

## **Inhibition of IL-17: efficacy in the entire axial spondyloarthritis spectrum**

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Axial spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the axial skeleton. The diagnosis of axSpA is clinical and based on pattern recognition of a combination of clinical, laboratory and imaging features.(1, 2)

Patients with axSpA can be further phenotyped into radiographic axSpA (r-axSpA; or ankylosing spondylitis [AS]) and non-radiographic axSpA (nr-axSpA), depending on the presence (or not) of definite SIJ abnormalities on pelvic radiographs.(3, 4) The burden of disease is high in axSpA, and similar between r-axSpA and nr-axSpA, with patients experiencing significant pain, stiffness, disability, poor quality of life and work impairment.(5)

The concept of nr-axSpA has been challenged, namely by the Food and Drug Administration (FDA).(6) In 2013, following the filing of applications for FDA approval for the use of the TNF-inhibitors Adalimumab and Certolizumab to treat active nr-axSpA, an FDA advisory committee raised concerns about the natural history of nr-axSpA, namely the possibility of spontaneous remission and the need for better prognostic markers, about the reproducibility of clinical trials due to local variability in interpretation of SIJ radiographs, and about the possible misuse of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria as a checklist to diagnose patient with axSpA.(6) Both Adalimumab and Certolizumab were rejected for the nr-axSpA indication, generating important differences between Europe and the US regarding the approval of biologics for nr-axSpA, with the first biologic for this indication (nr-axSpA with objective signs of inflammation, either elevated CRP levels or evidence of MRI inflammation) being approved by the European Medicines Agency in 2014 (Etanercept) and by the FDA only in 2019 (Certolizumab), following the publication of a trial comprising an 1-year placebo-controlled period and the ability to change background medication and to switch to biologic treatment, as recommended by the FDA.(7)

In *The Lancet*, Deodhar(8) and colleagues report the results of the COAST-X trial, a 52-week, randomised, double-blinded, placebo-controlled, parallel-group study conducted at 107 sites in 15 countries in Europe, Asia, and North and South America. The study randomised 303 adults with active nr-axSpA, objective signs of inflammation (by MRI/CRP) and inadequate response or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs), to receive subcutaneous 80mg Ixekizumab every 4 weeks (Q4W) (n=96, 46 (48%) women, 80 (83%) white, mean age 40.9 (SD14.5) years) or every 2 weeks (Q2W) (n=102, 53 (52%) women, 83 (81%) white, mean age 40.0 (12.0) years), or placebo (n=105, 61 (58%) women, 76 (73%)

white, mean age 39.9 (12.4) years). Primary endpoints were Assessment of SpondyloArthritis international Society-40 (ASAS40) response at weeks 16 and 52. Trial design was as recommended by the FDA and included the possibility of changing background medications and/or switching to open-label Ixekizumab Q2W after week 16 at investigator discretion (a decision made in a blinded fashion).

This is the first study demonstrating the efficacy of an IL-17 inhibitor in nr-axSpA. Treatment with Ixekizumab resulted in significant improvements in disease activity - ASAS40 at week 16 (ixekizumab Q4W: 34 [35%] of 96,  $p=0.0094$  vs placebo; ixekizumab Q2W: 41 [40%] of 102,  $p=0.0016$ ; placebo: 20 [19%] of 105) and ASAS40 at week 52 (ixekizumab Q4W: 29 [30%] of 96,  $p=0.0045$ ; ixekizumab Q2W: 32 [31%] of 102,  $p=0.0037$ ; placebo: 14 [13%] of 105), physical function, quality of life and SIJ inflammation compared with placebo (CRP results were not statistically significant). Safety findings were consistent with the known safety profile of Ixekizumab. There was no meaningful efficacy or safety difference based on the Ixekizumab starting dose (160 or 80mg) or continued dosing regimen (80mg Q2W or Q4W).

Following demonstration of efficacy of Secukinumab(9) and Ixekizumab(10, 11) in AS/r-axSpA, this study represents another step towards the unifying concept of axSpA as it extends evidence of efficacy of IL-17 inhibition to the nr-axSpA subgroup, fulfilling an unmet clinical need in this subgroup of patients. Positive Secukinumab (NCT02696031) data in nr-axSpA have also recently been presented in abstract format but the manuscript is still due to be published.(12)

The COAST-X trial was not powered to compare the two doses of Ixekizumab (80mg Q2W or Q4W), therefore not allowing direct comparison of dosing regimens. Moreover, the fact that, after week 16, changes in biologic background medications and switches to open-label active treatment were allowed without any pre-specified criteria, limits the interpretation of switching rates, as several unmeasured factors may have influenced the switching decision.

Following COAST-X, evidence of efficacy for two mechanisms of action - TNF and IL-17 inhibition - is now available for the entire spectrum of axSpA. Other mechanisms of action are being explored in axSpA, namely Janus Kinase (JAK) inhibition. Challenges for the future will be to determine which patients benefit the most from each drug, to compare the effectiveness of drugs (head-to-head trials required), to determine the most appropriate

individual treatment sequences and strategies, and to determine if any of these drugs will be able to stop or delay progression of structural damage (new bone formation).

Finally, in COAST-X, only 13% of patients remained on placebo for 52 weeks and achieved an ASAS40 response, and only 9% achieved Ankylosing Spondylitis Disease Activity Score (ASDAS) low disease activity. This supports the notion that nr-axSpA does not demonstrate spontaneous remission in the majority of patients with active disease, as previously suggested,(7) and that the separation between r-axSpA and nr-axSpA is artificial and we should move towards the unifying concept of axSpA, and using axSpA as single overarching nomenclature.

### **Authors' contributions**

PMM wrote the article and critically revised it for important intellectual content.

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