The need for international multicentre collaborative studies to better characterise the clinical profile of anti-Th/To-positive patients: reply to the comment by Sakaida *et al.*

Sirs,

We appreciate the interest of Sakaida *et al*. in our recent work on the long-term follow-up of pulmonary involvement in systemic sclerosis (SSc) patients with positive anti-Th/To (anti-Th/To+) antibodies (1).

In their comment, the authors described a case of an anti-Th/To+ patient with both interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) not fulfilling SSc criteria and provided aggregated data from exiting literature on the prevalence of ILD and PAH among anti-Th/To+ SSc patients: 49.4% and 19.5%, respectively (2).

While ILD is consistently reported in about half of anti-Th/To+ SSc patients (3), data about PAH prevalence exhibit discordance among various SSc cohorts. We observed ILD in 40% of the cases from our cohort, mostly with favourable outcome, as only 2 anti-Th/To+ SSc patients showed a functional worsening, only one required immunosuppressive treatment and none developed secondary pulmonary hypertension, needed oxygen supply, nor died due to SSc-ILD (1). Among the 13 anti-Th/To+ SSc patients of our cohort, despite a long median follow-up of 16 (6-20) years, we did not observe any case of PAH development (1).

We agree with Sakaida *et al*. that the variability in PAH prevalence among anti-Th/To+ patients may stem from differences in ethnicities, observation periods and disease definition. In our paper we proposed referral bias as an additional potential source of the discrepant observations of PAH prevalence among these patients (1). It is noteworthy that the highest prevalence of PAH (23.0%) was observed in the Pittsburgh cohort (4), in which 17% of the anti-Th/To+ SSc patients already had PAH since their first visit at this tertiary centre, but only an additional 6% developing PAH during a long and well-conducted follow-up (4). In our opinion, this might be highly suggestive of selection of more severe cases in this cohort.

We also underlined that, besides the association with PAH, many open questions regarding the clinical profile of anti-Th/To+ patients need to be addressed (1). These include, for example, the relationship with cancer: in previous literature both reduced frequency of cancer diagnosis within the first 3 years after SSc onset (5) and an overall increased long-term incidence of cancer in these patients (6) were reported. Furthermore, data concerning organ damage (7), which is linked to morbidity, mortality and reduction of patients' quality of life, are even more limited in anti-Th/To+ patients (1).

Given the low prevalence of anti-Th/To antibodies, only the analysis of large multicentric cohorts of anti-Th/To+ SSc patients with different geographic and ethnic origin will provide additional information on these clinically relevant issues. This is the reason why a clinical project focused on the clinical phenotype of anti-Th/To antibodies in SSc patients is currently undergoing in patients of the European Scleroderma Trials and Research group (EUSTAR; clinical project no. 144) database.

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