Response to 'Correspondence on "Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence" by Zhang *et al*

We thank Zhang *et al*[1] for their interest in our study, titled "Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence." We investigated long-term observational data using advanced statistical methods to determine whether changes in radiographic progression are affected by tumour necrosis factor inhibitors (TNFi) in patients with ankylosing spondylitis (AS).[2] However, our study did not consider the risk of osteoporosis or vertebral fractures while evaluating the effects of TNFi.

There are several studies on bone mineral density (BMD) in patients with AS. Compared with the general population, patients with AS have a lower BMD.[3–5] Furthermore, it is interesting that an increase in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) correlated with the decreased lumbar BMD.[4] These results are possibly related to decreased physical activity and functional capacity owing to pain and stiffness.[6] Importantly, AS is a chronic inflammatory disease, and inflammation plays a key role in bone loss. Therefore, it is conceivable that anti-inflammatory drugs can affect not only mSASSS but also BMD.

Tumour necrosis factor-α is an important cytokine for the regulation of bone homoeostasis in arthritis. Therefore, there are various experimental results showing that TNFi can affect osteoblast differentiation and osteoclastogenesis.[7] Studies have also assessed how TNFi affect osteoporosis in patients with rheumatic disease.[8 9] TNFi differ from existing osteoporosis medications (such as bisphosphonate or denosumab) with respect to the mechanism that affects bone remodelling in rheumatic diseases such as ankylosing spondylitis. However, the effect of TNFi on BMD in AS is unclear. In addition, there is insufficient evidence for determining the effects of TNFi on BMD because of time consuming and confounding by indication . Studying the role of TNFi in osteoporosis and fractures will provide important experimental and clinical evidence for pathogenesis of AS.

However, showing the effect of TNFi on osteoporosis was difficult using our data. First, patients with AS in our electronic medical records (EMR) were young (mean age, 33.1±9.8 years) and mostly men (90%). Moreover, there is no reason to routinely measure BMD in young patients in real-world clinical practice. Therefore, there is limited or no information on BMD in the EMR, and hence, it was impossible to study the relationship between TNFi and osteoporosis. Second, dual-energy X-ray absorptiometry and quantitative computed tomography along with several laboratory indicators have been used for measuring BMD using data from the EMR. However, incorporating these various methods into statistical models was difficult.

Notably, we showed that TNFi can affect the radiographic progression of AS with either direct or indirect effects via inflammation. Although further research is needed, these effects of TNFi may be considered similarly in the study for BMD.

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