Correspondence on 'Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence'

We recently read with great interest the article by Koo *et al.*¹ In this retrospective study, the authors evaluated the effect of tumour necrosis factor (TNF) inhibitors on radiographic progression in patients with ankylosing spondylitis (AS) using real-world patient data with long-term follow-up information. They found that the TNF inhibitors could significantly impede the radiographic progression of AS patients. We commend the authors for performing this important study as the results could be very helpful in guiding practice in clinics. However, we noticed that the authors did not clarify the influence of TNF inhibitors on osteoporosis or vertebral fracture risk on imaging in the patients.

Osteoporosis is a commonly recognised problem in AS population, which can lead to serious consequences for the patients. For instance, patients with AS may have severe fractures and resulting neurological dysfunctions even after minor trauma due to osteoporosis. Similarly, AS patients may be vulnerable to have complications (such as instrumentation loosening and displacement) after surgery because of poor bone quality. Given the potentially dismal outcomes, it is highly imperative to aggressively treat the osteoporosis in AS patients. Currently, the effect of TNF inhibitors on osteoporosis in AS remains inconclusive. Previous studies have shown that osteoporosis or bone loss in AS are mainly caused by the inflammatory activities mediated by TNF- α .² Considering that TNF inhibitors could effectively decrease the inflammatory response in AS, it is easy to speculate that TNF inhibitors may likely improve the osteoporosis of AS patients. In support of this, prior observations have suggested beneficial effects of TNF inhibitors on bone mineral density (BMD) at lumbar spine of AS patients,^{3,4} with infliximab, etanercept and adalimumab most commonly studied. However, most of these studies are observational cohort studies without long-term follow-up and control groups. In addition, impact of TNF inhibitors on hip BMD of patients is still unclear.⁴ A further comprehensive literature search revealed a lack of data with regard to the effect of other TNF inhibitors (including certolizumab and golimumab) on osteoporosis in AS. Moreover, studies have also demonstrated that TNF inhibitors fail to prevent vertebral fracture progression in AS patients.^{4,7} Therefore, according to these data available, we are still not able to determine the effect of TNF inhibitors on bone metabolism in AS. A recent systematic review and meta-analysis showed similar findings concerning this issue.⁸ Specifically, this study disclosed no strong evidence for TNF inhibitors in increasing BMD at hip and spine of AS patients.⁸ Given this situation, we recommend that more prospective and well-designed studies with appropriate sample size are needed to define the impact of TNF inhibitors on osteoporosis in AS. Noticeably, these studies should define the relationship between specific TNF inhibitors as well as their optimal regimen of administration (dosage, rhythm and duration) and osteoporosis in AS, considering that different drugs and administration methods may possibly have different therapeutic effects.

Published data have indicated that the osteoporosis in AS may also be attributed to other factors, such as age, menstrual status and pro-inflammatory interleukin-17 signalling.⁹ Considering these aspects, whether additional drugs should be prescribed in AS patients for osteoporosis amelioration deserves investigation.

Supporting this idea, a recent study evaluated the effect of a 2-year pharmacotherapy (combination of bisphosphonates and calcium/vitamin D supplements) on osteoporosis in AS patients and revealed a positive effect of this therapy on lumbar spine BMD of patients,¹⁰ similar to preceding findings.⁸ These preliminary data suggest an effective strategy to ameliorate osteoporosis in AS, although further confirmation is necessary. Importantly, this approach can also be further justified by previous reports showing bisphosphonates (including neridronate and pamidronate) as alone therapy or combination therapy with TNF inhibitors display beneficial effects on disease activity of patients with AS.^{11–13} Similarly, interleukin-17 inhibitors are also shown to be able to relieve symptoms and radiographic progression of AS patients.⁴ Evaluation of these drugs including those targeting other non-TNF mediated pathways (such as interleukin-6, JAK-STAT, CD20 and CTLA-4) on improvement in BMD of patients should be performed at present, as this result may impact the choice of osteoporosis treatment in AS.

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