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IL-23 and axial disease: do they come together?

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Abstract

IL-23 is a key cytokine in the pathogenesis of spondyloarthritides, including PsA and axial spondyloarthritis, as well as related conditions, such as psoriasis and IBD. Genetic associations, animal models and translational studies in humans demonstrate the key role played by IL-23, especially when coupled with downstream overexpression of IL-17 via stimulation of T helper 17 (Th17) and other cells by IL-23. Whereas IL-23 inhibition has shown clear-cut benefit in psoriasis and peripheral manifestations of PsA, trials of IL-23 inhibitors have failed in the treatment of ankylosing spondylitis. More recently, exploratory data from PsA patients with axial symptoms suggests that improvement may occur, but needs confirmation in dedicated axial spondyloarthritis (axSpA) trials. Hypotheses for these apparently conflicting findings about IL-23 inhibition in various forms of spondylitis are discussed.

Key words: interleukin-23, axial spondyloarthritis, psoriatic arthritis, axial psoriatic arthritis, interleukin-17

Rheumatology key messages

- IL-23 is a key cytokine involved in the pathogenesis of several related immune mediated inflammatory diseases: psoriasis, PsA, axSpA and IBD.
- Why have IL-23 inhibitors demonstrated substantial benefit in treatment of psoriasis, PsA and potentially in the axial component of PsA, but not in AS?
- Further research is needed to elucidate whether there are immunobiologic differences between axSpA and axial PsA that may account for differential therapeutic effects of IL-23 inhibition.

SUPPLEMENT

Introduction

Based on evidence from genetic, translational and animal studies, it is clear that the IL-23/IL-17 pathway plays an important role in the pathogenesis of the family of spondyloarthritides, including PsA, axial spondyloarthritis (axSpA), as well as psoriasis and IBD, and related conditions. Evidence from clinical trials of IL-23 and IL-17 inhibitors in humans shows clear-cut benefit for psoriasis, peripheral manifestations of PsA and IBD. Why then have trials of two treatments, the p19IL-23 inhibitor, risankizumab, and the p40IL-12/23 inhibitor, ustekinumab, failed in ankylosing spondylitis (AS) trials? This article addresses the role of IL-23 in spondyloarthritis pathogenesis and the controversy regarding its efficacy in AS *vs* axial PsA (axPsA). Has the apparent failure of IL-23 inhibition in spinal inflammation been a result of trial design, study population or dose, or is the immunobiology of axial inflammation different enough from peripheral joint, enthesial and skin disease that IL-23 inhibition does not control inflammation in the spine, for some reason. Further, how do we incorporate recent data that suggest that IL-23 inhibition may yield symptomatic benefit in the axial manifestations of PsA? Is this condition immunobiologically distinct enough from AS that IL-23 inhibition works in axial PsA (axPsA) and not in axial spondyloarthritis (axSpA)? To address these questions, we will begin with a review of the immunobiology of IL-23 in the spine followed by a review of clinical trial data, and end with a summary of next steps in the research agenda.

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The role of the IL-23/17 pathway in the pathogenesis of axSpA

In axial disease, such as axSpA and axPsA, the primary pathologies include sacroiliitis and spondylitis with demonstration of subchondral bone inflammation and fatty metaplasia of the sacroiliac (SI) joints (osteitis) and vertebral bodies on MRI, synovitis of the SI and facet joints, enthesitis and ligament inflammation of the spine [1, 2]. What is the evidence for the role of IL-23 in axial

disease? IL-23 is a member of the IL-12 superfamily and is a heterodimer consisting of both a p40 and p19 chain. It is produced primarily by dendritic cells, monocytes and macrophages. There is evidence that IL-23 can migrate from barrier sites such as the gut and skin, where dendritic cells have been activated, and travel to sites of disease pathogenesis, although further research is needed on this subject [3]. A key pro-inflammatory role of IL-23 is stimulation of T helper 17 (Th17) cells to produce IL-17, IL-22 and TNF. Genetic evidence for involvement of the IL-23/17 pathway has been derived originally from genome-wide association studies (GWAS) that demonstrated association of the IL-23 receptor gene and AS [4, 5], association of AS risk genes with STAT2/3 and other Th17 related genes [6]. Additionally, there are Th17 cell epigenetic elements associating AS, psoriasis and IBD [7]. Sherlock demonstrated that in SpA-prone mice, IL-23 administered in mini-circles migrated to enthesial insertion sites and the aortic root, binding to resident RORγt+CD3+CD4-CD8- lymphoid cells leading to inflammation and new bone formation [8]. Numerous studies have demonstrated elevation of Th17, Th22 and γδT cells in peripheral blood and increased levels of IL-17, IL-23 in serum and synovium of AS patients [9]. It has been shown that in the skin, monocytes and increased production of IL-23 is needed for excess production of IL-17 [10], driving pathogenesis of psoriasis. In bone marrow and synovium, the interaction between mesenchymal cells and T cells is sufficient for the production of IL-17 and the presence of monocytes and IL-23 is not as important [11]. These studies suggest that there may be a difference in the role of IL-23 in driving inflammation in different tissue compartments. It has also been demonstrated that various cells can produce IL-17 independent of the effect of IL-23, including mucosal-associated invariant T (MAIT) cells, innate lymphoid cell 3 (ILC3) and γδ T cells [12, 13]. Thus, differential activity of these cells in various tissue sites may contribute to a predominantly IL-17 rather than IL-23 driven pathology. In an HLA-B27 transgenic rat model, inhibition of IL-23 receptor abrogated development of [14] spine and peripheral arthritis, while similar treatment was not effective in ameliorating established disease [15]. IL-17A inhibition was able to reduce spine and peripheral arthritis both prophylactically and in established disease. This suggests that IL-23, at least in this model, may have a role in initiation but not maintenance of spondyloarthritis disease activity.

Numerous animal studies describe a link between gut inflammation and spondyloarthritis [3, 16, 17]. Spondyloarthritis-prone transgenic rats display an association between intestinal inflammation and increased expression of IL-23 and IL-17 in intestinal tissues. Human gut microbiota studies demonstrate dysbiosis of gut microbiota with either increased presence of certain bacteria and decreased presence of others compared with healthy controls. Dysbiosis of the gut can lead to dendritic cell activation and increased production of IL-23 [18]. It has been noted that axSpA patients have not only an increased prevalence of clinically diagnosed Crohn's disease and ulcerative colitis, but almost 50% will have evidence of sub-clinical intestinal inflammation on biopsy [19]. Increased IL-23 production in the intestine of AS patients compared with healthy controls has been demonstrated. There is also evidence of trafficking of IL-23 from the gut to pathologically involved musculoskeletal tissues in axSpA [3].

Clinical trial data

IL-12/23i and IL-23i in axSpA

An open label trial of ustekinumab, an IL-12/23 inhibitor that acts by binding to the p40 subunit of IL-12 and IL-23 was conducted in 20 patients in Germany [20]. Approved for psoriasis and PsA, the drug is considered to primarily act through inhibition of IL-23. The results were positive. Sixty-five percent of patients achieved Assessment in SpondyloArthritis international Society (ASAS) 40 response and spine MRI scans showed diminishment of inflammatory signal. Because the IL-17 inhibitor class, including secukinumab and ixekizumab, has demonstrated significant benefit in AS, and because it was thought that IL-23 and IL-17 were coupled, with IL-23 upstream of IL-17 due to its stimulatory role for Th17 cells which produce IL-17, this apparently positive result was met with optimism. Instead of performing a phase 2 placebo-controlled trial, three large placebo-controlled trials were designed and launched to assess effectiveness and safety in biologic-naïve AS, TNF inhibitor-experienced AS, and bio-naïve non-radiographic axSpA (nr-AxSpA). The first of these trials to complete, the biologic-naïve AS trial, did not show statistical separation from placebo in the primary or secondary endpoints [21]. The placebo, 45 mg and 90 mg ustekinumab arms demonstrated 28%, 31% and 28% achievement of ASAS 40 response. There was virtually no change in MRI inflammation signal. The other two trials, not yet completed, were terminated and the program was deemed unsuccessful. Meanwhile, a parallel phase 2 trial of the p19IL-23 inhibitor, risankizumab, also reported negative results, with no statistical separation between active treatment and placebo, nor was there a dose response effect [22]. In the placebo, 18 mg, 90 mg and 180 mg arms ASAS 40 response was 17.5%, 25.5%, 20.5%, 15%, respectively. Similar to the ustekinumab trial, improvement of inflammation visualized by MRI was not seen.

These findings prompted two editorials exploring the potential reasons for lack of success with a pure IL-23 inhibitor and a blended IL-12/23 inhibitor [23, 24]. Mease raised a number of hypothetical issues. Was it the study population? In biomarker analysis of the ustekinumab study, there was no difference between the placebo and treatment arms in concentration of IL-23, IL-17A, IL-17F, IL-22, IFNγ or IL-12p70 [23]. Did the high placebo rate disallow discrimination, noting that the traditional outcome measures that have reliably shown

discrimination and response in TNF and IL-17 inhibitor trials, such as ASAS 40, are patient-reported? But note that even objective markers, such as MRI, did not change. In truth, the trial populations of both of these studies mirrored the populations of successful trials with TNF and IL-17 inhibitors, so it seems less likely that the reason is related to trial-specific issues and is more likely related to immunobiology. It is now understood that IL-17 overexpression can emanate not only from Th17 cells, which are stimulated by IL-23, but also from other cells that express IL-17 independent of IL-23 activity, including resident lymphoid cells acting in the innate immune system. In an SKG mouse model, curdlan-induced elevations of TNF, IL-23 and IL-17 resulted in exuberant enthesophyte formation at ankle entheses and vertebral erosions in the spine [25]. Each of these findings was attributed to different immunobiologic mechanisms operating differentially in the periphery and spine. This example speculatively raises the possibility of different immunobiology of peripheral *vs* spine bone and enthesial pathology. Siebert similarly suggests that disease in the various tissue domains of spondyloarthritis may not share common pathogenic pathways, citing several lines of evidence. These include evidence of IL-23 independent induction of IL-17 from $\gamma\delta$T and innate lymphoid cells in animal models, which may also be applicable in humans as a source of IL-17 implicated in disease chronicity in AS [26]. RORγt acts as a key intracellular transcription factor in the IL-17 pathway and can function independent of IL-23 [26]. Siebert also postulates alternative cytokines other than IL-23 p19/p40 signalling through the IL-23 receptor to stimulate IL-17 production, possibly driven by local micro-trauma [26]. He goes on to posit that whereas IL-23 may be an important cytokine in the early stages of SpA pathogenesis, the mature immunophenotype may not respond to p19IL-23 inhibition. It is not typically feasible to enrol very early patients in clinical trials, thus it is impractical to target such a population to test if response will be different.

Trial data in axPsA

As a result of these failed trials in AS, trials of IL-23 inhibitors are not, at this time, being planned for this condition. What about patients with axPsA? Historically, it has been assumed that the expected efficacy of a medication or class of medications could be extrapolated from evidence in AS/axSpA clinical trials. Indeed, the various treatment recommendations for PsA have made these assumptions. Group for Assessment of Psoriasis and PsA (GRAPPA) treatment recommendations consider treatment efficacy in six clinical domains: peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis. In the last set of recommendations, published in early 2016, the group recommended to start with NSAIDs, followed by TNF and IL-17 inhibitors. Ustekinumab was also recommended based on the single positive open-label trial. In the next update of the recommendations, due shortly, this latter recommendation will be removed based on the failed placebo-controlled trials. There are several reasons why the axial domain has not been formally assessed in PsA clinical trials. A minority of patients have axial disease, so the study will not be powered to reliably demonstrate treatment response. There is, to date, no formal classification of axPsA, so there is a risk of mis-classifying axial patients to be studied. Analysing serial MRI scans of sacroiliac joints and spine is expensive and cumbersome. Some PsA trials have included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Use of the BASDAI outside of its original purpose to be used in axSpA, e.g. in a PsA cohort, has been criticized because by including several questions that do not solely relate to the spine, such as peripheral arthritis and enthesitis, fatigue, and stiffness, it is too non-specific. It can show elevated disease activity and improvement with treatment even in patients with no spine disease. To increase specificity, some trials have restricted its analysis to only those patients the investigator designates as having axPsA and also separately reported the single question related to spine pain. To date, only one clinical trial has been dedicated to axPsA, the recently presented MAXIMISE trial of secukinumab. Investigators enrolled PsA patients they thought had axPsA and elevation of measures used in axSpA trials, such as BASDAI and Ankylosing Spondylitis Disease Activity (ASDAS). ~30% were HLA-B27 positive, appropriate for an axPsA population. As might have been expected from axSpA studies with secukinumab, the trial was successful, with two-thirds of patients in both dose groups (150 and 300 mg) meeting the primary end point of ASAS 20 response and all key secondary measures *vs* a third of the placebo patients. MRI scans of pelvis and spine were obtained but MRI abnormality was not required for study inclusion. Of note, 40% of the population did not show inflammatory signal in either sacroiliac or spine MRI at the time of enrolment. Low or absent MRI signal in the spine of axial PsA patients has been noted previously [27]. In the 60% who did, significant reduction in inflammation signal was observed [28].

IL-12/23i and IL-23i in axPsA

In the absence of a dedicated trial of an IL-23 inhibitor in axPsA, can we glean any evidence from trials of IL-23 agents in PsA about axPsA? A substudy of the pooled PSUMMIT 1 and 2 studies of ustekinumab in PsA analysed 223 patients considered by their enrolling investigator to have axPsA, derived from 747 TNF-naïve patients in the two studies [29]. HLA-B27 positivity was noted in 25% of this group and mean spine pain, overall BASDAI and BASDAI without peripheral joint pain question was ~6.5 and ASDAS 3.8. Improvement in all measures: BASDAI, mBASDAI, spine pain and ASDAS demonstrated nominally superior efficacy compared with placebo, suggesting benefit for axial symptoms. A more recent set of trials of the p19IL-23 inhibitor, guselkumab, DISCOVER 1 and 2 [30, 31] showed highly significant improvements in skin manifestations of psoriasis,

peripheral arthritis, enthesitis and dactylitis, and all patient-reported outcomes of function, quality of life and fatigue. In these trials, a novel approach was used to more objectively identify a subset of patients with axPsA [32]. The patients in this cohort were (i) identified as having axPsA by the investigator, (ii) had BASDAI and spine pain $\geq$4, and (iii) had imaging consistent with sacroiliitis. Regarding this last point, the patients from DISCOVER 1 had historical imaging of the pelvis, read locally by radiologist and/or rheumatologist, consistent with sacroiliitis. The patients from DISCOVER 2 had pelvic X-rays at baseline, locally read, consistent with sacroiliitis. Out of a total of 1120 patients in both studies, 312 qualified for this substudy, i.e. ~30%. Of these, ~30% were HLA-B27 positive. At the primary end point of the study, 24 weeks, significant improvement, similar to the improvement seen in successful axSpA trial, in both guselkumab dose arms was noted for overall BASDAI, question 2 of the BASDAI related to spine pain, modified BASDAI (with peripheral arthritis question removed), Ankylosing Spondylitis Disease Activity-C-reactive protein (ASDAS-CRP), ASDAS clinically important improvement, major improvement and inactive disease. Thus, it appeared there was at least symptomatic improvement. MRI was not assessed. These substudy results are considered exploratory. Significant limitations include such factors as local *vs* central read of the baseline X-rays (which may explain the unexpected high prevalence of 'axial disease'), lack of standardization of what the investigator considered as axPsA, and awareness that the improvement of the outcome measures could have been significantly influenced by improvement in peripheral musculoskeletal domains and the skin. As an exploratory study, however, it does open the door to the possibility that treatment of axPsA with an IL-23 inhibitor may yield a different result than treatment of AS. In order to validate these findings, a dedicated trial in axPsA, including serial MRI assessment of sacroiliac joints and spine, will need to be done.

These trials, especially the IL-23 inhibitor substudy, raise the question, how similar or different is axPsA from axSpA? A number of studies, particularly longterm PsA and axSpA registries, have identified key differences and similarities. At a genetic level, HLA-B27 is present in both conditions, but typically in just 30% of PsA patients and over 85% of axSpA patients [2]. Genes observed in axPsA patients include HLA-B08, HLA-B38, HLA-B39, HLA-Cw*07:02 [2]. HLA-B08 has been associated with the asymmetric sacroiliitis, whereas HLA-B27 is associated with symmetric sacroiliitis [2]. Numerous clinical differences exist. Five to 28% have evidence of axPsA in early stages of PsA while 25% to 70% show evidence of it in longstanding PsA, unlike axSpA in which the disease is wholly manifest early in the course of the disease. AxSpA patients, particularly those showing sacroiliac damage on X-ray, are predominantly male, whereas axPsA includes a larger number of female patients [2]. Patients with axPsA may be asymptomatic despite evidence of imaging changes consistent with the disease, and are less likely to endorse inflammatory back pain criteria questions, and less impairment of spine mobility [2]. Up to a quarter of axPsA patients may not demonstrate sacroiliac changes but will show characteristic imaging changes in the cervical or lumbar spine. On X-ray, axPsA patients are more likely to demonstrate asymmetric sacroiliitis, non-marginal/'chunky' syndesmophytes, and syndesmophyte involvement that is asymmetric and may skip vertebral levels. Further, in axPsA there is a greater percentage of female patients, less HLA-B27 positivity, less inflammatory back pain, and overall less spinal disease severity [33, 34]. Missing from this list of characteristic differences is evidence for immunobiologic difference at the tissue level. This is a consequence of the impracticality of obtaining tissue samples from bone, joint and entheseal sites in the spine for analysis. In the absence of such evidence, we must derive conclusions from genetic, clinical, imaging and treatment result differences. Further, a combined research effort between GRAPPA and ASAS is now underway to develop formal classification criteria for axPsA and study in an appropriate way the true magnitude of the axial disease problem in PsA. This will involve a careful study—clinical, genetic, biomarker, imaging—of several hundred patients with PsA, including axial involvement [35]. Having such criteria will aid future research by helping to identify the correctly classified patients for study.

Conclusion

IL-23 plays a key role in the pathogenesis of spondyloarthritides, including PsA and axSpA, as well as related conditions, such as psoriasis and IBD. Its specific role in the induction and maintenance of inflammation and tissue destruction/remodeling in the spine is not as well understood, partly due to difficulty in obtaining spine bone, enthesial and joint tissue by biopsy in that location for immunohistochemistry analysis. Two clinical trials of IL-23 inhibitors in AS show no benefit for symptomatic relief or MRI measures of inflammation. This is in contrast to studies showing striking benefit of these agents for psoriasis and solid benefit for peripheral musculoskeletal domains of PsA such as arthritis, enthesitis and dactylitis. An exploratory sub-study of the guselkumab phase 3 trials in PsA appears to show symptomatic benefit of spine symptoms in patients with imaging-confirmed sacroiliitis. Despite the fact that there are a number of relevant methodological issues with this type of subanalyses, the finding raises the possibility that IL-23 inhibition may possibly benefit axPsA, requiring further study to confirm, and which illuminates potential immunobiologic differences between axSpA and axPsA.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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