Correspondence on 'Shared epitope defines distinct associations of cigarette smoking with levels of anticitrullinated protein antibody and rheumatoid factor' by Ishikawa *et al*

We read with great interest the paper of Ishikawa *et al*,[1] which addressed the link between smoking and the levels of anti-citrullinated protein antibodies(ACPA) and rheumatoid factor (RF) in a total of 6239 Japanese rheumatoid arthritis (RA) patients. We particularly appreciate the detailed smoking history collected that allowed a very detailed analysis. The authors collected information about the number of cigarette packs smoked per day, the years smoking and the time of smoke cessation when it was present. They also distinguished the ever smoker patients in three categories: smokers at disease onset, ex-smokers before onset and smokers after onset, which looks like a very pertinent stratification for exploring the pathogenic role of cigarette smoking. The study found a significant and dose-dependent association between smoking and antibody positivity for ACPA or RF antibodies, as well as, an association with high titres of ACPA or RF antibodies, which was only dose-dependent regarding RF. In both cases, the association was stronger with RF than ACPA. Moreover, the association of smokers with ACPA levels only was significant in the subgroup of patients with shared epitope (SE) alleles in the HLA-DRB1. In contrast, the association of smoking with RF was significant independently of the SE alleles. The authors conclude that these results suggest that the development of RF and ACPA is driven by different mechanisms without further detailing the implications. Perhaps, it is possible to obtain more information about these differences from the Ishikawa *et al* data. This would be very useful because there is currently a lot of interest in the relationship between smoking and the autoantibody-defined subgroups of RA patients.[2–6] Specifically, we think it will be informative to know if smoking introduced a differential association between the two subsets of patients with SE and high ACPA described in figure 3B in the Ishikawa *et al* article. Also, we think that a conditional analysis of one antibody on the other autoantibody, or stratified analyses on the serologically defined subgroups, could clarify the interpretation of the results regarding specific autoantibodies given the common concurrent presence of RF and ACPA. An analysis of this type has been recently reported in a large Swedish study that also counted with high-quality information on cigarette smoking.[2] In this study, both smoking and the presence of the SE conferred independent disease risk for RA with the two antibodies, ACPA and RF, whereas the $ACPA^{-}/RF^{+}$ patients showed an increased risk of disease among smokers, which was only marginally affected by the presence of the SE, and the $ACPA^{+}/RF^{-}$ patients were predominantly associated with the SE. These results have been interpreted as meaning the smoking may be a critical driver of RF production whereas the SE could be the main driver of ACPA development.[3] In this inquiry on the specific factors contributing to the RA subsets, we think the additional information regarding the Japanese population studied by Ishikawa *et al* will be very welcomed.

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