

## Response to: Correspondence on 'No efficacy of anti-IL-23 therapy for axial spondyloarthritis in randomised controlled trials but in post hoc analyses of psoriatic arthritis-related 'physician-reported spondylitis'?' by Braun and Landewé

With great interest we have read the comments of Gladman *et al*<sup>1</sup> to our viewpoint.<sup>2</sup> We are especially grateful that we were able to provoke a statement of such a large and distinguished group of experts in psoriatic arthritis (PsA). However, it looks like that there is little reason for dissent. Thus, Gladman *et al* agree with us that post hoc analyses of randomised PsA trials have very little value beyond the generation of testable hypotheses per se, that patient-reported outcomes alone do not suffice to declare axial PsA a distinguishable entity, and that Bath ankylosing spondylitis (AS) disease activity index (BASDAI) and AS disease activity index (ASDAS) are instruments developed to measure disease activity in axial spondyloarthritis (axSpA). Of course, the latter does not necessarily imply that they will not be responsive or discriminatory in PsA — with — or without axial symptoms. There seems to be also agreement that simply relying only on radiographic sacroiliitis to confirm the presence of axPsA is a limitation to post hoc analyses such as performed for the trials on the IL-23 inhibitor guselkumab in active PsA despite standard therapies (DISCOVER).<sup>3</sup>

One concern, however, remains and that pertains to the authors' reference to enthesitis, general pain and fatigue, all patient-reported symptoms that are common in patients with psoriasis, PsA or axSpA. While the suffix —itis in enthesitis suggests an inflammatory genesis that may require or even justify treatment with biologic (b) — or targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs), the finding of enthesitis in more than 50% of patients in some modern trials is spurious and better reflect some enthesiopathy than 'real' or better inflammatory enthesitis. Indeed, our trial instruments for enthesitis at best assess pain spontaneously or at pressure, and not pain necessarily caused by inflammation. Obviously, 'real' imaging proven enthesitis does also exist and has been reported in these diseases but this is far rarer. Recent insights into the existence of central sensitisation mechanisms such as in secondary fibromyalgia can be held responsible for generalised pain or 'widespread enthesitis', fatigue and other patient-reported symptoms. While this does not detract from the notion that common including residual symptoms of pain and fatigue represent an unmet need, we should not forget that there is no direct inflammatory link. This means they will most likely not be sensitive to drugs with a presumed anti-inflammatory mode of action and a different working spectrum. Sky high placebo response rates in some of these trials add to the impression that mechanisms not related to inflammation including expectation bias are responsible, and that improvements in active drug arms are at least in part non-specific. The net effect of most bDMARDs and tsDMARDs on symptoms such as 'enthesitis' or better enthesiopathy, fatigue and widespread pain will likely be disappointing, unlike sponsors of these drugs sometimes proclaim. Of interest, commonly used classification criteria for PsA (CASPAR) have not included enthesitis at all<sup>4</sup> and ASAS classification criteria for peripheral spondyloarthritis<sup>5</sup> just included enthesitis on the same level as arthritis and dactylitis without defining how it had been assessed and diagnosed. In the publication of the CASPAR

criteria diffuse enthesitis pain and inflammatory heel pain were differentially studied and found to have rather limited sensitivity. This documents the clinical and scientific challenges we are facing with diagnosis and classification of enthesitis and axial involvement in both axSpA and PsA.

In summary, we see more agreement on the issued raised by us<sup>2</sup> than dissent and we are — similar to our colleagues — eagerly waiting for more results of clinical trials and cohort studies<sup>5</sup> designed to shed more light on the interesting issue of more or less similarity and difference between involvement of the axial skeleton in PsA and axSpA. Finally we would like to mention that both, patients with axSpA and (axial) PsA are not protected from degenerative and other reasons for back pain — a major challenge to the differential diagnosis in these frequent chronic inflammatory rheumatic diseases.

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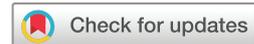
**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Commissioned; internally peer reviewed.

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**To cite** Landewé RBM, Braun J. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2022-222359

Received 15 March 2022

Accepted 16 March 2022



► <http://dx.doi.org/10.1136/annrheumdis-2022-222161>

*Ann Rheum Dis* 2022;0:1. doi:10.1136/annrheumdis-2022-222359

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