

Comment on: Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis by Humby *et al.*

Sirs,

We read the article by Humby *et al.* with great interest (1). They presented synovial biopsies of 164 rheumatoid arthritis (RA) patients, according to histological classification as B-cell poor or rich and RNA sequencing by B-cell molecular signature between 2013 and 2019. They found the RNA sequencing-based stratification of RA synovium showed stronger associations with clinical responses and tocilizumab was more effective than rituximab for patients with B-cell poor synovium. However, there are raising concerns to be answered.

Using only composites indexes may not have accurately reflected the actual disease activity state RA, and musculoskeletal USG is very useful in detecting subclinical inflammation (2). The study group used not only disease activity measures such as DAS-28, CDAI and SDAI, but also ultrasonography (US) parameters for gray scale and power Doppler. The comparison of treatment groups was given in terms of primary endpoint measure of the study of the study based on CDAI. Baseline assessment of US parameters were shown in the tables (1). However, we did not find any follow-up data for US parameters neither in the paper or in the appendix. It would be interesting to describe US changes at 16th week and compare between treatment groups. Any data regarding such histopathological sequencing and possible relationship of US changes would have

many additional impacts on disease assessment and prognostic value.

In Humby *et al.* research, all patients included were long-standing RA. Recently, a prospective study on synovial biopsies obtained from patients with early (<6 months) and long-standing (>5 years) RA confirmed the gross similarity between the two subgroups in terms of infiltration by CD20+ B lymphocyte, but the decrease in stromal cell activation for the long-standing RA group was found to be lower at 6th month, suggesting greater plasticity of synovitis as the disease progresses (3). We think that stromal cell activation responsible for synovial plasticity may be important in these patients more than B cell infiltration.

In addition, serious adverse events unrelated to the study drug were reported in 14 patients (6%), and there is a 5% difference between treatments. How were these adverse events defined and were any of them related with synovial biopsy? These concerns should be better defined.

The efficacy of bDMARDs has been proven in the treatment of RA, but they are nevertheless more expensive and carry ongoing cost-effectiveness and sustainability concerns. Considering the results demonstrated in Humby *et al.* study, is teh cost-effectiveness of synovial biopsy according to histological classification and RNA sequencing a realistic goal?

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All other authors declare no competing interests.

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