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NEW FRONTIERS IN SJOGREN'S SYNDROME DIAGNOSIS AND TREATMENT: A LITERATURE REVIEW

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ABSTRACT – Sjogren's syndrome (SS) is an autoimmune disease involving mainly the exocrine glands, resulting in dryness of the mucous surface (especially the oral and ocular ones). However, the clinical presentation can range from simpler manifestations such as mucosal dryness, arthralgias, and modest purpura, to even relevant systemic manifestations; association with lymphoma, especially non-Hodgkin lymphoma, is also frequent.

Histologically, SS is characterized by a lymphocitic infiltration of tissues resulting in their destruction. Pathogenetic mechanisms are not fully understood but cellular B hyperactivity with auto-antibody production plays an important role.

The main immunological markers are anti-nuclear antibodies (the most frequently detected), anti-Ro/SSA, and La/SSB (the most specific). It is also important to recognize cryoglobulinemia, hypergammaglobulinemia, hypocomplementemia, and rheumatoid factor positivity as prognostic markers; this may help define to whom to target more aggressive treatments.

Indeed, this review aims to focus on the practical management aspects of the patient with SS, focusing on diagnosis and treatment.

Referring to diagnosis, it is important to emphasize that although several classificatory criteria have been developed over the years, these do not represent diagnostic criteria; the diagnosis is up to the clinician, possibly aided by instrumental investigations including ultrasound, high-frequency ultrasound (useful as helping instrument in labial biopsy) and magnetic resonance of parotids.

Instead, treatments (from the symptomatic ones to new biological therapies) should be modulated on the severity and the organ commitment of the disease, monitoring serologic changes and stratifying patients for the risk of developing NHL, in order to choose where to apply earlier and more aggressive therapies.

KEYWORDS: Sjogren's syndrome, B cells, Diagnosis, Therapy, Lymphoma, Autoimmunity.

INTRODUCTION

Sjogren's syndrome can be defined as primary, or secondary if associated with other pathologies; both are characterized by glandular involvement from which ocular and oral dryness results [1].

Focusing on primary Sjogren's syndrome (pSS) is a systemic autoimmune disease generally prevalent in women around 50 years of age [2]; in particular, as we said, this syndrome affects the exocrine glands, causing dryness of the main mucous surfaces [3]. There are, however, several clinical spectra [4] of this pathology, including, in addition to glandular involvement, systemic manifestations with extra glandular non-specific or peri epithelial involvement, immunocomplex-associated disease (resulting from

B-cell hyperactivity) or even complicated with the occurrence of lymphoma [5]. In fact, there is a higher incidence of lymphoma, especially malignant non-Hodgkin lymphoma, in patients with pSS [6]. Clinical manifestations are thus variable from simple multidistrict dryness to forms with possible arthritis, organ involvement, or cytopenia [1]. The wide spectrum of possible clinical presentations correlates with the presence of different pathogenetic mechanisms. While not yet fully understood, the role of cytokines, B/T cells, and antibodies seems different in the various presentations [1].

Histologically, pSS is characterized by the destruction of the tissues involved and a dense lymphocytic infiltration. There is a marked hyperactivity of B-cells: this is evidenced by the frequent presence of hypergammaglobulinemia, increased risk of type B lymphoma, elevated blood-free light chains, and production of autoantibodies [7]. Key immunological markers of pSS include antinuclear antibodies (ANA), the most frequently detected (59-85%); anti-La/SSB and anti-Ro/SSA antibodies, the most specific; cryoglobulinemia, hypergammaglobulinaemia, RF positivity and hypocomplementemia, in addition, are the main prognostic markers associated with a more severe disease presentation [8]. Often, in the face of a marked activation of the immune system with a sometimes-striking serological response, the clinic is modest. In most patients, symptoms such as arthralgia, dry syndrome, and modest purpura, are predominant. Anyway, as we said above, the clinic may extend to systemic manifestations, especially in young-age patients or those with a long a long history of disease. This is important to understand to use more aggressive treatment and closer monitoring when necessary [8]. In this review of the literature, we focused on how to make the diagnosis of Sjogren's syndrome and on therapeutic possibilities, also analysing new therapeutic frontiers.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of pSS is clinical and based on the physician's judgment; there are no optimal diagnostic criteria for that condition, although there are classification criteria. There have been several classificatory criteria over the years (1993, 2002, 2012) [9-11]; the latest described (reported in Table 1) are those of 2016 [12]. The latter, applicable if the inclusion criteria are met, are positive with a score ≥ 4 [12].

Table 1. The 2016 EULAR/ACR criteria for pSS[12].

Inclusion criteria: Eye or oral dryness ≥ 3 months in the absence of any other plausible explanation or ESSDAI ≥ 1. If this criterion is met and none of the exclusion criteria is present, other items can be evaluated.

Positive score ≥ 4

ITEMS	SCORE
Anti-SSA/Ro positivity	3
Focus score ≥ 1 and presence of focal lymphocytic sialoadenitis on labial biopsy	3
Ocular staining score ≥ 5 (otherwise ≥ 4 on van Bijsterveld score)	1
Minimum one eye with ≤ 5 mm/5 min value on Schirmer test	1
Saliva flow rate without stimulation, ≤ 0.1 mL/min	1

In this 2016 EULAR/ACR criteria, exclusion criteria for the diagnosis of pSS are also given; these include IgG4-related disease, AIDS, sarcoidosis, amyloidosis, graft *vs.* host disease (GVHD), or history of head-neck radiation treatment [12]. In the past, HCV positivity also ruled out the diagnosis of SS since, as the virus is scialo/lympho/hepatotropic, it could mimic Sjogren's syndrome [12]. However, this may not be true where the virus occurs endemic, so more attention should be paid to this condition today.

While diagnostic criteria must be sensitive, given the need to identify the greatest number of subjects with the specific pathology, classificatory criteria need to be highly specific; the 2016 EULAR/ACR criteria, referring to a Japanese study conducted on patients with clinic diagnosis of pSS or suspect SS

that compared the different classification criteria, seem to be more sensitive and less specific than their predecessors [13]. Thus, this reiterates the need not to use them to make diagnoses, but to compare different trials or to develop new trials or therapies; some cases of disease may escape classification criteria if we use them to make diagnosis [14].

Considering the above, it emerges the need to identify possible tools and imaging techniques for making SS diagnoses or helping in disease work-up. So, what is the clinical role of labial salivary gland biopsy? Generally, pSS at biopsy is characterized by focal lymphocytic sialoadenitis (FLS), which is a collection of mononuclear cells represented predominantly by lymphocytes, localized at the periductal and perivascular levels, near normal acini [15]. There are two different scores that can be calculated on the biopsy specimen to determine the severity of the disease: Chisholm-Mason grade (from 1 to 4) and Daniels-Whitcher grade or focus score (from mild to severe). Only the severe forms (corresponding to 3-4 of Chisholm- Mason grade), that are with one or more foci (aggregate of 50 lymphocytes or more in 4 mm^2 of tissue) as there is in the 2016 criteria, are pathological. In fact, the important parameters to be evaluated are the number of foci and the area of the biopsy sample [16]. However, this focus score has limitations including the surface area examined, multilevel cuts, not taking into account the size of the foci, and inter-observer variability [15]. Although the SICCA protocol and other studies have attempted to develop standardization methods [15], in this regard, several other studies [17,18] have shown that although the reliability of scores used for biopsies is good, there is a need for even more standardization at the international level. Otherwise, there is a risk of falling into diagnostic errors if biopsy samples are not evaluated by medical experts[17]. In clinical practice, we are then helped by the use of other tools such as ultrasound (US) or ultra-high frequency ultrasound (UHFUS), which is also useful for echo-guiding labial biopsy, and magnetic resonance imaging of the parotids.

The ultrasound of salivary glands (SGUS) is certainly an important diagnostic tool, non-invasive and repeatable; even if it is still operator-dependent, its use in expert hands and in association with other criteria, results of considerable diagnostic and follow-up importance [19,20]. What is generally observed, to support the diagnosis of pSS, is an altered echogenicity of the gland, with areas of increased (fibrosis or fat, even if fat is probably well evaluated by magnetic resonance) or reduced (inflammatory cells) echogenicity [20,21]; anyway, there is no consensus in defining a US scoring. Many studies [22-26] support that including these techniques in EULAR/ACR criteria can be useful in terms of better and easier diagnosis and higher sensitivity of the criteria.

Nevertheless, although it has a demonstrated higher sensitivity and specificity than other diagnostic tools, it is still not included in the 2016 classification criteria or even in specific diagnostic criteria for pSS; this is probably related to the still-present divergence of opinion among different physicians in defining certain ultrasound features [19,22]. In addition to its diagnostic role, it is important to investigate its potential use for prognostic evaluation purposes; despite the current absence of sufficient longitudinal data to demonstrate for sure its prognostic role, there appear to be correlations between what is assessed by SGUS and the risk of systemic manifestations or lymphoma or high disease activity [20,21,27].

A more recent breakthrough is the UFHUS, an ultrasound technique that works at higher frequencies (30-100 mHz instead of 22 mHz) and higher axial resolution than normal ultrasound [20]. UFHUS of major salivary glands can be useful, although further studies are still needed, to make potential earlier diagnoses due to the greater ability of this technique to highlight areas of inhomogeneity. Even more important is its role in the evaluation of the minor salivary glands, which otherwise cannot be evaluated with the conventional US [20]. Although it is an outstanding tool for evaluating these glands, further studies, a defined scoring system, and training on the methodical, are needed to define with certainty its applicability in clinical practice [20].

Certainly, this is a promising tool that can be used for labial biopsies; the latter indeed, still have an important role in prognostic stratification. A very severe score in fact (>3 foci) correlates with poor prognosis: it is generally related to increased disease activity, the risk of developing a lymphoproliferative disease, and more severe clinical and serology [28-30]. The ultrasound, and specifically UFHUS, can be useful to biopsy precisely the areas of altered echogenicity and to easily obtain better samples, with an adequate sample area; this is relevant in order to optimize an invasive procedure as the biopsy and to potentially identify salivary glands changes before performing the biopsy [31]. A preliminary study conducted in 2020 on 128 patients [32] with suspected SS, assumed UFHUS of labial salivary glands, as a useful tool to identify potentially negative samples at a following biopsy. This would be certainly important to avoid invasive procedures, but further studies are still needed to define the accurate clinical role of this technique. The same study found also that seropositive patients (only anti-Ro/SSA positivity or both anti-Ro/SSA and anti-La/SSB) had more alterations at UFHUS than seronegative patients[32].

Another important instrument is the magnetic resonance (MR) of parotids; a study conducted in 2015 on 23 patients with SS and 11 controls [33], demonstrated that diffusion-weighted imaging (DWI) of parotids on a small region of interest, can be useful in SS diagnosis and even in treatment evaluation. In this regard, from another study conducted in patients with SS and rheumatoid arthritis [34], the utility of the DWI resonance tool in predicting therapeutic response to abatacept, appears to be emerging. Here it is good to emphasize the important role of using MR in combination with magnetic resonance sialography (which has surpassed the traditional sialography, much more invasive) and labial salivary gland biopsy to improve diagnostic sensitivity [35]. Certainly, MR in comparison with ultrasonography it is less easily applicable in daily clinical routine and certainly more expensive; however, it is good to recognize its relevant role in diagnosing pSS, especially pSS-related lymphomas of the neck and the head and their staging [22,29].

To date, the clinical diagnosis must still be based on the subjective judgment of the medical expert, aided by increasingly developing instrumental investigations, each with its own advantages and needs for improvement [29]. Also, not to be underestimated is the potential use of the different techniques for possible future prognostic and treatment algorithm use.

TREATMENT

The primary goal in pSS's treatment is to relieve symptoms of mucosal dryness and prevent its complications, as well as identify and treat systemic manifestations, glandular and lymphoproliferative disease, occurring in about one-fifth of patients [8]. In this regard, in addition to general recommendations that patients with pSS should follow in everyday life (such as quitting smoking, doing caries prevention, and air humidification of the environment), for patients with mild disease, in whom sicca manifestations alone are present, the treatment lies in collaboration with the relevant specialists (ophthalmologists, dentists, and otolaryngologists) to allow adequate mucosal humidification [1].

Currently, various tear and saliva substitutes are available, even if there is no clear evidence to support a specific topical therapy as more effective than others [36,37]. Patients with mild reduced saliva production should also use lubricants and mechanical stimulation as chewing gum, in addition to adequate oral hygiene and fluoride toothpaste to avoid caries emergence; patients with moderate-severe oral dryness, instead, should use oral muscarinic agonists that stimulate the M1 and M3 receptors present on salivary glands, such as pilocarpine or cevimeline [1]. Patients with refractory or severe ocular dryness, after excluding other ocular processes not related to pSS, as defined by the latest EULAR recommendations, should be referred to an ophthalmologist, who can use topical drugs as non-steroidal anti-inflammatory drugs (NSAID) or corticosteroids; topical ciclosporin A (CyA) can also be considered in these patients after several cycles of topical steroids[38].

Patients with moderate to severe forms of pSS, including extra glandular involvement, may also need systemic therapies; the specific treatment is chosen by the level of disease activity and by the organ system involved. Due to pSS' multiple extra glandular manifestations, EULAR developed also a score named "EULAR SS disease activity index" (ESSDAI) to help in the disease activity assessment, evaluating 12 clinical domains [38]. Most frequently these patients present general symptoms such as arthralgia/arthritis and fatigue/weakness; these cases are usually managed with symptomatic therapies such as NSAIDs and, following the indication given also in other autoimmune rheumatic diseases, with hydroxychloroquine (HCQ) [39]. If treatment with HCQ is not effective, methotrexate (MTX) can be considered as second-line therapy or as add-on therapy, in combination with HCQ [40,41]. Moreover, in cases that are refractory to previously cited therapy, other immunosuppressive therapies like leflunomide, sulfasalazine, and azathioprine can be used [42]. Furthermore, cases characterized by systemic involvement can be treated with high-dose methylprednisolone and cyclophosphamide [1].

The treatment of systemic organ-specific manifestations may follow general rules applied also in other diseases. Indeed, pruritus, for example, is largely managed symptomatically. Annular erythema is treated initially with topical steroids or calcineurin inhibitors, or, in case of a more severe or widespread disease, with oral glucocorticoids; for recurrent skin lesions, therapies used in other autoimmune diseases such as HQC or low-dose weekly methotrexate, are indicated [43]. Similarly, other manifestations such as cardiopulmonary (interstitial lung disease, pulmonary hypertension, or pleuropericarditis), Raynaud phenomenon, gastrointestinal involvement, or neurologic manifestations are treated as in other rheumatic diseases [38].

Therefore, pSS can be described as a heterogeneous disease due to its different clinical phenotypes, depending on the presence of glandular or extra glandular manifestations. Given the different manage-

ment of these clinical phenotypes and the possibility of using new biological therapies, it is essential to determine the severity and the extension of the disease to choose patients eligible for receiving more aggressive therapies.

It has been reported that serological aspects as the presence of cryoglobulins, monoclonal paraproteinaemia, or the positivity of anti-Ro/SSA, anti-La/SSB, and rheumatoid factor, are associated with a poor prognosis (lymphoma occurrence and severe extra glandular features for example) [8]. The serological finding of lymphocytopenia and hypocomplementemia at pSS diagnosis represents a powerful predictor of lymphoma development [44]. Contrariwise, positivity for anti-Ro/SSA or anti-La/SSB appears to have a little prognostic role for lymphoproliferative disease progression [8]. Anyway, a higher attendance of visceral complications occurs in patients who present two or more serological; so, these patients often require the use of systemic immunosuppressive therapy [8].

Given the etiopathogenesis of this disease, based on an elevated B-cell activity, therapies targeting B-cells are the most frequently attempted between biological therapies; included among these are rituximab (RTX) and more recently even epratuzumab and belimumab [38,45]. Rituximab, the first widely studied anti-CD20 monoclonal antibody, has been moderately recommended, using the regimen of 2 doses of 1 g administered 2 weeks apart from each other [46], in cases of pSS presenting with inflammatory arthritis or other systemic manifestations such as vasculitis (even if associated with cryoglobulinemia), severe parotid swelling, lung disease or neuropathies (as mononeuritis) [47]. After a literature review, EULAR declared that RTX may be considered in refractory and severe disease presentation, taking into account belimumab as a salvage treatment [38].

Results from the open-label BELISS phase II study showed that belimumab 10 mg/kg (at time zero, 2 and 4 weeks and then monthly until week 24) can possibly improve clinical signs such as parotid swelling or serological markers representative of the reduced B-cell activity; to a lesser degree can possibly improve symptoms as dryness [48]. Considering the open design of the study, further clinical trials are needed [48].

Additionally, it has been demonstrated that the combination of belimumab and rituximab is comparable in terms of safety to monotherapies, resulting in greater depletion of B cells in the salivary glands compared to the latter [49]. Instead, for humanized anti-CD22 antibody (epratuzumab), there is only one small open-label study that demonstrated a significant reduction in fatigue, but larger studies are needed to confirm that [50].

Other promising therapies, given the pathophysiology of pSS, are treatments targeting the Treg/Th17. A recent study demonstrated *in vivo* how SSA/Ro-antigen-specific Treg cells can reduce the inflammatory infiltration of the salivary gland, downregulating the production of CD4+ T cell-related IFN-γ; to match this endpoint, researchers used combination treatment with anti-CD4 monoclonal antibody and autoantigen-specific peptide Ro 480 [51]. This can be useful for potential future therapies.

Following the same pathophysiological principle, trials were performed with either anti-IL1 or anti-TNFα drugs e.g., etanercept, infliximab, both with negative results [1,52,53]. Similarly, anti-TNF agents did not achieve primary endpoints in double-blind, randomized, controlled trials [54].

The use of tocilizumab was also studied in a multicentre double-blind randomized placebo-controlled trial, although this showed that this drug does not seem to induce an improvement in symptoms and systemic manifestations [55].

Since IFNs and IL-6 generate many of their biological effects through the activation of JAK/STAT pathways, it has been considered also to use JAK inhibitors as a new therapeutic strategy [1,56]. JAK inhibitors e.g., baricitinib or filgotinib, have been used to treat various autoimmune diseases, and recently have been studied also in pSS [57]. The treatment with baricitinib, analyzed in a pilot non-controlled trial [58] at the dose of 2 mg/day and followed up at 3 and 6 months, appears promising even if these data should be confirmed through randomized controlled clinical trials [57]. An improvement was observed both through the use of ESSDAI scores and in clinical manifestations such as skin rash or arthritis, weight loss, blood count values, and also lung involvement [57,58]. Instead, a recent study using filgotinib at the dosage of 200 mg/day for 48 weeks, didn't highlight a statistically significant difference *vs.* placebo [59]. Tofacitinib is also a candidate drug for pSS, given its role in inhibiting inflammation in salivary glands, reducing the expression of IL-6 [56]; another promising drug is ruxolitinib, thanks to its inhibition of IFNs effects [56,57]. Moreover, another example of cytokine-based therapy in pSS is abatacept, whose mechanism of action lies in negatively modulating the antigen presentation mechanism [1]; recently it has been demonstrated its positive effects on systemic involvement, reducing glandular infiltrates and title of rheumatoid factor and IgG levels [1,60,61]. Thus, several drugs are being studied for further investigation (Table 2).

Table 2. New therapeutic perspectives in pSS.

Targeting B-cells	Rituximab (RTX)	anti-CD20 monoclonal antibody	Ramos-Casals et al[38,46]
	Belimumab	anti-cytokine BLyS monoclonal antibody	Mariette et al[48]
	Belimumab and Rituximab	anti-BLyS and anti-CD20	Mariette et al[49]
	Epratuzumab	anti-CD22 antibody	Steinfeld et al[50]
JAK/STAT pathways	Baricitinib	JAK1/JAK2 inhibitor	Bai et al[58]
	Filgotinib	JAK-1 inhibitor	Price et al[59]
Agents in trials	SSA/Ro-antigen-specific Treg *in vivo*	anti-CD4 monoclonal antibody and autoantigen-specific peptide Ro 480	Xu et al[51]
	Tofacitinib	JAK-1 inhibitor	Zhan et al[56]
	Ruloxitinib	JAK1/JAK2 inhibitor	Gandolfo et al[57]

Among the systemic manifestations of pSS, lymphoma is one of the worst complications [62]. Overall, the prevalence of non-Hodgkin's lymphoma (NHL) in pSS patients has been estimated to be around 5-10% [62]; the most common subtype described in this disease seems to be the mucosa-associated lymphoid tissue (MALT) lymphoma [63]. Risk factors for progression to lymphoma include widening of lymph nodes, spleen, and of the parotid gland, purpura/skin vasculitis, serum cryoglobulins, reduction of complements, white blood cells, and gamma globulins, raise of β2-microglobulin and monoclonal gammopathy [44,64]. Once diagnosed with lymphoma, the therapeutic approach must be evaluated on the patient case-by-case, taking into account the location and stage of the NHL and also the specific histological subtype, defined referring to the WHO 2016 classification [65]; certainly, the current guidelines for therapies must be followed, in collaboration with the haematologist or oncologist [38,66]. Overall, SS survival and prognosis are comparable to those of the general population, even though purpura, cryoglobulinemia, and low C4 levels, represent adverse prognostic factors if coexisting[66].

In conclusion, patients with only sicca syndrome as disease presentation, are different from those with systemic involvement; for this reason, treatments must be chosen on a case-by-case basis, also considering IFN-γ levels, and stratifying patients based on the risk of developing NHL, taking into account risk factor as parotid enlargement, complement reduction and years of illness [38,64].

CONCLUSIONS

The spectrum of pSS can range from a benign, slowly progressive autoimmune exocrinopathy to a heterogeneous, potentially life-threatening, systemic disease also characterized by an increased risk of non-Hodgkin lymphoma. The subgroup of pSS patients at high risk for systemic complications is characterized by a serologic profile suggestive of chronic B lymphocyte activation.

It is very important to point out that classification criteria are not diagnostic criteria. To date, clinical diagnosis must still be based on the subjective judgment of the medical expert, aided by increasingly developing instrumental investigations. Labial biopsy, present in the classificatory criteria, may be a confounding factor if not read by an expert pathologist; on the other side, it can be very useful in prognostic stratification.

Lots of new therapies have been studied, but it's important to remember that, faced with a disease with extra glandular involvement, like other connective tissue diseases, treatment choices depend on organ involvement and severity. In clinical practice, patients with two or more serologic abnormalities should be more closely monitored and may benefit from more aggressive immunosuppressive therapy from the early stages of the disease. Talking about the diagnosis and treatment of pSS, it is always important to remember that often, even with a marked activation of the immune system with a sometimes-striking serologic finding, the clinical is modest.

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