

Limited efficacy of targeted treatments in Sjögren's syndrome: why?

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Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease characterised by a remarkably diverse clinical picture, extending from exocrine organ involvement to systemic disease and lymphoma. The hallmark of the disease are round cell infiltrates affecting the epithelium of the exocrine glands and other organs, including the lungs, kidneys and liver. In the past three decades, the critical role of the interaction between the affected epithelium and the immune cells, including B and T cells was highlighted, justifying the term "autoimmune epithelitis" (1). The disease follows a slowly progressive course with a stable clinical picture, and the majority of pSS patients seek medical advice many years after the onset of sicca symptoms (2). However, the disease starts even earlier, since anti-Ro and anti-La antibodies may be found in sera of healthy individuals, many years before the appearance of clinical symptoms (3). Similarly with the clinical picture, the lymphocytic infiltrates around the affected epithelium present also heterogeneous features, varying according to lesion severity, with T lymphocytes in mild and B cells to predominate in severe lesions (4). Interestingly, B cells participating in simple aggregates within the inflammatory lesion have a different biological significance and behaviour compared to those constituting the ectopic germinal centres (GC) like structures, that are observed in around one fifth of patients (5), pointing that the level of diversity is extending to single cell populations and therefore, to different pathogenetic mechanisms, that constitute the endotypes of the disease. In this context of chronicity, clinical heterogeneity and immunopathologic diversity, several molecules have been proposed to mediate disease pathogenesis.

An in depth understanding of the biology and the possible molecular pathways shared in many autoimmune diseases, combined with the treatment experience, primarily from rheumatoid arthritis, prompted the scientific community to assume that certain treatments targeting successfully molecules in RA, could also serve as potential therapeutic agents for pSS. However, although certain biological agents have been tested for the treatment of pSS, over the last 12 years, no significant impact on symptoms or quality of life was found. The primary end points, designed for the initial clinical trials assessing TNF inhibitors (etanercept, infliximab), anti-B depletion agents (rituximab, belimumab) and IL-1receptor antagonist (anakinra), included mainly disease subjective parameters such as fatigue, mucosal dryness, pain and in some cases salivary flow, as an objective measure of hyposalivation (6, 7). Although improvement was achieved to some extent, the efficacy was considered limited, with questionable modification of the underlying immunopathologic processes which drive the disease pathogenesis. Newer indexes such as ESSDAI and ESSPRI have been designed and validated to better assess disease activity and outcomes, while ongoing clinical trials targeting T cell costimulation, B-cell depletion, IL-6 pathway and type I interferons are currently carried out (6). Although these novel therapies seem promising, a criticism on the frame of these clinical trials is necessary to interpret and understand the possible reasons for the inefficacy of biological treatments in SS, so far. First, the chronicity and the slowly progressive nature of the disease, already at the time of diagnosis and when targeted treatments are instituted, suggests that the underlying pathogenetic mechanisms are well established and

the disease is advanced (2, 8). Therefore, it is rational to assume that the expected therapeutic window has been narrowed in the majority of patients. On the other hand, some clinical faces of the disease, such as those attributed to the B cell compartment are more dynamic, explaining the partial beneficial effects of anti-B therapies in pSS patients with cryoglobulinaemic mediated clinical manifestations. Second, in most clinical trials the observation time was limited to either 24 or 48 weeks, a relatively short period to record a significant improvement in clinical manifestations, in a chronic and slowly progressive disease. The usage of reliable biomarkers for early diagnosis and recruitment of patients and the extension of observation time in clinical trials could potentially reveal the efficacy of biologic treatments, at least in some aspects of the disease (9). Third, the diversity of phenotypes and endotypes of the disease, may also interfere with the outcomes and the primary end points of many clinical trials conducted to assess biologic treatments in SS. The remarkable heterogeneity of clinical and histopathologic phenotypes has not been taken into account during study design of clinical trials for pSS patients, putting “apples and oranges” together. On the contrary, patients in these studies have been recruited based on the overall disease activity as reflected by the ESSDAI index. Therefore, it is critical, in the development of future therapeutic trials, more sophisticated patient stratification methods to be applied, according to both clinical phenotype but also the underlying pathogenetic mechanism. This patient stratification may unmask potential beneficial effects of biological agents in certain clinical subsets or disease manifestations (9). Last but not least, is the fact that we do not, yet, understand all pathophysiologic mechanisms, participating in different phases of the disease. The best example is probably the administration of anti TNF- α agents in the early ages of targeted therapies in pSS. The scien-

tific community and pharma industry, decided that TNF- α is a molecule of interest in pSS, based on: a) the fact that TNF- α is found in abundance in the affected salivary glands and b) anti-TNF agents worked very well in rheumatoid arthritis. However, TNF inhibitors showed low efficacy in pSS, implying that TNF- α exert immunoregulatory rather than proinflammatory properties in pSS pathogenesis (10), a finding that was proved in the laboratory, since TNF- α knock out animals cannot form secondary germinal centres (11).

Despite the revolutionary explosion of biotechnology, it is still challenging to identify potential therapeutic targets mainly because of the plasticity of the immune system – at the cellular and molecular level – and the complex regulatory mechanisms of gene expression. As mentioned previously, the introduction of biologic agents in the treatment armamentarium of pSS was based on the experience from other autoimmune diseases and the shared fundamental mechanisms of autoimmunity. Dissecting in depth the cellular and molecular aspects of the disease may reveal unique and specific pathogenic mechanisms in pSS resulting in novel and pSS specific therapeutic targets.

Taken together all the above, it seems that past and ongoing clinical trials assessing the efficacy of various biologic agents should be designed considering the specific features of pSS. The chronic and mild nature of the disease in the majority of patients, the various clinical subsets and outcomes and the possible underlying immunopathologic events, should be taken into account when considering a new targeted treatment in pSS. A thoughtful approach of the different phases of the disease is needed. The detection of anti-Ro and anti-La antibodies in healthy individuals will offer the opportunity to track the preclinical phases of the disease, where immune tolerance intervention may safely be applied. The discovery of new biomarkers mirroring the diverse endotypes of the disease will offer the

opportunity for early diagnosis, more effective patient stratification, as well as, an estimation of response to specific treatments. New biologic therapies are expected not only to control the clinical manifestations of the disease and improve the quality of life but also to modify the disease course and the adverse outcomes including lymphoma.

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