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17 and 23: prime numbers for ankylosing spondylitis?

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Treatment options for patients with ankylosing spondylitis have improved considerably over the last decade with the availability of tumor necrosis factor- α (TNF)-inhibitors. Traditional disease-modifying anti-rheumatic drugs like methotrexate that are effective in rheumatoid arthritis, have no proven benefit for spinal inflammatory arthritis, the hallmark of ankylosing spondylitis. TNF-inhibitors are often recommended when first-line therapy with NSAIDs fails to control disease activity, and they are effective at reducing inflammation and symptoms of spinal pain and stiffness, and improve function in the majority of patients¹. However, 20–40% either do not respond or respond inadequately to TNF-inhibitors, and it remains unclear whether this class of biologics can slow new bone formation and resulting spinal fusion, although recent evidence is encouraging.² Thus, despite advances in treatment, there is a need for new drugs that can improve the outcome of this disease.

The IL-23/IL-17 axis has emerged as an important piece of the pathogenesis puzzle in several immune-mediated inflammatory diseases including multiple sclerosis, psoriasis, inflammatory bowel disease, rheumatoid arthritis and spondyloarthritis. In ankylosing spondylitis this evidence derives from a remarkable convergence of discoveries from genome-wide association studies,³ animal models,⁴ and translational studies,^{5–8} that implicate not only IL-17, but also upstream cytokines like IL-23 that may drive pathogenesis and the unique phenotype,^{4,8,9} in part by promoting IL-22 production⁹. However, despite strong evidence supporting the importance of IL-17 in several inflammatory diseases, clinical trials blocking this cytokine or its receptor have met with mixed success. In psoriasis there is clear evidence of benefit,^{10,11} while in Crohn's disease results have been disappointing.¹² In rheumatoid arthritis, psoriatic arthritis, and uveitis the results are less than clear; while in some cases there is evidence of clinical benefit, primary endpoints of these trials were not met.^{13–15}

In this issue of *The Lancet*, Baeten and colleagues provide the first evidence that targeting IL-17 with secukinumab may be beneficial in the treatment of active ankylosing spondylitis.¹⁶ The primary evidence of efficacy was that a larger proportion of patients in the secukinumab arm (59.2%) than in the placebo arm (24.5%) achieved an ASAS20 response. An ASAS20 response is a composite measure of change in four patient-reported outcomes (patient global assessment, spinal pain, physical function limitations, and morning stiffness, each measured on a 0–10 scale) that requires improvement in at least three of these outcomes by at least 20% and by at least 1 unit, with no worsening in the remaining measure. This is a well-accepted response criterion, and a reasonable choice for the primary efficacy endpoint in a proof-of-concept study. The ASAS20 response to secukinumab was comparable to those seen in many trials of TNF-inhibitors. More stringent criteria such as ASAS40 and ASAS5/6 responses used as secondary outcomes also appeared greater in the secukinumab group, but were not assessed for statistical significance. Bayesian methods

were used to compare ASAS20 responses between treatment groups, leveraging information on placebo responses in trials of TNF-inhibitors to supplement the observed data of placebo-treated subjects. Because this approach permits studies with fewer placebo-treated subjects, Bayesian methods are increasingly used in phase I and II trials. Of interest in this trial is the peak ASAS20 response at week 6 and the abrupt drop at week 8, a change not mirrored by the ASAS40, ASAS5/6, or the Bath AS Disease Activity Index. This may indicate that the ASAS20 is more sensitive to treatment effects than the other measures, but in trials of TNF-inhibitors, these measures tend to move coordinately.¹⁶

The results of this study need to be viewed with recognition of both the short duration of treatment and the small sample. Treatment effects were evaluated at 6 weeks, after subjects had received two loading doses of study medication. Although subjects were randomized, the treatment groups were not particularly well balanced, which can occur when the sample is small. More women and subjects with more enthesitis and less spinal inflammation on magnetic resonance imaging were in the secukinumab arm, and whether differences in these characteristics influenced the results is also not clear.

The glimmer of a clinical effect targeting IL-17 is welcome news for a condition that needs more treatment options. However, as with many proof-of-concept studies, we are left wanting more. Will there be continued clinical efficacy with more prolonged treatment, and what are the effects of secukinumab on serum or tissue cytokines and T cells in the IL-23/IL-17 pathway? Will secukinumab have an impact on spinal fusion, and what can we expect for a long-term safety profile? If proven efficacious, future studies will need to address treatment strategies, and whether IL-17 blockade can provide relief for patients who have failed TNF-inhibitors, or serve as an alternative to TNF inhibition in patients who fail NSAID treatment. If targeting IL-17 is beneficial in ankylosing spondylitis, can IL-23 be far behind? Modulating the effects of IL-17 and IL-23 may hold the key to breakthroughs in the treatment of ankylosing spondylitis – at least until we can begin to focus even further upstream on the question of what is driving activation of the IL-23/IL-17 axis.

References

1. Sieper J. Developments in therapies for spondyloarthritis. *Nat Rev Rheum.* 2012; 8:280–287.
2. Haroon N, Inman RD, Learch TJ, et al. The impact of TNF inhibitors on radiographic progression in ankylosing spondylitis. *Arth Rheum.* 2013 Accepted Article. [Epub ahead of print]. 10.1002/art.38070
3. Reveille JD. Genetics of spondyloarthritis – beyond the MHC. *Nat Rev Rheumatol.* 2012; 8:296–304. [PubMed: 22487796]
4. DeLay ML, Turner MJ, Klenk EI, et al. HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. *Arth Rheum.* 2009; 60:2633–43. [PubMed: 19714651]
5. Bowness P, Ridley A, Shaw J, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. *J Immunol.* 2011; 186:2672–80. [PubMed: 21248258]
6. Appel H, Maier R, Wu P, et al. Analysis of IL-17+ cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. *Arth Res & Ther.* 2011; 13:R95. [PubMed: 21689402]
7. Noordenbos T, Yeremenko N, Gofita I, et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondyloarthritis. *Arth Rheum.* 2012; 64:99–109. [PubMed: 21968742]
8. Appel H, Maier R, Bliel J, et al. In situ analysis of IL-23 and IL-12 positive cells in the spine of patients with ankylosing spondylitis. *Arth Rheum.* 2013 Accepted Article. [Epub ahead of print]. 10.1002/art.37937

9. Sherlock J, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR γ t+ CD3+CD4-CD8- enthesal resident T cells. *Nat Med*. 2012; 18:1069–77. [PubMed: 22772566]
10. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *New Engl J Med*. 2012; 366:1181–89. [PubMed: 22455412]
11. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *New Engl J Med*. 2012; 366:1190–99. [PubMed: 22455413]
12. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomized double-blind placebo-controlled trial. *Gut*. 2012; 61:1693–1700. [PubMed: 22595313]
13. Genovese M, Durez B, Richards HB, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomized, placebo-controlled study. *Ann Rheum Dis*. 2013; 72:863–69. [PubMed: 22730366]
14. McInnes IB, Sieper J, Braun J, et al. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomized, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis*. 2013 Accepted Article. [Epub ahead of print]. 10.1136/annrheumdis-2012-202646
15. Dick AD, Tugal-Tutkun I, Foster S, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. *Ophthalmology*. 2013; 120:777–87. [PubMed: 23290985]
16. Baeten D, Baraliakos X, Braun J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2013; 382 in press.
17. Davis JC Jr, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (Etanercept) for treating ankylosing spondylitis. *Arth Rheum*. 2003; 48:3230–36. [PubMed: 14613288]