Correspondence on 'Effectiveness of secukinumab versus an alternative TNF inhibitor in patients with axial spondyloarthritis previously exposed to TNF inhibitors in the Swiss Clinical Quality Management cohort' by Micheroli *et al*

We read with great interest the article by Micheroli *et al*[1] for comparison of effectiveness between secukinumab (SEC) and tumour necrosis factor inhibitor (TNFi) in axial spondylitis (axSpA), with evidence conform to the current recommendation in a Swiss real-world setting.

According to current guidelines,[2 3 4]interleukin-17 inhibitor (IL-17i) or alternative TNFi are both recommended as the switch option of biological disease-modifying antirheumatic drug in patients with previous TNFi failure. Although head-to-head comparison clinical trials between IL-17 inhibition and TNF blockade have been conducted in psoriatic arthritis recently[5 6] and is ongoing in axSpA, we appreciated Micheroli *et al*[1] for their new information in this real-world indirect comparison study. However, some issues can be further discussed.

First, regarding the study design, it was not mentioned whether treatment adjustment was due to drug inefficacy or intolerability and the types of TNFi, receptor fusion protein or monoclonal antibody were unclear in the study. Since the administration time of SEC in the market was relatively short, subgroup analysis might be inconclusive due to underpowered sample size.

Second, there are huge difference in baseline clinical features between two groups. At baseline, patients in the SEC group had higher disease activity indexes including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), poorer physician and patient global assessments, higher C-reactive protein (CRP) as well as worse Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI), and even higher health-related index of EQ-5D:Euro-Qol-5 Dimension (EQ-5D), compared with those in the TNFi group. Although authors had done propensity score matching and multiple regression models to adjust this baseline incomparability, residual confounders existed, for example, comorbidities should be adjusted or stratified. This confounding by indication may explain the high infection rate in the SEC group. Physicians may tend to choose SEC in high infection risk patients.

Third, for effectiveness, the primary outcome in this study was drug retention rate at year 1. The secondary outcome was to assess the proportion of patients reaching 50% reduction in the BASDAI (BASDAI50) at 1 year. We agreed that drug retention rate is a good endpoint for composite effectiveness and safety. But we suggest that ASAS20, ASAS40 and ASDAS-CRP would be more suitable endpoints to be presented to compare with existing literatures. Furthermore, previous studies showing that ASAS20 and ASAS40 were both higher in patients treated with ixekizumab (IXE) in COAST-V[7] study than in those in COAST-W[8] study, implicating the superiority of IXE in patients with TNFi naive over TNFi failure. We suggest that authors should discuss on this inconsistency.

Fourth, for the safety aspects, 18.4% to 27.4% of patients discontinued treatment due to the adverse events. Other adverse events including headache, generalised peripheral pain and acne conglobata were much higher in the TNFi group then in the SEC group. These non-specific adverse events might attribute to a wider and more potent proinflammatory effect of TNF than IL-17. Infection seemed to happen more frequently in patients treated with SEC. Among them, even one severe infection requiring hospitalisation occurred with unclear infection site and pathogen. Recurrence of breast cancer was identified in one patient treated with TNFi, which was considered possibly unrelated and inconclusive to the treatment from our point of view. For inflammatory bowel disease, conclusion was unfavourable and consistent with former randomised controlled trials (RCTs).[9–11] No uveitis developed in patients treated with SEC, which was inconsistent with former RCTs and required further investigation. Paradoxical psoriasis happened in two patients treated with SEC. It would be of great value to clarify the underlying mechanism for psoriasis pathogenesis despite IL-17i treatment.

Finally, for the reason of discontinuation, the percentage of ineffectiveness was comparable between TNFi and SEC (60.3% vs 58.1%), implying that over 50% of patients experienced unfavourable response to both drugs. We agree that there is still an unmet need for the treatment of the axSpA population. More therapeutic targets are required to improve the present status of treatment.

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