numerically higher in the rituximab group (11 [58%] of 19) *vs* 3 [16%] of 19 for placebo). In patients with relapsing disease, this proportion numerically favoured the placebo group (1 [25%] of 4 for rituximab *vs* 2 [40%] of 5 for placebo), but these results should be interpreted with caution due to the small groups.

Overall, the extension of this proof-of-concept trial supports the sustained efficacy of rituximab. Further research is needed to confirm these promising results for rituximab,[7,8] as well as for the interleukin-6 receptor inhibitor tocilizumab.[9,10] Future trials can use glucocorticoid-free remission as the primary endpoint and the individual composite domains (cumulative glucocorticoid dose and items of PMR-AS) as secondary endpoints to explore which particular domains are responsive to treatment. Furthermore, it is important to adequately power both subgroups of newly diagnosed and relapsing patients to investigate the clinical efficacy and therapeutic window of opportunity in these patients. Imaging for occult giant cell arteritis, which is associated with a refractory disease course in polymyalgia rheumatica, should also be considered in this context. Hopefully, these efforts will eventually lead to the official licensing of systemic biological treatments for the indication of polymyalgia rheumatica, broadening treatment options in this disease.

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*Suzanne Arends, Kornelis SM van der Geest, Maria Sandovici
**s.arends@umcg.nl**

Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, 9700 RB, Groningen, Netherlands (SA, KSMvdG, MS)

1 Arends S, de Wolff L, van Nimwegen JF, et al. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure. *Lancet Rheumatol* 2021; **3:** e553–62.
2 Seror R, Baron G, Camus M, et al. Development and preliminary validation of the Sjögren's Tool for Assessing Response (STAR): a consensual composite score for assessing treatment effect in primary Sjögren's syndrome. *Ann Rheum Dis* 2022; **81:** 979–89.
3 Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2015; **74:** 1799–807.
4 Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Ann Rheum Dis* 2017; **76:** 543–46.
5 Mackie SL, Twohig H, Neill LM, et al. The OMERACT core domain set for outcome measures for clinical trials in polymyalgia rheumatica. *J Rheumatol* 2017; **44:** 1515–21.
6 Leeb BF, Bird HA. A disease activity score for polymyalgia rheumatica. *Ann Rheum Dis* 2004; **63:** 1279–83.
7 Marsman DE, den Broeder N, van den Hoogen FHJ, den Broeder AA, van der Maas A. Efficacy of rituximab in patients with polymyalgia rheumatica: a double-blind, randomised, placebo-controlled, proof-of concept trial. *Lancet Rheumatol* 2021; **3:** e758–66.
8 Bolhuis TE, Marsman DE, den Broeder AA, den Broeder N, van der Maas A. 1-year results of treatment with rituximab in polymyalgia rheumatica: an extension study of a randomised double-blind placebo-controlled trial. *Lancet Rheumatol* 2023; published online March 6. https://doi.org/10.1016/S2665-9913(23)00032-2.
9 Bonelli M, Radner H, Kerschbaumer A, et al. Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomised controlled trial. *Ann Rheum Dis* 2022; **81:** 838–44.
10 Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, et al. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: a randomized clinical trial. *JAMA* 2022; **328:** 1053–62.

# Methotrexate in rheumatoid arthritis—another brick in the wall

Methotrexate has remained the mainstay in rheumatoid arthritis therapy, and the most recent EULAR recommendations emphasise methotrexate as part of the first-line treatment strategy unless contraindicated or not tolerated.[1] This recommendation is based on more than 35 years of experience with methotrexate, its well characterised clinical efficacy, inhibition of radiographic progression, improvement of functional capacity, and reduction of cardiovascular morbidity and mortality.

At the cellular level, methotrexate interferes with several pathways that mediate immune suppression including the inhibition of dihydrofolate reductase, an increase of adenosine, and suppression of proinflammatory cytokines.[2]

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