Correspondence to 'Comparative effectiveness of first-line tumour necrosis factor inhibitor versus non-tumour necrosis factor inhibitor biologics and targeted synthetic agents in patients with rheumatoid arthritis: results from a large US registry study'

We read with great interest the article by Pappas *et al*¹ who evaluated the comparative effectiveness of a tumour necrosis factor inhibitor (TNFi) such as adalimumab, etanercept, certolizumab pegol, golimumab or infliximab versus a non-TNFi (abatacept, tocilizumab, rituximab, anakinra or tofacitinib) as the first-line treatment in patients with rheumatoid arthritis (RA). The authors concluded that there were no statistically significant differences observed between the TNFi and non-TNFi treatment groups for the outcomes assessed, including the Clinical Disease Activity Index (CDAI), the 28-Joint Modified Disease Activity Score, the Health Assessment Questionnaire Disability Index, EuroQol-5 Dimension score, morning stiffness and fatigue. In this observational study, data collected from 1 October 2001 to 31 January 2018 within a large US healthcare registry were evaluated, and 4816 patients who had a non-remission CDAI score at baseline were selected for further assessments. We would like to draw attention to some important points in this study.

First, the two key clinical outcomes in this study were 'achievement of low disease activity (CDAI $\leq$ 10) among those with moderate or high baseline disease activity at baseline' and 'achievement of remission (CDAI $\leq$ 2.8) among those with low, moderate (10<CDAI $\leq$ 22) or high (CDAI>22) disease activity at baseline'. Although there was no statistically significant difference in the mean CDAI scores between the TNFi and non-TNFi treatment groups at baseline, it did not mean that the proportion of patients with moderate or high disease activity at baseline in the two groups was not significant. We think it could be a key effect modifier of the treatment outcome and should be adjusted in advance.

Second, the therapeutic effect of the different treatments used in patients with RA varies depending on whether conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are used alone or in combination. The American College of Rheumatology (ACR) guidelines² for patients with RA recommends a treat-to-target approach that is guided by disease stage and treatment history. At baseline, there was no statistically significant difference in the proportion of patients receiving concomitant csDMARDs between the two groups. However, the proportions of patients receiving csDMARDs as monotherapy, dual therapy or triple therapy in the two groups during the 1-year follow-up visit were not specified in the study. Additionally, residual confounders, such as smoking status, baseline haemoglobin levels and dosage of the csDMARDs used, could exist.

Third, the number of patients on anakinra treatment in the non-TNFi group was only 14. The sample size of this subgroup was too small to extrapolate conclusions with statistical confidence in a study where the total number of patients was in the thousands. Considering its lower clinical efficacy than that of other biologics and the lack of long-term observational studies, most rheumatologists only prescribe anakinra for patients with RA who are intolerant to TNF- α inhibitors.^{3,4} Anakinra was not

included in the 2015 ACR guideline² for the treatment of RA because of insufficient data.

Finally, in the study design section, the sentence 'Patients who did have a non-remission CDAI score ... were excluded from analysis' should be revised to 'Patients who did not have a non-remission CDAI ...'. In figure 2, the term 'Non-TNFi' stated in the lower-left corner should be changed to 'Favours TNFi'.

Above all, we appreciate this real-world study that compared the effectiveness of individual TNFi and non-TNFi treatments in patients with RA. We recommend that in the proportion of patients with moderate or high disease activity and csDMARDs monotherapy, dual therapy or triple therapy, some residual confounders should be matched to ensure balanced baseline comparability.

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