Reply to comment on:
Disease evolution in a long-term follow-up of 104 undifferentiated connective tissue disease patients

Sirs,
We read with interest the comment by Yamashita and colleagues on our retrospective experience on undifferentiated connective tissue disease (UCTD), focusing on disease evolution (1).

While it is still unclear which patients with UCTD will later in life develop a more severe disease potentially with organ involvement, it is now widely accepted that UCTD patients can be distinct in two separated populations (Fig. 1). On the one hand, the disease might be relatively mild, with a benign prognosis with a prevalence of musculoskeletal involvement, and with a scarce change of developing flares during the course of the follow-up. On the other hand, patients (especially at younger age of diseases onset) might develop new clinical and/or laboratory manifestations during follow-up, with higher frequency of organ damage and flares, ultimately classifying them as having a definite CTD (2).

Several studies highlighted the importance of antibody-profiling to help distinguish the two distinct populations (3). As pointed out by Yamashita and colleagues some studies reported that specific positivity of anti-Ro/SSA antibodies might help identify patients with a more stable disease or are known to be more frequesntly associated with false positive (e.g. malignancies in the case of Ro52+Ro60- antibodies) (4, 5). When considering antibody-profiling, one should also consider other screening strategies: in fact, evidence suggested that the cumulative number of positive antibodies in a patient can be and indicator of the evolution towards a definite CTD (6). Interestingly, Lu et al. showed that SLE subjects have a mean of 0.3 new antibody specificities per year and a mean of 3 antibody specificities at the time of diagnosis (7).

While researchers are making a great effort in discovering novel laboratory techniques and antibody specificities, a diagnostic gap still exists, and patients should be diagnosed sooner, as potentially evolving to a CTD. It is known that patients with less than 6 months' diagnostic delay may experience lower flare rates and organ damage, that ultimately translates to an overall better prognosis, quality of life, less health care utilisation and lower cost for the health care system (8). This is particularly important for those patients with major organ involvement, such as lupus nephritis or pulmonary hypertension: in these cases, delay in prompt diagnosis and initiation of immunosuppressive therapy has been linked to long-term adverse outcomes and increased irreversible damage (9).

While we agree with Yamashita and colleagues that new classification criteria are needed for both UCTD and other diseases,

Fig. 1. Two distinct undifferentiated connective tissue disease patients' populations at follow-up. CTD: connective tissue disease; UCTD: undifferentiated CTD; MCTD: mixed CTD; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome.
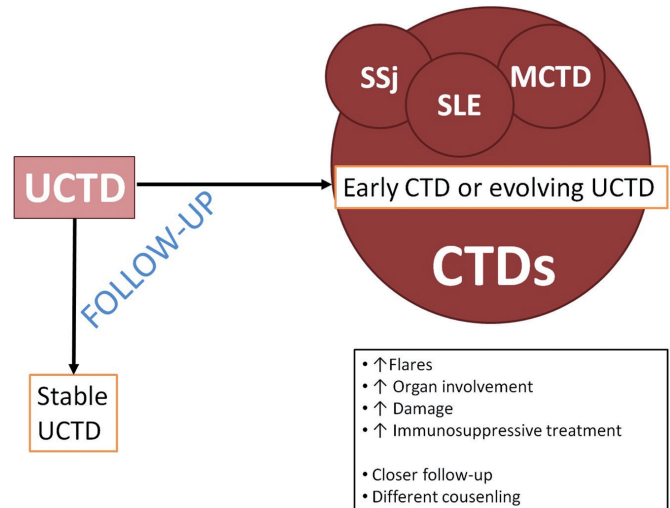
such as mixed CTD, it is important to underline that while the immunological laboratory might help clinicians in identifying patients at higher risk of developing a more severe disease course, clinical manifestations must be at the forefront when considering prognosis and treatment. It is widely recognised that a portion of patients with UCTD will develop a definite CTD in a 5 years' time and the early identification of this subgroup would deeply impact their clinical management, leading for example to a closer follow-up. Similarly, different treatment options might be considered, and the patients might be counseled differently in specific higher risk settings, such as pregnancy or when planning a surgery. The lack of both international recommendations and classification criteria for UCTD is impacting on possibly underestimating or neglecting patients with a severe course and ultimately miss-diagnosing them.

Antibody testing represents a cornerstone in autoimmunity; however, clinical suspicion based on the presence of clinical signs and symptoms should primarily guide the management. New criteria and recommendations, alongside with prospective studies are needed in order to identify early predictors of disease evolution in UCTD patients.

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Competing interests: none declared.

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