

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 $p \leq 0.001$) and had shorter symptom duration at inclusion (median (interquartile range) of 3 months (2–7) vs 5 months (2–9), $p \leq 0.001$). 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}

Henning Zeidler

Correspondence to Professor Dr Henning Zeidler, Department of Immunology and Rheumatology, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany; zeidler.henning@mh-hannover.de

Citation: Ajeganova S, van Steenberg HW, van Nies JAB, *et al*. Disease-modifying antirheumatic drug-free sustained remission in rheumatoid arthritis: an increasingly achievable outcome with subsidence of disease symptoms. *Ann Rheum Dis* 2016;75:867–73 (Clinical and epidemiological research)

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.



CrossMark

To cite Zeidler H. *Ann Rheum Dis* 2017;76:e16.

Accepted 28 November 2016

Published Online First 22 December 2016

Ann Rheum Dis 2017;76:e16. doi:10.1136/annrheumdis-2016-210887

REFERENCES

- 1 Ajeganova S, van Steenberg HW, van Nies JA, *et al*. Disease-modifying antirheumatic drug-free sustained remission in rheumatoid arthritis: an increasingly achievable outcome with subsidence of disease symptoms. *Ann Rheum Dis* 2016;75:867–73.
- 2 Masi AT, Maldonado-Cocco JA, Kaplan SB, *et al*. Prospective study of the early course of rheumatoid arthritis in young adults: comparison of patients with and without rheumatoid factor positivity at entry and identification of variables correlating with outcome. *Semin Arthritis Rheum* 1976;5:299–326.
- 3 Alarcon GS, Koopman WJ, Acton RT, *et al*. Seronegative rheumatoid arthritis. A distinct immunogenetic disease? *Arthritis Rheum* 1982;25:502–7.
- 4 Wolfe F. The natural history of rheumatoid arthritis. *J Rheumatol* 1996;44 (Suppl):13–22.
- 5 Edelman J, Russell AS. A comparison of patients with seropositive and seronegative rheumatoid arthritis. *Rheumatol Int* 1983;3:47–8.
- 6 van Schaardenburg D, Hazes JM, de Boer A, *et al*. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. *J Rheumatol* 1993;20:45–52.
- 7 Barra L, Pope JE, Orav JE, *et al*. Prognosis of seronegative patients in a large prospective cohort of patients with early inflammatory arthritis. *J Rheumatol* 2014;41:2361–9.
- 8 Burns TM, Calin A. The hand radiograph as a diagnostic discriminant between seropositive and seronegative 'rheumatoid arthritis': a controlled study. *Ann Rheum Dis* 1983;42:605–12.
- 9 Husby G, Gran JT. What is seronegative rheumatoid arthritis? *Scand J Rheumatol* 1988;(Suppl. 75):269–71.
- 10 Zeidler H. Systemic literature review of the performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: good news of debatable significance. *Ann Rheum Dis* 2013;72:e21.
- 11 van der Helm-van Mil AH, Zink A. What is rheumatoid arthritis? Considering consequences of changed classification criteria. *Ann Rheum Dis* 2017;76:315–7.