Drug-free sustained remission or spontaneous remission by natural history in rheumatoid arthritis? An unsolved question: comment on the article of Ajeganova *et al*

Dear Editor, I read with interest the article by Ajeganova *et al*[1] reporting disease-modifying antirheumatic drug (DMARD) free sustained remission in rheumatoid arthritis (RA) as an increasingly achievable outcome with subsidence of disease symptoms. The conclusion of their study was that more intensive treatment strategies increased the chance for DMARD-free sustained remission, indicating that RA chronicity can be influenced. Of note, 'Patients who achieved DMARD-free sustained remission, compared with those who did not, were less often anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF) positive (18% vs 62%, and 31% vs 65%, both p≤0.001) and had shorter symptom duration at inclusion (median (interquartile range) of 3 months (2–7) vs 5 months (2–9), p≤0.001)'. Moreover, patients included in the more recent inclusion groups had fewer number of swollen joints, and lower acute phase reactants. Although all patients studied fulfilled the 1987 criteria for RA, this may suggest that these patients had somewhat milder disease at the time of diagnosis.

The low rate of ACPA and RF positivity, the shorter duration of patients with drug-free remission, the fewer number of swollen joints and the lower acute phase reactants prompt several questions. Did the proportion of the diagnosis of patients with seropositive and seronegative RA changed in the various collection periods stratified for the different treatment strategies? What was the frequency of erosive disease in patients with drug-free remission? Did the frequency of erosive disease varied in the collection periods stratified for the different treatment strategies? The answers to these questions are important to exclude that the observed remissions are in part spontaneous instead of the suggested result of the different treatment strategies.

Seronegative RA represents a disease entity clinically and immunogenetically distinct from seropositive RA, tend to have milder disease, less erosive disease, fewer subcutaneous nodules and better prognosis.[2–7] The correct diagnosis and classification of seronegative RA is challenging in case of those patients with a persistently seronegative inflammatory arthropathy who have neither overt coexistent disease like psoriasis or inflammatory bowel disease nor a B27-related spondyloarthropathy.[8 9] Was there any predefined diagnostic programme or application of inclusion and exclusion criteria to differentiate seronegative RA from other seronegative arthritis in the collected cohorts? Were the roentgenological bony erosions characteristic of RA in the patients classified as seronegative RA? The issue of spontaneous remission especially of seronegative RA should be discussed when one is describing drug-free sustained remission following disease-modifying anti-rheumatic agents.

The distinction between spontaneous remission by natural history and drug-induced by the present advanced treatment strategy will be nearly impossible by retrospective data analysis instead of prospective controlled trials, especially with the increasing use of the less specific 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[10 11]

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