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Title: Efficacy of Guselkumab, a Monoclonal Antibody that Specifically Binds the p19 Subunit of IL-23, on Axial Involvement in Patients with Active PsA with Sacroiliitis: Post-hoc Analyses Through Week 52 from the Phase 3, Randomized, Double-blind, Placebo-controlled DISCOVER Studies

Editorial - How should we define disease and outcomes in axial PsA?

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Axial involvement (inflammation of sacroiliac joints and/or spine) is reported in 25-70% of psoriatic arthritis (PsA).

In this issue of The Lancet Rheumatology, Philip Helliwell and colleagues report results of guselkumab on axial signs and symptoms of PsA within a pooled analysis of the DISCOVER 1 and 2 studies. For this analysis, patients with axial involvement defined by local imaging evidence of sacroiliitis were selected. This showed a significant improvement in multiple axial outcomes including the Bath ankylosing spondylitis disease activity index (BASDAI), modified BASDAI (excluding question 3), spinal pain, and ASDAS.

Although IL-23 inhibitors such as guselkumab have proven efficacy in psoriasis and peripheral PsA, their efficacy has been questioned in axial disease following negative trials in axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS) for other IL-23 inhibitor agents.^{1,2} These results were surprising given the efficacy of IL-23 inhibitors in peripheral PsA and the efficacy of IL-17 inhibitors in PsA and axSpA.

The reason for the lack of efficacy of IL-23 blockade in the axial skeleton in AS is not well understood. It has been hypothesized that in bone marrow IL-17 and TNF production might be (partially) independent of IL-23 signalling³. Furthermore, there is an open question whether there is a pathophysiological difference in the process of axial inflammation between primary axSpA and PsA potentially determining different treatment response.

In previous PsA trials, the presence of axial involvement was defined by local investigators. In DISCOVER 1 and 2, investigators were required to report imaging evidence of axial involvement (sacroiliitis by radiographs and/or magnetic resonance imaging - MRI) but these were only read locally. Whilst the requirement for imaging may improve specificity, previous research has raised concerns about the accuracy of axial imaging reporting, particularly by non-specialist radiologists.^{4,5} Thus, a central evaluation of imaging (with focus on MRI that – despite some limitations – has a better reliability than radiographs and is able to detect early inflammatory changes) would be necessary for any prospective study addressing axial PsA.

There is an urgent need for accurate classification criteria for axial PsA to support future research. In order to close this gap, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Assessment of Spondyloarthritis International Society (ASAS) have started a joint initiative to develop a unified definition for axial PsA including the pivotal role of imaging for the objective confirmation of axial PsA. A prospective cohort study (AXIS) has been designed to comprehensively characterise axial involvement in PsA and is underway now.⁶

The other key issue is how to measure axial disease activity. Typically, only 2-5% of patients with PsA have sole axial disease, so most patients have active peripheral arthritis, enthesitis, dactylitis and skin disease. Composite endpoints such as BASDAI or ASDAS may be impacted by disease activity, and therefore treatment response, in other disease domains. Previous research has shown similar BASDAI in patients with/without axial involvement and correlates highly with a patient global score.^{7,8} The authors sought to mitigate this by reporting results of a modified BASDAI excluding question 3 (peripheral joint pain). However, a recent study found that all of the individual BASDAI questions showed similar baseline disease activity levels and standardised response means after effective treatment in those with and without peripheral disease, even question 2 which asks about spinal pain.⁹

Therefore, the results of this analysis, while encouraging, raise a concern that response – if measured by composite instruments including non-axial domains – would be seen due to the improvements in PsA symptoms even if the drug were not effective in the spine. In any case, a confirmation in a prospective, randomized controlled trial in patients with centrally confirmed evidence of axial PsA on imaging is required to answer the question about IL-23 efficacy in the axial domain. Imaging can be used for patient inclusion and an outcome measure in prospective trials. A recent study specifically addressing efficacy of secukinumab, an IL-17 inhibitor, in axial PsA included MRI scans in addition to clinical outcome measures to provide objective evidence of efficacy.¹⁰ Although relying on MRI imaging may also have limitations, this is currently the only way to provide objective evidence of spinal efficacy.

Studies addressing efficacy of different therapies in axial PsA are of high importance for treatment guidelines and for daily clinical practice. Current treatment guidelines in PsA rely largely on the results of studies in primary axSpA. Evidence of efficacy in axial PsA would certainly affect not only the guidelines but also a choice of an appropriate treatment option in an individual patient.

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