

REVIEW

# Chronic Autoimmune Epithelitis in Sjögren's Syndrome and Primary Biliary Cholangitis: A Comprehensive Review

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## ABSTRACT

Within the spectrum of autoimmune diseases, Sjögren's syndrome and primary biliary cholangitis are exemplary and can be coined as chronic epithelitis based on their frequent coexistence in clinical practice and the highly specific immune-mediated injury of the small bile ducts and the exocrine glands. The pathogenic mechanisms underlying the diseases are similar, with apoptosis being the key element leading to organ-specific immune-mediated injury directed against the small bile ducts and salivary gland epithelia, respectively along with

similar epidemiological features, such as female predominance and the age of onset in the fifth decade of life. Indeed, novel insights into the pathogenesis of the diseases have been obtained in recent years, including a better definition of the role of B and T cells, particularly Th17 cells, and the mechanisms of autoantibody-mediated tissue injury, with anti-mitochondrial antibodies and SS-A/SS-B being identified as specific for primary biliary cholangitis and Sjögren's syndrome, respectively. These findings have opened the possibility to new targeted therapies, but most clinical needs remain unmet, particularly from a therapeutic standpoint where options diverge, with bile acids being the predominant treatment strategy in primary biliary cholangitis and immunomodulators being used to treat Sjögren's syndrome. Here we provide a comprehensive review of the most recent findings on the pathogenesis, clinical manifestations and therapeutic options for Sjögren's syndrome and primary biliary cholangitis, respectively, while stressing the common traits between these conditions. Our cumulative hypothesis is that similarities outnumber differences and that this may prove advantageous towards a better management of patients.

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## INTRODUCTION

Sjögren's syndrome (SS) and primary biliary cholangitis (PBC) are chronic organ-specific autoimmune diseases that affect the exocrine glands, especially the salivary and lacrimal glands, and biliary epithelia, respectively, ultimately leading to their progressive immune-mediated destruction [1, 2].

The nomenclature of PBC has been recently changed from cirrhosis to cholangitis to rectify the inaccuracy of the term and to remove the consequences of the cirrhosis stigma in patients, as well as all of the misunderstandings, disadvantages and discrimination associated with this misnomer [3–5]. This change was necessary given recent dramatic improvements in the diagnosis, prognosis and treatment of PBC, with the result that the natural history of the disease is now significantly better than previously. Currently, an early diagnosis of PBC can be established with the more accurate measurements of markers of cholestasis and improvements in the detection of the classic serologic hallmark, anti-mitochondrial antibodies (AMA), while treatment has improved with the introduction of orthotopic liver transplantation and ursodeoxycholic acid (UDCA) treatment [6, 7].

Similar to other autoimmune diseases, SS and PBC are diagnosed significantly more often in women than in men, and it is the fifth decade of life which is most frequently affected [8–11]. The two diseases often co-occur, and shared genetic associations have been reported [12]. SS can be primary or secondary to other systemic autoimmune diseases; up to 43% of PBC patients are also affected by another autoimmune condition, in particular chronic thyroiditis and systemic sclerosis [8, 13], with SS found in up to 40% of patients with PBC [14]. On the other hand, as many as 20% of SS patients manifest liver abnormalities [15]. Interestingly, when both diseases co-occur, few cases are severe, as severe SS occurs in 10.5% of PBC cases, while the PBC disease is usually milder and at early stage (stage I–II at liver histology) when SS is also present [14, 16].

From a serology standpoint, antinuclear antibodies (ANA) are detected in both SS and

PBC, with a higher prevalence in SS compared to PBC [17], while both conditions are associated with the presence of disease-specific autoantibodies, namely anti-Ro/SSA (Sjögren's-syndrome-related antigen A) and AMA, respectively. In this review we discuss the most recent findings on the immunopathogenesis of the PBC and SS autoimmune epithelitis and focus on common clinical manifestations and current and future therapeutic options. This review is based on previously conducted studies and does not involve new studies of human or animal subjects performed by the authors.

## A COMMON IMMUNOPATHOGENESIS

Both SS and PBC are chronic autoimmune diseases associated with an immune-mediated destruction of the epithelia [18]. Similar to many autoimmune diseases, in SS and PBC genetics and environmental factors interact to result in disease onset [19, 20]. In this context, over the past decades, mouse models of both SS and PBC have been extensively developed and studied, and they remain an invaluable tool in the search for an understanding of disease pathogenesis and to test novel therapeutics. Mouse models for SS are categorized as spontaneous, genetically engineered or experimentally induced animal models. Despite the numerous achievements and advantages of mouse models, no single mouse model has replicated each and every aspect of human SS and PBC to date. In addition, the initiation of the disease in mouse models is highly artificial, especially in the induced models, and the treatment is usually initiated very early in the disease course, unlike the clinical situation. Due to these limitations, an appropriate control of animals for disease onset and progression and cautious interpretation of the results are compulsory [21].

### Genetics of SS and PBC

In the case of PBC, genetics play a predominant role in disease susceptibility, as suggested by the higher frequency of PBC among relatives of

affected individuals than among the general population. The term ‘familial PBC’ has been coined to indicate families in which more than one case of PBC occurs [22–25]. Conversely, in SS there is a large variability in genetic factors in ethnic groups, in particular within the human leukocyte antigen (HLA) system [26]. As for many autoimmune disorders, genetic factors are known to play a decisive role in conferring PBC susceptibility, but these are not related to a single gene but to a complex multigene trait. The relevance of the multifactorial genetic basis in PBC has become more apparent recently, including a higher concordance rate among monozygotic (identical) than dizygotic twins and the observation that peripheral lymphocytes from women with PBC preferentially lose one X-chromosome [27, 28]. Indeed, PBC is not only associated with the HLA DRB1\*08 allele but also with two protective alleles, HLA DRB1\*11 and DRB1\*13 [12]. Furthermore, a genome-wide association study confirmed that HLA class II loci play a key role in PBC, and also demonstrated that genes encoding for interleukin (IL)-12 and its receptor are associated with susceptibility to PBC [29], similar to what has been reported for SS [30, 31].

### Association of Infections with SS and PBC

Overall, it may be hypothesized that other factors, including epigenetics and exposure to environmental triggers, such as infections or xenobiotics, may play a role complementary to genetics [32–37]. Infections are thought to increase susceptibility to PBC and SS based on molecular mimicry which ensues when an infectious agent, bacterial or viral, presents antigens with a significant amino acid similarity to self-proteins [38]. In PBC, pyruvate dehydrogenase E2 (PDC-E2) shares a well-conserved sequence across various species, with a high degree of similarity to microbial PDC sequences of *Escherichia coli*, *Helicobacter pylori* and others [39, 40]. *Novosphingobium aromaticivorans*, a ubiquitous xenobiotic-metabolizing Gram-negative bacterium, may represent the ideal candidate for PBC initiation because it contains proteins with the highest degree of homology

to the major epitope of PDC-E2, while being able to metabolize organic compounds and estrogens. Moreover, *N. aromaticivorans* is recognized by PBC but not control sera [41]. Viral agents have been postulated to be involved in priming or triggering PBC and SS. In this context, in SS, several viruses have been suggested, particularly *Herpesviridae*, including Epstein–Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus, all of which express tropism for salivary and lacrimal glandular tissue [42]. EBV genetic material is frequently detected in peripheral lymphocytes, liver and salivary glands from the majority of PBC patients [43], and several lines of evidence support the notion that the immune response against EBV-infected epithelial cells play a role in the perpetuation of salivary gland destruction in SS [44, 45]. The presence of EBV in salivary gland and saliva samples is associated with more severe SS and marked abnormalities in immunoglobulin levels [46]. EBV-DNA is also detected in up to 88% of SS lacrimal glands [47]. CMV can induce a SS-like pathology in the C57B1/6-lpr/lpr mice model [48]. Persistent CMV infection induces an alteration of cell surface expression in certain tissues, initiating tissue destruction, and the expression of autoantigens Ro/SSA, calreticulin and major histocompatibility complex class I proteins which can elicit an immune response [49].

### Immunobiology

Once the immune response is established, its perpetuation and the development of autoimmune epithelitis takes several steps [50–53]. First, the epithelial cells become apoptotic, after an initial stimulus, and aberrant autoantigens are expressed on biliary and exocrine gland epithelia, which may lead to an increased presentation to autoreactive T cells [12]. More importantly, disease-specific molecules, i.e. PDC-E2 and PDC-E2-like molecules, are have been demonstrated to be expressed in salivary gland epithelial cells (SGEC) from 50% of patients with SS and PBC [17, 54, 55]. Moreover, SGEC and biliary epithelial cells (BEC) have the unique capacity to release intact autoantigens

after apoptosis via apoptotic blebs and bodies [56–60]. In healthy tissues, apoptotic cells are cleared by antigen presenting cells and neighboring phagocytes, such as epithelial cells [61], but in both SS and PBC this capacity is impaired and may account for the prolonged availability of autoantigens to stimulate an immune process [62, 63]. More importantly, it has been shown that BEC can phagocyte the apoptotic cells, but then present the novel self-peptides and pathologic epitopes on their membrane [61, 64, 65].

Once the autoantigens have been presented, a multi-lineage T- and subsequently B-cell response develops. CD4+ and CD8+ T cells directly infiltrate the target organs, as well as B cells and macrophages, where also an increased expression of proinflammatory cytokines, chemokines and adhesion and costimulatory molecules is found. Proinflammatory cytokines play a crucial role in promoting systemic inflammation and affect the proliferation and maturation of the infiltrating lymphocytes [12, 66, 67]. It has been reported that while BEC produce IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ), minor SGEC cells express IL-1 and IL-6 [68]. Overall, an increased T-helper 1 (Th1) and Th17 response is observed. T cells likely contribute both directly and indirectly to tissue damage and systemic manifestations through production of cytokines (Th1, Th17 cells) and maintenance of B cell-mediated responses (Tfh cells) [69]. Elevated serum levels of interferon-gamma, necessary for Th1 differentiation, are detected in SS and PBC patients [70]. It has recently been demonstrated that Th17 cells are also involved in the pathogenesis of both diseases. In SS, elevated levels of Th17-related cytokines, i.e. IL-17, IL-6 and IL-12, are present in serum, while transforming growth factor-beta, IL-6 and IL-23 are found in abundance in minor salivary glands. A recent study has further clarified that elevated IL-17F levels are found in SS sera and are associated with increased levels of immunoglobulin G (IgG) and IgM, higher titers of ANA and anti-SSA antibodies and lower levels of C3 and C4; in contrast, the serum IL-17A level was only increased in patients with longer disease duration and showed little correlation with clinical and

laboratory features [71]. In PBC, IL-12/IL-23-mediated the Th1/Th17 signaling pathway is involved in PBC and correlates with disease severity [72]. Interestingly, it has been reported that the Th17 response may be present in an early phase of the disease, since changes in the expression profile of IL-17 and IL-23 are also present in patients with pre-clinical SS and non-autoimmune sicca syndrome [73].

Both SS and PBC are associated with altered B-cell function, as exemplified by the presence of serum autoantibodies and hyper-IgM levels [74–77]. Indeed, therapeutic B-cell depletion therapy may ameliorate both diseases and decrease antigen presentation by B cells, but current data are conflicting or inconclusive [78–82]. Substantial evidence supports the role of B-cell activating factor (BAFF) overexpression leading to changes in B-cell differentiation, and it could act as a potential biomarker of immune dysregulation in autoimmune diseases [75]. BAFF levels are elevated in both PBC and SS, especially if testing for anti-SSA/SSB is positive, and correlate with histopathologic findings and serum IgG levels [83]; however, this finding is not specific as BAFF is elevated in several autoimmune diseases [84]. The BAFF transgenic mouse, developed and investigated in 1999 for its phenotype of autoimmune-related conditions, develops a SS-like condition, showing infiltration in the salivary glands and loss of secretory function and has provided insight into the role of BAFF in prolonged B-cell activity in SS-like autoimmune exocrinopathy [21]. Regarding PBC, a significant correlation has also been reported between BAFF and cholestatic enzyme levels, AMA titers, and disease stage [85, 86]. Despite anti-SSA and AMA being highly specific for these two diseases, no direct pathogenic role has been demonstrated. Moreover, B-cell hyperactivity in SS has been associated with extraepithelial immune complex-mediated manifestations, such as vasculitis, purpura, glomerulonephritis and peripheral nephropathy and the development of lymphoma. The production of cryoglobulins and the deposition of immune complexes to the affected tissues represent the main mechanisms that drive the pathogenesis of the extraepithelial manifestations [87].

## CLINICAL MANIFESTATIONS

The epithelia targeted in SS include exocrine glands, i.e. lacrimal, salivary, sweat, mammary and digestive system glands, with the latter group including parts of the pancreas, liver and gallbladder. In PBC, the small intrahepatic bile ducts are mostly involved. However, in both conditions, systemic manifestations may occur with significant frequency. Most importantly, approximately one-third of PBC patients will manifest another autoimmune condition (i.e. thyroid disease, other systemic autoimmune rheumatic diseases), of which SS is among the most frequent, while almost 5% of patients with SS manifest biochemical and histologic features of PBC [87].

### Sjögren's Syndrome

Sjögren's syndrome can be coined an organ-specific disease, as the main clinical manifestations are oral and eye dryness which are present at the time of diagnosis, with systemic manifestations, such as vasculitis, that sometimes may precede the classical sicca symptoms. A significant percentage of patients with SS complain of systemic dryness involving the nose, trachea, vagina and skin, suggesting that other glands are also affected in the context of exocrine involvement [87]. Although glandular manifestations vary in severity and may affect the quality of life of patients with SS, these have not been associated with increased mortality and follow a rather stable clinical course for many years. Systemic extraglandular manifestations are present in 10–15% of patients with SS, and are the result of the typical lymphocytic infiltration around the epithelium of target organs, such as the liver, kidney and bronchi/bronchioles, or of the systemic form of the disease presenting with the clinical picture of vasculitis. In the kidney, the lymphocytic infiltration of the interstitium and involvement of tubular epithelium may lead to distal renal tubular acidosis, which manifests as hypokalemic hypochloremic metabolic acidosis with normal anion gap and nephrolithiasis/nephrocalcinosis [88]. Subclinical interstitial nephritis

is observed in 30% of patients with SS, but the rate of overt disease ranges between 5 and 10% [88]. The most common type of pulmonary involvement is lymphocytic bronchitis/bronchiolitis, which affects nearly 20% of patients and is characterized by dry irritant cough with an obstructive respiratory pattern at functional tests [87]. Extraglandular manifestations evolve slowly with favorable outcome, although in some cases, the ongoing pathologic process may lead to severe organ impairment and end-stage organ failure. Vasculitis manifests with palpable purpura of the lower extremities and occasionally leg ulcers in 10% of patients with SS. Peripheral neuropathy due to inflammation of the vasa vasorum affects 1% of patients with SS and usually manifests as sensorimotor axonal polyneuropathy and mononeuritis multiplex. In the kidney, immune complexes are deposited within the glomerulus to result in various clinical manifestations, such as nephritic or nephrotic syndrome [89]. The extraepithelial manifestations appear late during the natural history of SS and have been associated with increased morbidity and mortality, in contrast to PBC. Patients of this group have an increased risk of developing lymphoproliferative disorders, since palpable purpura and low C4 serum levels have been found to be predictors of lymphoma [87].

### Primary Biliary Cholangitis

Symptoms of PBC in the early phases are classically described as fatigue and pruritus and physical findings may include skin hyperpigmentation, hepatosplenomegaly and (rarely) xanthelasmas, while end-stage symptoms are those common to all types of liver cirrhosis, including ascites, jaundice, hepatic encephalopathy and upper digestive bleeding [90, 91]. Nonetheless, a more pragmatic approach is needed. Pruritus is becoming largely a symptom of minor importance in current clinical series and fatigue is a nonspecific symptom present in 70% of patients with PBC, particularly middle-aged women, that is often overlooked. The severity of fatigue is independent of the stage of PBC or its cholestatic



**Table 1** The 2016 American College of Rheumatology/European League Against Rheumatism Sjögren's syndrome classification criteria

Item	Weight/score
The classification of primary Sjögren's syndrome (SS) applies to any individual who meets the inclusion criteria <sup>a</sup> , does not have any of the conditions listed as exclusion criteria <sup>b</sup> and has a score of $\geq 4$ when the weights of the five criteria items below are summed	
Labial salivary gland with focal lymphocytic sialadenitis and focus score of $\geq 1$ foci/4 mm <sup>c</sup>	3
Anti-SSA/Ro-positive	3
Ocular staining score $\geq 5$ (or van Bijsterveld score $\geq 4$ ) in at least one eye <sup>d, e</sup>	1
Schirmer's test $\leq 5$ mm/5 min in at least one eye <sup>d</sup>	1
Unstimulated whole saliva flow rate $\leq 0.1$ mL/min <sup>d, f</sup>	1

<sup>a</sup> These inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following questions [1]: Have you had daily, persistent, troublesome dry eyes for more than 3 months [2]? Do you have a recurrent sensation of sand or gravel in the eyes [3]? Do you use tear substitutes more than three times a day [4]? Have you had a daily feeling of dry mouth for more than 3 months [5]? Do you frequently drink liquids to aid in swallowing dry food?—or in whom there is suspicion of SS from the European League Against Rheumatism Sjögren's syndrome Disease Activity Index questionnaire (at least one domain with a positive item)

<sup>b</sup> Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude the diagnosis of Sjögren's syndrome and participation in Sjögren's syndrome studies or therapeutic trials because of overlapping clinical features or interference with criteria tests [1]: history of head and neck radiation treatment [2], active hepatitis C infection (with confirmation by PCR) [3], acquired immunodeficiency syndrome, [4] sarcoidosis, [5] amyloidosis [6], graft-versus-host disease [7], immunoglobulin G4-related disease

<sup>c</sup> The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using the protocol described by Daniel et al. [134]

<sup>d</sup> Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness

<sup>e</sup> Ocular staining Score described by Whitcher et al. [135] and by the van Bijsterveld score described by van Bijsterveld [136]

<sup>f</sup> Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar [137]

features (pruritus), nor does it depend on psychiatric factors. Pruritus has a similar frequency as fatigue, being present in 70% of patients with PBC and jaundice. It may long precede jaundice onset and typically worsens at night, following contact with wool, or in warm climates. Portal hypertension is found in patients with PBC and, importantly, does not require the presence of liver cirrhosis as it can be pre-sinusoidal. Over one-half of untreated patients will develop portal hypertension over a 4-year period; the recommendations to diagnose and treat PBC-associated portal hypertension are not different from those for other chronic liver diseases.

Metabolic bone disease appears earlier in patients with PBC when compared to sex- and age-matched healthy individuals [92]. Hyperlipidemia is common in up to 85% of patients with PBC, and both serum cholesterol and triglyceride levels can be elevated. Interestingly, however, such alterations are not accompanied by an increased incidence of cardiovascular events or atherosclerosis and do not correlate with disease stage. Similar to other types of cirrhosis, end-stage PBC can be complicated by the occurrence of hepatocellular carcinoma, and patients with intense nodular liver structure at ultrasound should be monitored by computed tomography [2, 93, 94]. There is no

**Table 2** Commonly described autoantibodies in Sjögren's syndrome

Autoantibody	Prevalence (%)	Properties	Clinical association
Anti-Ro/SSA	50–70	Disease marker	Younger age at diagnosis Severe and extraglandular disease Pathogenic in congenital heart block
Anti-La/SSB	25–40	Disease marker	Extraglandular disease Pathogenic in congenital heart block
Rheumatoid factor	36–74	Phenotype marker	Extraglandular disease
Anti-CCP	3–10	Phenotype marker	Arthritis
Antimitochondrial antibodies	3–10	Phenotype marker	Elevated liver enzymes
Anticentromere antibodies	3–27	Phenotype marker	Raynaud's phenomenon

SSA/SSB Sjögren's-syndrome-related antigen A/B, CCP cyclic citrullinated peptide

increased frequency of lymphoproliferative diseases in PBC patients.

## DIAGNOSIS AND CLASSIFICATION CRITERIA

The diagnosis of SS and PBC has to take into account several features of the diseases, and histology remains crucial, especially when testing for serum autoantibodies is negative. To assist the clinician in the diagnosis and, more importantly, to harmonize patients enrolled in clinical trials, criteria need to be followed for both conditions [95].

### Sjögren's Syndrome

The American College of Rheumatology (ACR) and European League Against Rheumatism

(EULAR) developed their first SS classification criteria in 2016 (Table 1). The sensitivity and specificity of these criteria for clinician-expert-derived case/non-case status in the final validation cohort were high, i.e. 96% [95% confidence interval (CI) 92–98%] and 95% (95% CI 92–97%), respectively [96]. Serum autoantibodies are a crucial tool for the diagnosis of SS and may be present years before the manifestation of connective tissue diseases [97], similar to other connective tissue diseases. The most frequently detected autoantibodies in SS are ANA, anti-Ro/SSA, anti-La/SSB, rheumatoid factor (RF) and anti-U1RNP (Table 2). Anti-Ro/SSA and anti-La/SSB are considered to be hallmarks of the disease and are associated with systemic disease, but they are also present in the sera of patients with systemic lupus erythematosus. The Ro/La particle is a protein–RNA complex formed by the association of the Ro60, and La/SSB proteins with small cytoplasmic RNA (hyRNA). Various methods

**Table 3** Diagnostic criteria for primary biliary cholangitis

Parameters
Elevated alkaline phosphatase level of $>2 \times$ ULN or elevated $\gamma$ -glutamyltransferase level of $>5 \times$ ULN
Positivity for antimitochondrial antibodies
Chronic granulomatous cholangitis at liver biopsy

Diagnosis is defined by the presence of at least 2 of the 3 criteria [138]

ULN Upper limit of normal

have been used to detect anti-Ro/SSA and anti-La/SSB antibodies, and while RNA precipitation is considered to be the gold standard method, other techniques, such as counter-immunoelectrophoresis, immunodiffusion and enzyme linked immunosorbent assay are more frequently used. Anti-Ro/SSA and anti-La/SSB antibodies are detected in 50–70% of patients with SS, depending on the method applied. While anti-Ro/SSA is usually independent of anti-La/SSB antibody, the contrary is rare [98]. Of note, anti-La/SSB antibodies, along with ANA and RF, have been removed from the classification criteria, and some authors suggest that this may mean that the guidelines are not adequate for extraglandular disease, necessitating the definition of “seronegative” SS [99]. Other autoantibodies are associated with different autoimmune diseases, but they may identify patients with SS with unique clinical features. Histology is the gold standard for SS diagnosis and is necessary in patients who test negative for anti-Ro/SSA and anti-La/SSB antibodies. There is growing evidence to suggest that histology should be performed in all SS patients (even those who otherwise fulfil the criteria), as it provides additional prognostic information with respect to the future development of severe systemic involvement and lymphoma [100]. Salivary gland biopsy is most easily performed by labial biopsy of the minor salivary glands, which is a simple procedure that can be performed under local anesthesia by a dentist/otolaryngologist trained in the appropriate collection procedure, with the collection of five to ten minor salivary glands by blunt dissection via an incision through normal-appearing mucosa [101].

Functional tests are of great help when there is a suspicion of sicca syndrome. The Schirmer test for dry eyes is easily performed in an outpatient environment. Normal tear production usually results in wetting of  $\geq 15$  mm of the strip over a 5-min period, with  $\leq 5$  mm considered to be positive (abnormal). Moreover, evaluation of the ocular surface is most frequently performed by an ophthalmologist, fluorescein is used to determine the integrity of the corneal epithelium, with rose bengal or lissamine green used for evaluating the integrity of the conjunctiva. Both dyes stain the same features of the ocular

surface, including mucus strands, filaments and areas of epithelium unprotected by normal mucin components of the glycocalyx [102].

### Primary Biliary Cholangitis

The diagnosis of PBC is based on the presence of two out of three internationally accepted criteria, i.e., detectable serum AMA (titer  $>1:40$ ), increased enzyme levels indicating cholestasis [i.e. alkaline phosphatase (ALP)] for  $>6$  months and a compatible or diagnostic liver histology (Table 3). In a large number of cases (20–60%), the diagnosis of PBC is established in the absence of symptoms indicating a liver condition or cholestasis, and the proportion of asymptomatic cases at diagnosis has been increasing in recent years. At presentation, PBC is suspected if a biochemical cholestatic pattern (increased plasma ALP or  $\gamma$ -glutamyltransferase) is present, with no similar increase in plasma aminotransferase levels. Serum IgM levels are typically elevated in PBC patients, with no correlation with AMA titers or levels of other immunoglobulin subtypes. Once cirrhosis has developed, biochemical alterations are similar to those seen in other types of cirrhosis.

Serum AMA are highly specific for PBC and can be detected in nearly 100% of patients when sensitive diagnostic methodologies based on recombinant antigens are used. In most clinical settings, however, indirect immunofluorescence techniques are used for initial screening of the cases and these may provide falsely positive or negative results [103–106]. AMA are directed against components of the 2-oxoacid dehydrogenase family of enzymes within the mitochondrial respiratory chain, most frequently the E2- and E3-binding protein components of the pyruvate dehydrogenase complex and the E2 components of the 2-oxo glutarate dehydrogenase and branched-chain 2-oxo acid dehydrogenase complexes. In all three antigens, epitopes contain the DKA motif, with lipoic acid covalently bound to the lysine (K) residue [107]. The pathogenic role of AMA is highly likely, despite the apparent absence of a clinical correlation and the observation that animal models developing serum AMA do not



develop PBC-like liver lesions [108]. Autoantibodies other than AMA can be found in 76% of PBC patients [109–111]. ANA can be found in 50% of PBC patients, with the most common patterns being “nuclear rim” or “multiple nuclear dots.” ANA-positive patients are more frequently AMA-negative, possibly due to the lack of a masking effect of these latter antibodies in such sera. The pathogenic role of ANA in PBC remains enigmatic, although cross-sectional and longitudinal data demonstrate an association between ANA positivity and a worse prognosis [112].

Histology remains the gold standard for PBC diagnosis and staging. The typical PBC histological lesions can be classified in four stages. Stage I manifests with portal tract inflammation with predominantly lymphoplasmacytic infiltrates, resulting in vanishing septal and inter-lobular bile ducts (diameter <100 µm). At this stage, bile duct obliteration and granulomas (possibly found at all stages) are strongly suggestive of PBC. In stage II, a periportal inflammatory infiltrate is observed, and signs of cholangitis, granulomas, and florid proliferation of ductules are typical. Septal or bridging fibrosis is present in stage III, with ductopenia (over half of the visible inter-lobular bile ducts having vanished) and copper deposition in periportal and paraseptal hepatocytes observed. Stage IV corresponds to frank cirrhosis and cannot be discriminated from cirrhosis of other etiologies [113]. The observation of eosinophils in the portal tract is a specific finding in PBC histology.

## CURRENT AND FUTURE THERAPEUTIC OPTIONS

The treatment of SS and PBC, similar to that of other autoimmune diseases, has dramatically changed in recent years as a result of the development of new targeted drugs.

### Sjögren’s Syndrome

The treatment of SS ranges from topic agents aimed to alleviate sicca syndrome, secretagogue agents and immunosuppressants. Dry eyes and

mouth remain the features which most impair the quality of life and limit activity most in patients with SS, and patient education is critical to successful management. In fact, patients with mild, episodic dry eye can be managed with modification of their environment, i.e. avoiding dry or windy environments, and activities of daily living.

### Topical Treatments

The first line of therapy for dry eye in SS are “artificial tears”, of which the main ingredients are lubricants with a polymeric base or viscosity agent. Topical cyclosporine 0.05% has been used to treat dry eye disease. Although the mechanism of action was initially thought to be primarily mediated by inhibition of activation of T-lymphocytes, further study has confirmed that it has multiple inhibitory properties, including the ability to inhibit apoptosis in other cell types. The recommended therapy is topical application of one drop of cyclosporine in each eye twice daily [102]. With regard to dry mouth, salivary substitutes are currently available for the amelioration of xerostomia; however, a Cochrane review found no strong evidence that any topical therapy is effective for either relieving the symptom of dry mouth or preventing caries [114].

### Secretagogues

The secretagogue oral pilocarpine, a muscarinic receptor agonist, has been shown to be effective in reducing symptoms and objective findings of dry eye and mouth [115]; however, it can cause uncomfortable side effects, such as nausea, flushing, sweating, and urinary frequency, and should be used with caution in patients with cardiac disease or asthma because of the risks of bradycardia and bronchospasm. To avoid these effects, pilocarpine should be started at low dose, i.e. 5 mg, and titrated upward as needed and tolerated, to a maximum of 30 mg daily in three or four divided doses [102].

### Immunosuppressants

The treatment of SS with disease-modifying agents is mainly empirical, and evidence-based recommendations for the treatment of

systemic disease manifestations are lacking. No therapy has been shown to significantly affect disease course. Hydroxychloroquine (HCQ) is useful for the treatment of extraglandular manifestations; however, a recent randomized clinical trial showed that HCQ was no better than placebo in improving dryness, pain and fatigue in a cohort of 120 patients with SS during 24 weeks of treatment [116]. Methotrexate is frequently used to treat inflammatory arthritis, with little evidence to support its use in SS [117]. Biologics targeting TNF $\alpha$  have failed to achieve primary outcomes in SS, while rituximab, an anti-CD-20 B-cell-depleting therapy, had shown promising results in reducing systemic disease manifestations, including parotid swelling and pulmonary and articular involvement [78, 79, 118, 119] in selected cases. However, the authors of a recent randomized clinical trial has concluded that rituximab treatment in SS is neither clinically nor cost-effective [120]. The BAFF/BLyS antagonist belimumab, currently approved for systemic lupus erythematosus, has been evaluated in SS, and recent data suggest that long-term use is effective in reducing disease activity, while the salivary flow, Schirmer test and the focus score of salivary biopsy did not change [121]. Abatacept, an anti-CTLA4 biologic agent currently approved for the treatment of rheumatoid arthritis, has also been evaluated in patients with SS; the main findings of these studies show that this agent could also be effective for treating SS features [122, 123].

### Primary Biliary Cholangitis

Current treatments for PBC are currently based on UDCA, which is the only approved drug for this rare disease. To date, however, the mechanism of action of UDCA is incompletely understood, although depending on the various phases of the disease, different therapies may be effective [124–128].

During the early (pre-cirrhotic) phases of the disease, short-term treatment with glucocorticoids might be effective, although there are concerns about the safety of long-term use of

such medications. Budesonide, due to its high first-pass metabolism, has minimum systemic adverse effects, and, at 6–9 mg daily has been demonstrated to be superior to UDCA both in terms of histology and biochemical markers. Other immunosuppressants, such as methotrexate and azathioprine, have also been suggested, and there is evidence supporting the use of the latter in PBC patients with autoimmune hepatitis overlap syndrome. In recent years mainly thanks to the better understanding of PBC pathogenesis, new targeted therapies have been tested, especially against the IL-17/-23 axis with ustekinumab, a monoclonal antibody against the p40 subunit. However, albeit being associated with a modest decrease in ALP after 28 weeks of therapy, it did not lead to otherwise major changes in ALP [129]. Other therapies targeting T cells, specifically through CTLA-4 with abatacept and with a CD40-antagonist (FFP104), are under investigation [130–132].

When the disease has already progressed and bile is accumulated, obeticholic acid (OCA), an analog of chenodeoxycholic acid, a bile acid with a higher affinity to the Farnesoid X receptor, has been shown in a recent Phase III trial to decrease bile synthesis, promote secretion and induce liver regeneration in animal models [133]. In that same trial, OCA administered with UDCA or as monotherapy for 12 months resulted in decreases from baseline in ALP and total bilirubin levels that differed significantly from the changes observed with placebo [133].

Ultimately, UDCA remains the cornerstone therapy of PBC, and dosages ranging from 13 to 15 mg/kg are currently used and lead to optimum bile enrichment, with 50% of patients achieving normalized ALP levels. Other immunosuppressive treatments should be started only in combination with UDCA.

Liver transplantation is the ultimate treatment for patients with end-stage PBC, with survival rates of 92 and 85% at 1 and 5 years after transplant, respectively. Recurrence is common, with recurrence rates seemingly influenced by certain immunosuppressive regimens. The use of UDCA for recurrence is safe and recommended.

## CONCLUSIONS

More data are now supporting the thesis that SS and PBC are both immune-mediated epithelitis with similar pathogenetic mechanisms. While we are currently witness to a major converging of the management options for these conditions between rheumatologists and hepatologists, which ameliorates the therapeutic choices, there remain several unmet needs, including better treatment tailoring, earlier diagnosis and the possibility to provide shared treatments which may tackle both conditions. We may surmise that the newly available large-scale technological platforms for biomarker discovery or single cell analysis should be applied to PBC and SS to determine which degree of similarity is indeed relevant for the physician in 2017.

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