# Unmet needs in primary Sjögren's syndrome and the never-ending quest for the perfect biomarker

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Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease mainly affecting females and characterized by chronic inflammation of exocrine glands[1]. Although signs and symptoms of mucosal dryness are a hallmark of the disease, the clinical spectrum of pSS is more complex and heterogeneous with a consistent proportion of patients, up to 70% in some cohorts, experiencing fatigue, pain and extra-glandular manifestations (EGMs)[2, 3]. EGMs may occur at any time during the disease course, worsen disease prognosis and require prompt immunosuppressive treatment. They range from mild arthralgia to life-threatening vasculitis, with non-Hodgkin B cell lymphoma being the most severe complication of the disease. On this basis it could be reasonable to argue that disease activity would represent the main determinant of poor quality of life (QoL) in pSS patients with active disease[1]. However, recent data demonstrated that patient reported symptoms such as dryness, pain and fatigue are those affecting QoL the most[4]. In this regard, the spectrum of clinical symptoms encompassed by the terms 'dry eye' and 'dry mouth' is wide and multifaceted including burning, photophobia, blurred vision, dysgeusia, dysphagia and impaired speech. Furthermore, the discrepancy between objective measurement of dryness, disease activity and patient-reported symptoms adds a layer of complexity to this scenario[5]. This is of particular relevance in light of the results of clinical trials of biologic agents in pSS that proved to be more effective on EGMs than on dryness, albeit reducing glandular inflammatory infiltrate, fatigue and pain[6]. To note, however, patient reported outcomes such as visual analogue scales aimed at quantifying dryness may not capture the wider spectrum of symptoms induced by impaired glandular function and therefore the actual effect of various compounds may be underestimated.

It becomes evident that a variety of disease subsets, based on the risk to develop not only objective severe manifestations but also highly disabling subjective symptoms should be identified and biomarkers may help to detangle, at least in part, this complex issue.

It is well established that pSS patients displaying anti-SSA and anti-SSB antibodies are prone to develop a more severe clinical picture[2]. However, the absence of autoantibodies and of other serological biomarkers pointed as predictors of EGMs, such as hypergammaglobulinemia, low complement fractions and cryoglobulinemia, does not rule out the possibility to develop EGMs, albeit reducing the risk[7]. The advent of omics-based research shed additional light on this matter identifying a variety of putative biomarkers over or under-expressed in the serum, tears and saliva of patients with pSS but although promising, no conclusive data is still available. Nevertheless, the evidence of a differential expression of proinflammatory cytokines in different biologic samples and at different disease stages, namely a different sample-specific molecular signature, may reflect pathogenic mechanisms that have not been elucidated yet. Examples may be IL-17 whose expression in pSS serum is dependent on disease duration, or B cell activating factor (BAFF) whose over-expression is related to disease activity, B-cell clonal expansion and may be linked to lack of response to rituximab[8-10]. Hence it is intriguing to speculate that this and other evidence may help identifying patients who could benefit from different targeted treatments and at different disease stage. Likewise, the predictive role for future EGMs and NHL of histological biomarkers such as a higher focus score or the presence of germinal center (GC)-like structures in minor salivary glands (MSG) at the time of disease diagnosis is still a matter of debate[11, 12]. In this case, however, the main issue is the technical heterogeneity across studies that yielded conflicting results. In this regard and adding to existing standards[13], an agreement on how to detect GC-like structures (namely via haematoxilin/eosin staining, by identifying B/T cell segregation or by using other markers such as CD21 and B-cell lymphoma 6 (Bcl-6) pro-

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tein) and on which sample (parotid glands vs MSG) is advisable[14].

Taking together all the above, even if some biomarkers have more solid evidence, we are far from the implementation of most of the others in clinical practice and patients that are classified as having pSS based on validated criteria[15], are further stratified into more or less severe disease subsets only once the EGM is clinically evident. Unfortunately, it is not yet clear how to identify patients who will develop more severe symptoms related to dryness but also fatigue and this remains a major unmet need since this subgroup of patients has the highest risk of poor QoL.

In recent years, new biologic drugs have been introduced for the treatment of autoimmune diseases, and, interestingly, most of these target molecules are potentially implicated in pSS pathogenesis. In particular, given the central role of B-lymphocytes in the development of pSS, the most interesting results were obtained with B-cell-targeted therapies[6]. However, none of these biologic targets was found essential in maintaining the disease process of pSS, therefore these biologic drugs only scratch the superficial layer of precision medicine in pSS.

The major weakness of our current treatment approaches is again the lack of biomarkers to stratify pSS patients and inform the therapeutic decision, and the heterogeneity of inclusion criteria and primary outcomes likely accounts for the variability in the results of randomized trials and open-label studies.

In conclusion, the search for reliable biomarkers allowing to stratify pSS patients for prognistic and therapeutic purposes is still ongoing and unfortunately the recurring concept derived by most studies on this matter is that 'further studies are needed to shed additional light'. In this historical moment, we think that big data is an essential part of precision medicine and represents a power tool to increase the knowledge on pSS. The integration of multi-source data continues to be a challenge in practical application but the joined efforts of international consortia will hopefully overcome this barrier, allow to make significant progress in the never-ending search for biomarkers in pSS, and ultimately improve the care of patients with this disease.

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