Sjögren's syndrome: from pathogenesis to novel therapeutic targets

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease, characterised by a chronic infiltration of exocrine glands, mainly salivary glands, with the histological features of focal lymphocytic sialoadenitis. Disease spectrum is broad and the occurrence of several extra-glandular manifestations, and in rare cases lymphoma development, is well known. A specific approved treatment for pSS is still lacking and the detection of novel therapeutic biologic target is ongoing. The identification of biological fingerprints seems essential in order to stratify patients both in clinical trials and in real life. Discovery of new components of the inflammatory response will be the key in the future for the identification of novel additional therapeutic options.

Sjögren's syndrome: clinical and social relevance

Primary Sjögren's syndrome (pSS) is a relatively common chronic inflammatory autoimmune disease, with a higher incidence in female patients (9:1) and a prevalence of ~0.5% in the general population (1, 2). Autoantibody production and chronic infiltration of the exocrine glands, in particular salivary glands, with the histological features of focal lymphocytic sialoadenitis (FLS) represent pSS pathognomonic hallmarks and provide criteria for classification and diagnosis (3, 4). Inflammation results in loss of glandular function and it is responsible for the classical symptoms of dryness, increased incidence of cervical cavities and teeth loss. Ocular involvement is also typical with development of keratoconjunctivitis sicca, often complicated by infections.

The spectrum of pSS extra-glandular manifestations is broad and includes fatigue, vasculitis (leucocytoclastic vasculitis), peripheral neuropathy, joint involvement characterised by polyarthralgia and in some cases synovitis, kidney involvement with renal tubular acidosis, interstitial lung disease, lymphoproliferative disease and immunological abnormalities (5-7). Approximately 5% of patients with pSS develop lymphoma, conferring a higher mortality risk (8, 9). Histologically, the malignancy is predominantly a non-Hodgkin's lymphoma that forms in extra-nodal sites and mainly within the acquired mucosal associated lymphoid tissue (MALT) harbouring within the affected salivary glands (9, 10). Evolution of MALT into diffuse large B cell lymphoma has been described (9). Systemic manifestations and lymphoma development are most commonly observed in immunologically active patients characterised by B cell hyperactivation, high titers of anti-SSA/Ro and anti-SSB/La autoantibodies and presence of rheumatoid factor (5, 11, 12).

PSS represents a significant health and economic burden also in patients that do not develop lymphoma (13-15). Recent data highlight the increased cardiovascular risk (16) and the reduced quality of life associated to pSS (17, 18). Direct health care costs have been estimated at £1,831 to £2,546 per pSS patient per year in the UK, while indirect costs range between £7,677 and £13,502, which is approximately 80% of the costs associated with RA in the era preceding the use of biological therapy. PSS patients are significantly less likely to be in gainful employment, and are more likely to work reduced hours, be in receipt of benefits, or access health care services frequently (13, 14).

One third of pSS patients presents extraglandular manifestations, in rare cases with severe complications. In this cases the use of short courses of steroids might display limited efficacy being often not sufficient to induce and

maintain remission. Disease-modifying drugs (DMARDs) can be used in severe organ involvement with variable results. For this reason, as will be further discuss, new hopes have been put in novel biological therapies that target pathways, molecules or cell types involved in disease pathogenesis.

Novel biologics in pSS: targets and challenges in clinical trial design

PSS presents a multifactorial pathogenesis. On the presence of a predisposing genetic background several external factors, mainly viruses, may act as trigger of the disease. In this context, different types of immune system cells and biological molecules provide their contribute in driving and maintaining the inflammatory response. In principle all these pathways could be targeted therapeutically. The role of IFN signature and its over expression along the development of pSS is well known. Despite the lack of clinical trials investigating the utility of anti interferon type I agents in pSS, some evidences supporting the efficacy and the rationale for using these compounds in pSS derives from studies in patients with systemic lupus erythematosus (https://clinicaltrials.gov).

Overexpression of several inflammatory cytokines in minor salivary glands has been demonstrated, including TNFa, IL-6, IL-1, IL-18 and IL-22 (19-26). While blocking TNF and IL-1 has been unsuccessful (27) other cytokine blocking or modulations is currently contemplated. Similarly, biological agents capable to interfere with T cells migration are currently under investigation alongside molecules able to interfere with T cell homeostasis or differentiation (https://clinicaltrials.gov). Targeting costimulatory molecules such as CTLA-4, ICOS and CD40L with the aim of interfering with the cross talk between T and B cells or T and dendritic cells represents another promising possibility (https://clinicaltrials.gov).

In pSS the use of new biological compounds has been hampered by several factors, mainly related to study design, with a key challenge represented by the variety of outcome measures to assess therapeutic efficacy. Available are indexes that reflect systemic involvement, local disease (salivary flow) or a combination of the two (6, 28-31). Whilst no rationale is currently used to allocate specific tools to a population or compound, it is preferred to recruit into trials patients characterised by moderate to significant systemic involvement according to the ESSDAI, a composite score of disease activity (28). Unfortunately, currently available biological compounds, failed to demonstrate significant success in terms of ESSDAI changes in randomised clinical trials, inducing a general reflection on the ability of the clinicians to use this complex tool, the sensitivity of the index to detect changes in a short period of time and to discriminate between active arm and placebo.

An additional challenge faced when designing pSS trials is represented by the difficulties in the selection of the target population. Given the nature of the ESSDAI, used as entry criteria in a significant number of trials, the recruited population might comprise a rather heterogeneous spectrum of patients, only aligned by the common trait of B cell hyper-activation. While extremely broad in terms of clinical manifestations, this population is, however, relatively small when compared to the majority of the pSS patients, that display limited systemic involvement and are mainly characterised by dryness (32). These considerations raise ethical and practical issues when looking at the broader picture of pSS therapy.

Process driven stratification in pSS

There is a general consensus that strategies should be implemented to stratify patients and recruit into clinical trial patients identified by specific biological fingerprints. In this context, research for serum, saliva and tissue biomarkers has been implemented in several trials with the aim to stratify patients, predict and monitor response to treatment.

Baseline stratification according to biological fingerprints and correlation with clinical phenotype is also pursued. It has been recently shown that immunophenotyping of blood as well as tissue isolated cells can be used to stratify patients in clusters defined by different degree of disease activity and level of glandular inflammation (33).

Changes occurring in different biological pathways in response to therapy have been only recently investigated in pSS. Using transcriptomic analysis in pre and post treatment samples from patients undergoing treatment with Rituximab differential expression of genes belonging to the IFN pathway between responders and non-responders has been demonstrated (34). Similarly, histology based stratification has been recently used in the context of clinical trials as predictor of response with contrasting results (35-38).

Several trial protocols have been recently implemented to encompass the histological analysis of salivary gland biopsies and include detailed measurements that capture changes in infiltrate size and degree of organisation, presence of germinal centres and, in selected cases transcriptomic analysis. Whilst providing a biological outcome measure of drug efficacy, the possibility to use these data in retrospective analysis to stratify responders to treatment is also considered.

Targeting stromal cells in tertiary lymphoid structures: a new therapeutic approach in pSS

The association between the degree of organisation of the salivary glands infiltrate in pSS and sieric and clinical features has been clearly shown. The ectopic lymphocytic aggregates, correctly defined as tertiary lymphoid structures (TLS), have been classically associated with negative disease prognosis and lymphoma development (39, 40). Local production of autoantibodies and clonal B cell expansion (41, 42) has been also observed within fully formed TLS, thus supporting the direct pathogenic role of those structures and the rational to target TLS formation therapeutically.

B cell targeting is, in this context, expected to modify the degree of TLS formation and interfere with the functional ability of TLS to sustain disease progression. Interestingly, this appears not to be the case. Despite the strong

rational supporting the use of B cell depleting agents in pSS, early results from randomised clinical trials using Rituximab are conflicting. Resistance to B cell depletion and loss of clinical response appears to correlate with systemic and local rebound of the levels of the B cell survival factor BAFF. This, in turn supports the homeostatic expansion of pathogenic B cell clones in the periphery and in the salivary gland during the phase of repopulation (43-45). Novel strategies aimed to overcome this problem and improve B cell targeting are under consideration and involve either combination therapies with anti BAFF neutralising agents or novel compounds aimed to broadly interfere with immune cells intracellular signals (clinicaltrials.gov).

We and others demonstrated that the activation of resident tissue stromal cells is a cardinal feature of pSS. TLS aggregates in patients with PSS contain networks of Podoplanin/gp38+ stromal cells and networks of follicular dendritic cells, whose organisation closely resemble the stroma compartment that support secondary lymphoid organs (SLOs) (46). These non-haematopoietic stromal cells are increasingly recognised as essential counterparts to leucocytes in pathogenicity.

In SLOs, the stromal cell compartment provides the scaffold that enable leucocytes migration and interaction, alongside survival and homeostatic factors required to sustain the haematopoietic cells. More recently, stromal cell have been demonstrated able to influence the size and shape of the immune cell repertoire by modulating the availability of lymphocyte survival factors and inducing deletion or expansion of auto-reactive cell clones. This central role in balancing immune stimulation *versus* peripheral tolerance is achieved by the ability of stromal cells in the lymph nodes to present a range of peripheral tissue restricted antigens and limit T cell expansion and priming through a series of mechanisms, among which the release of nitric oxide (47-56). TLS stromal cells also sustain cell migration, activation and survival of the immune compartment in persistent inflammatory conditions, likely enabling disease persistence, even when lymphocytes have been depleted (46).

Within TLS, persistent antigenic stimulation and presence of pro-inflammatory cytokines is responsible for the conversion of stromal cells into a lymphoid tissue-like cell phenotype. Similarly cytokines and genetic predisposition influence the epithelial compartment to contribute to disease establishment in pSS. It is well known that areas of "lymphoepithelial proliferation" or LESA represent a pathogenic histological element in the process of lymphomagenesis. The close cellular introduction between pathogenic nursing epithelial cells able to provide chemoattractive (57) and survival factors (45, 58) and the aberrant B cell clones often characterised by rheumatoid factor activity is understood to play a key role in the establishment of autoimmune associated MALT (59).

Resident stromal cells, including epithelial cells, fibroblasts, endothelium and lymphatic cells are therefore responsible for establishing the chemokines and survival factors gradients that enable migration and organisation of the pathogenic clones within the glands. CXCL13, major B cell chemoactractive factor, ligand for CXCR5, is preferentially expressed within the inner part of the aggregates and in the germinal centres by activated fibroblasts, follicular dendritic cells and few activated T cells (19, 60, 61). Its expression is regulated by lymphotoxin, TNF (62, 63) and, as recently described by our group, by proinflammatory cytokines such as IL-22 (19). The areas characterised by malignant B cell infiltration display, on the contrary, preferential expression of CXCL12 (57). Interestingly, IL-22, that is responsible for CXCL13 expression by resident activated fibroblasts, induces on epithelial cells the expression of CXCL12, thus suggesting differential regulation of the fibroblasts and epithelial compartments in the context of chronic inflammation and TLS establishment. Abrogation of the IL-22 pathway by genetic modification and therapeutic intervention leads to TLO disaggregation and loss of autoantibody production (19). These data suggest the exciting prospective of targeting the pathogenic microenvironment to affect the survival and migration of the haematopoietic component.

Conclusions

To date there is no approved, specific treatment for pSS. Patients are managed with a combination of immunosuppressive drugs and, in some cases, systemic disease is treated with steroids. Efforts to identify biological fingerprints are ongoing, favoured by international initiatives and collaborative efforts, such as the EULAR endorsed Study Group for Sjögren's syndrome (www.eular.org/myUploadData/files/Investigative_Study_Group_Sjogren.pdf) with the aim to design algorithms for process driven stratification and apply precision medicine to pSS. Alongside this critical efforts are aimed to define the role of undervalued components of the inflammatory response and will provide, in the next future additional and exciting therapeutic opportunities for this orphan disease.

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