The risk stage of subclinical inflammation is not comparable to the stage of clinical arthritis. Response to 'Comments and perspectives on the TREAT EARLIER study'

Sirs,

We thank E. Bilgin for his interest in the results from the TREAT EARLIER trial (1, 2). Discussion of research findings is of utmost importance, as it provides context and perspective. Our study showed that that the development of anti-citrullinated protein antibody (ACPA)-negative rheumatoid arthritis (RA) can be prevented by a one-year course of methotrexate in individuals with clinically suspect arthralgia (CSA) who are at increased risk of developing RA. This ACPA-negative increased risk group is actually at increased risk due to the presence of extensive subclinical joint inflammation. Bilgin raised two relevant issues: first, he suggests that patients with subclinical joint inflammation on MRI and tender joints at physical examination fulfil the criteria for RA. Thus, the author suggests that these patients already had RA at the time of CSA diagnosis. This is a misinterpretation that is relevant to discuss because it is made more often. The crucial issue is that subclinical joint inflammation is not similar to having clinical arthritis. The 2010 ACR/EULAR classification criteria for RA are only applicable to patients with clinically swollen joints (3). As seen in the Kaplan Meier curves from the placebo arm of the TREAT EARLIER trial, as well as the results from observational CSA cohorts, a majority of patients with CSA and subclinical joint inflammation never develop clinically apparent arthritis/RA (4, 5). This is also evident from worldwide observational cohort data that ultimately informed the recently published EULAR/ACR risk stratification criteria for RA development in patients with arthralgia (6). So being at risk for RA is not similar to having RA and methods are designed to inform about the risk for progression from CSA to RA. Relaxing the distinction between risk and actual disease can lead to overtreatment and potential harm.

Second, the author mentions that a better understanding of the mechanisms driving the progression from CSA to RA is essential, and suggests studying the role of smoking, obesity and oral dysbiosis. We fully agree with this. Some of these studies have already been done. Current data suggest that smoking and obesity primarily influence the development of autoimmunity during the asymptomatic risk stage, that precedes the symptomatic risk stage of arthralgia. The HLA-shared epitope alleles in contrast do not seem to influence ACPA-development, but may support maturation of the autoimmune response in the asymptomatic risk stage as well as progression of subclinical joint inflammation to RA (7, 8). The potential impact of oral dysbiosis on the development of RA, and the timing of this possible influence, remains to be determined. We agree that the processes that ultimately result in RA are insufficiently understood, both in ACPA-positive and ACPA-negative disease. A better pathophysiological understanding may point to novel targets that can be addressed in future prevention trials.

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Competing interests: none declared.

Clin Exp Rheumatol 2025; 43 (Suppl. 136): S8.

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