Primary Sjögren’s syndrome: new clinical and therapeutic concepts

M Ramos-Casals, A G Tzioufas, J Font

Sjögren’s syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary SS. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy) to a systemic process with diverse extraglandular manifestations. An increasing number of SS related publications in the past 5 years have contributed to a better understanding of the systemic involvement and the outcome of the disease. Advances in the treatment of sicca and extraglandular features are especially noteworthy. This review summarises recent work focused on extending and characterising the extraglandular involvement of primary SS and evaluating new therapeutic approaches.

CUTANEOUS INVOLVEMENT
Cutaneous features are considered one of the most characteristic extraglandular manifestations of primary SS. A recent study has described a wide spectrum of cutaneous lesions in patients with primary SS, with vasculitis being detected in 10% of patients. The main characteristic of SS associated cutaneous vasculitis in that study was the overwhelming predominance of small (leucocytoclastic) versus medium vessel vasculitis, with life threatening vasculitis being closely related to cryoglobulinaemia. Other authors have demonstrated the association of cutaneous purpura with lymphoma development and mortality. Taken together, these studies show the clinical significance of cutaneous vasculitis in the prognosis and outcome of patients with primary SS.

“Cutaneous vasculitis is significant in the prognosis and outcome of patients with primary SS”

Patients with primary SS may also present a wide range of non-vasculitic lesions. One of the most characteristic are polycyclic, photosensitive cutaneous lesions, previously reported in Asian patients with primary SS (annular erythema) and recently described in white patients. These lesions are clinically identical to those seen in patients with subacute cutaneous lupus erythematosus, suggesting a common cutaneous disease (closely related to anti-Ro/SSA antibodies) in patients with either primary SS or systemic lupus erythematosus (SLE). Table 1 summarises other cutaneous processes which have been described in patients with primary SS.

PULMONARY INVOLVEMENT
Various studies have recently described the predominance of bronchial/bronchiolar involvement rather than interstitial disease. Franquet et al described bronchiolar abnormalities in one third of their patients, with a higher frequency of air trapping in lower lobes. Pappiris et al described small airway disease as the main functional disorder, and Taouli et al found that large and/or small airway disease was the predominant computed tomography scan pattern in more than 50% of their patients. The results of pulmonary functional tests often correlated with the computed tomography scan pattern, although no correlation was found in some cases, suggesting the need to combine both diagnostic procedures in patients with suspected pulmonary disease. Subsequent diagnostic procedures may include bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. The natural history of pulmonary involvement in primary SS was demonstrated by Davidson et al, who found that although lung disease usually occurred early in the course of SS (predominantly in Ro+ patients), most of these patients

Abbreviations: ANA, antinuclear antibodies; CNS, central nervous system; ESR, erythrocyte sedimentation rate; GMN, glomerulonephritis; IFNα, interferon α; PSN, pure sensory neuropathy; RA, rheumatoid arthritis; RP, Raynaud’s phenomenon; SHL, sensorineural hearing loss; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; SSC, systemic sclerosis; TIN, tubulointerstitial nephritis

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Raynaud’s phenomenon (RP) is probably the most common vascular feature seen in primary SS, with a prevalence of 13%. The clinical significance of RP in patients with primary SS is twofold. On the one hand, RP may be the first feature seen in some patients, suggesting a diagnosis of primary SS. On the other hand, RP may identify a specific subset of patients having positive immunological markers suggestive of systemic sclerosis (SSc).

“Raynaud’s phenomenon is often the first feature seen in SS but may also suggest the presence of limited SSc.”

In this latter group, a specific search for anticentromere antibodies should be performed, especially when high titres of antinuclear antibodies (ANA) with negative anti-Ro/La antibodies are present. This clinic-immunological subset of patients with SS, RP, and anticentromere antibodies need a closer follow up, paying special attention to the development of an associated limited form of SSc. These patients should be considered as having SS associated with SSc rather than SS “secondary” to SSc, as Manoussakis et al have suggested for the case of coexisting SS and SLE.

### VASCULAR INVOLVEMENT

Although previous studies described glomerulonephritis (GMN) in a substantial percentage of patients with primary SS and renal disease, the frequency of bronchial/bronchiolar disease in patients with primary SS did not develop a progressive pulmonary disease. Clinically, the frequency of bronchial/bronchiolar disease in patients with primary SS with pulmonary involvement shown by several studies, and the slow progression and insidious clinical course often seen in these patients, should be borne in mind.

### NEUROLOGICAL INVOLVEMENT

Although earlier studies described central nervous system (CNS) involvement as a common extraglantular manifestation of primary SS, symptomatic CNS involvement is rarely found in large published series. Evaluation of the clinical significance of CNS features in patients with primary SS is difficult owing, on the one hand, to the broad spectrum of both CNS and psychiatric processes that may be seen and, on the other hand, to the possible epidemiological overlap between SS and various CNS processes often observed in older patients, such as cerebrovascular disease, Alzheimer’s disease, or multi-infarct dementia. An illustrative example is the clinical significance of the white matter lesions detected in asymptomatic, older patients with primary SS. These lesions are often seen in control groups matched for age and sex and are also known to increase with age. Various studies have described other CNS processes in patients with primary SS, including cerebral amyloid angiopathy, multiple sclerosis-like disease, and myelopathy.

### RENAL INVOLVEMENT

Although renal disease in patients with primary SS has usually been considered as predominantly tubular, several studies have described glomerulonephritis (GMN) in a substantial percentage of patients with primary SS and renal disease. Of the 27 patients with SS and documented renal biopsy, 15 patients showed tubulointerstitial nephritis (TIN), 11 GMN, and one had both entities. In these patients, the most common glomerular diseases were membranoproliferative GMN in seven patients, mesangial proliferative GMN in six, and membrane GMN in two. Cryoglobulinaemia was detected in half of the patients and only two finally developed chronic renal failure requiring haemodialysis. These two types of SS related renal disease (tubular and glomerular) have important pathogenic, clinical, and prognostic implications. TIN is considered to be a specific tubular epithelitis that is usually found in younger patients, and is characterised by an indolent subclinical course without development of renal failure. In contrast, GMN should be considered a severe extraepithelial manifestation closely associated with cryoglobulinaemia and hypocomplementaemia, appearing late in the course of primary SS and associated with higher morbidity and mortality.

A renal biopsy is probably unnecessary in patients with a suspected TIN, while those with GMN require early diagnosis and therapeutic management.
chronic evolution (73%). Clinically, PSN usually responds poorly to treatment with corticosteroids or immunosuppressive agents, although stabilisation of symptomatology (spontaneously or after treatment) during very long periods is often seen.40

**AUTONOMIC NEUROPATHY**

Several studies have described autonomic disturbances in patients with primary SS, including interstitial cystitis-like symptoms49 50 and autonomic cardiovascular abnormalities.31–34 Andonopoulos et al reported a higher prevalence of autonomic neuropathy in a small series of patients with primary SS, with abnormal responses to cardiovascular tests in 69% and severe autonomic cardiovascular neuropathy in 87.5% of patients, but in none of the healthy controls.51 In another study, patients with primary SS showed signs of both sympathetic and parasympathetic dysfunction, especially those with anti-Ro/SSA and anti-La/SSB antibodies, and had an abnormal blood pressure reaction to tilt compared with controls.52 However, two recent studies have found contrasting results,53 54 The small number of patients tested for autonomic disturbances in these studies and the wide variability inherent in autonomic tests does not allow definitive conclusions to be drawn.

**MUSCULAR INVOLVEMENT**

Two studies have analysed the prevalence and clinical significance of muscular involvement in patients with primary SS, with a predominance of subclinical myositis55 rather than other types of myopathies such as inclusion body myositis.56 Lindvall et al described myalgias in nearly 30% of patients with primary SS, although the causes were diverse, including both non-inflammatory (mainly fibromyalgia) and inflammatory (mainly myositis) processes.57 A muscle biopsy was performed in 36 patients, with muscle inflammation being detected in 26 (72%) biopsies. No correlation was found between histological and clinical myositis. This study suggests that subclinical muscle inflammation is often seen in patients with primary SS and that, in nearly 50% of cases, histological evidence of myositis may be detected in asymptomatic patients.

**SENSORINEURAL HEARING LOSS**

Since 1997, several studies have evaluated hearing loss in primary SS, describing sensorineural hearing loss (SHL) in 38/140 (27%) patients studied37–40 (table 4). Some of these studies suggested an association with immunological variables such as antiphospholipid antibodies,57 ANA, Ro or La.57 59 Boki et al found that primary SS is associated with SHL, affecting preferentially the high frequencies,59 although clinically significant defects are not common. No specific recommendations have been made on the clinical management of SHL related SS, although a similar approach to that applied in other autoimmune SHL is suggested.60

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<th>Table 4 Sensorineural hearing loss in patients with primary SS: prevalence and immunological markers</th>
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<td>Tumiati et al37</td>
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<td>Ziarra et al38</td>
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<td>Boki et al39</td>
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<td>Hatzopoulos et al40</td>
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<td><strong>Total</strong></td>
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Results are shown as No (%).

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<th>Table 5 Haematological abnormalities in patients with primary SS: recent studies</th>
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<td><strong>Chronic agranulocytosis</strong></td>
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<td><strong>Platelet count</strong></td>
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<td><strong>Other abnormalities</strong></td>
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<td><strong>Hypergamma globulinaemia</strong></td>
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<td><strong>Antiphospholipid antibodies</strong></td>
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**HAEMATOLOGICAL ABNORMALITIES**

Various studies have emphasised the prevalence and significance of haematological manifestations in patients with primary SS.52–57 (table 5). In a series of 400 patients,64 the most common haematological features were cytopenia (33%), raised erythrocyte sedimentation rate (ESR; 22%), and hypergammaglobulinaemia (22%). Although usually asymptomatic, some of these haematological features, such as Coombs’s positive haemolytic anaemia, agranulocytosis,11 40 and thrombocytopenia,64 may present symptoms. Owing to the high prevalence of haematological features in patients with primary SS and the close relationship with the main immunological SS features,65 their possible inclusion in a future revision of the current diagnostic criteria, as has happened in SLE, should be considered.

**LYMPHOMA**

Lymphoma is traditionally considered as the main complication in the natural history of SS, although cross sectional studies have reported that only 98/2311 (4%) patients with primary SS developed lymphoma.62 Only one study has prospectively analysed the incidence of lymphoma, which was found in 7/103 (7%) patients with primary SS followed up over 5 years,68 while Ioannidis et al recorded 38 diagnoses of lymphoma during 4384 person-years of follow up. The main clinical characteristics of B cell lymphoma in primary SS have been well described in a recent multicentre European study including 33 patients followed up at nine centres.69 Lymphadenopathy, skin vasculitis, peripheral nerve involvement, fever, anaemia, and lymphopenia were observed significantly more often than in the general SS population.
B cell lymphoma was primarily located in the marginal zone (49%), with a predominantly extranodal involvement (79%), mainly in the salivary glands (55%). Patients with lymphoma had a significantly worse survival rate, with high to intermediate grade lymphoma, B symptoms (fever, night sweats, and weight loss), and a large tumour diameter (>7 cm) being independent risk factors for death.70

**EVOLUTION AND OUTCOME**

The past 5 years have led to much greater knowledge of the outcome of patients with primary SS. Although not a benign condition, primary SS usually progresses very slowly, with no rapid deterioration in salivary function or dramatic changes in symptoms.26 The exceptions to this benign course are the high incidence of lymphoma and the development of extraglandular manifestations, of which two types are found with a differential prognostic significance. A more stable, chronic SS course is usually found in patients with predominantly periepithelial lesions (such as interstitial nephritis, liver or lung disease), while those with predominantly extraepithelial expression (GMN, polyneuropathy, purpura, and vasculitis) present higher morbidity and mortality.72,73 Cryoglobulinaemia probably has a central aetio-pathogenic role in this latter group of patients, contributing to the development of the main extraepithelial manifestations. These features are associated with the highest risk of developing life threatening situations,7 with these patients requiring high doses of corticosteroids and immunosuppressive agents and closer monitoring. In contrast, corticosteroids/immunosuppressive agents can be used less frequently in patients with periepithelial lesions, and visits may be scheduled every 6–12 months.

**NEW THERAPEUTIC AGENTS**

At present, no treatment can modify the evolution of SS. The effects of local treatments such as artificial tears or oral sprays are limited, whereas systemic treatment offers the advantage of dealing with a wider range of symptoms.77 New therapeutic approaches include muscarinic agonists and biological agents (table 6).

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<th><strong>Table 6 New therapeutic agents for the treatment of patients with primary SS</strong></th>
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<tr>
<td><strong>Dose</strong></td>
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<td><strong>Muscarinic agents</strong></td>
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<td>Pilocarpine</td>
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<td>Cevimeline</td>
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<td><strong>Biological agents</strong></td>
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<td>Etanercept</td>
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<td>Octreotide</td>
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<td>2-Chloro-2’-deoxyadenosine</td>
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“**Muscarinic agonists and biological agents are new treatments, respectively, for the sicca symptoms and extraglandular features of SS**”

**Muscarinic agonists**

Two muscarinic agonists (pilocarpine and cevimeline) have recently been approved for the treatment of the sicca symptoms of SS. These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function. Clinical studies with pilocarpine (Salagen) tablets in the United States have demonstrated significant subjective and objective benefit for xerostomia and related oral symptoms at doses of 20 mg/day or more.77 Vivino et al reported that administration of 5 mg pilocarpine tablets four times daily (20 mg/day) was well tolerated and produced significant improvement in sicca symptoms, including dry mouth, dry eyes, and other sicca features.81
Recently, Tsifetaki et al published a 12 week randomised study in which 29 patients with SS were treated with a lower dose of oral pilocarpine (10 mg/day). Compared with controls, patients receiving pilocarpine showed a significant subjective improvement of dry eyes, with an improvement in the rose bengal test results. No patient discontinued the study because of side effects.

Two recent studies have analysed the use of cevimeline hydrochloride, a cholinergic agent with muscarinic agonist activity prominently affecting the M1 and M3 receptors prevalent in exocrine glands. Fife et al, in a double blind, randomised, placebo controlled trial in the United States, reported that treatment with cevimeline, 30 mg three times daily, was well tolerated and provided substantial relief of xerostomia symptoms, while Petrone et al reported improvement of saliva and tear flow rates, and improvement of subjective sicca symptoms.

Further controlled studies of these muscarinic agonists at different doses are needed in patients with SS, including an individual evaluation of elderly patients or those with comorbid processes, such as cardiovascular, pulmonary, or hepatic diseases.

**Biological agents**

Recent studies have analysed the role of biological agents for the treatment of primary SS. In a single centre, open label pilot study, Steinfeld et al found an improvement in clinical and functional measures in 16 patients with primary SS treated with three infusions of infliximab (3 mg/kg) at 0, 2, and 6 weeks. In a 1 year follow up study including 10 of these 16 patients, the same authors found a significant decrease in global and local disease manifestations in all 10 patients. Although treatment was generally well tolerated, the main side effect was a mild, self limiting infusion reaction in four (40%) patients (one of them presenting with generalised rash, fever, and arthralgia), while two (20%) developed infectious processes (enteritis and tonsillitis). In addition, the main improvement was only observed in subjective symptomatology, with no changes in the ESR or IgG levels. Martin Martin et al reported improved salivary secretion in four patients with RA and associated SS treated with infliximab, while Caroyer et al recently reported the successful treatment of a patient with severe sensory neuropathy with infliximab. However, the results of a multicentre randomised, double blind study of infliximab versus placebo, involving 103 patients with primary SS, clearly showed a lack of efficiency of infliximab in primary SS.

Recent studies have analysed the role of biological agents for the treatment of primary SS. Three studies have analysed the safety and efficacy of interferon α (IFNα) in primary SS. Chip et al reported improved salivary output and reduced xerostomia, with no significant adverse medical events, while Shiozawa et al reported increased salivary production accompanied by decreased lymphocytic infiltration. Recently, Cummins et al presented the results of a combined phase III study of 497 patients with primary SS receiving 150 IU of human IFNα versus placebo three times daily by the oromucosal route, with improvement of seven of eight sicca symptoms, although no significant increment of the stimulated whole salivary flow was seen.

A promising treatment for primary SS is rituximab (anti-CD20). CD-20 is considered to be a specific marker for B cells, highly expressed on the surface of pre-B lymphocytes and both residing and activated mature B cells, but not expressed in other cells. In late 1997, rituximab became the first therapeutic monoclonal agent approved by the FDA for the treatment of B cell lymphoma, and it has been used to treat patients with non-neoplastic autoimmune disorders, such as autoimmune thrombocytopenia, SLE, RA, haemolytic anaemia, and mixed cryoglobulinaemia. In primary SS, recent reports suggested a role for the treatment of associated lymphoma. The specific target of rituximab (B cells) might suggest a role in modifying the aetiopathogenic events of patients with primary SS, a disease specifically characterised by B cell hyperactivity.

**Other treatments**

The role of corticosteroids and antimalarial drugs in the treatment of SS is being re-evaluated. Zandbelt et al described a patient with SS who underwent salivary gland biopsies before and after treatment with high doses of corticosteroids, and demonstrated an improvement in the main clinical, histological, and immunohistological features after treatment. Miyawaki et al treated 20 patients with prednisolone, with a significant decrease in serum IgG, anti-Ro/SSA, anti-La/SSB antibodies, and rheumatoid factor levels and partial decreases of IgA and IgM levels. In an experimental study Izumi et al found that local corticosteroid irrigation significantly increased the salivary flow rate in patients with SS. However, Tishler et al found a significant reduction of SS salivary inflammatory markers in patients treated with 200 mg/day hydroxychloroquine, which has previously been shown to be effective for treating SS related arthralgias, myalgias, and asthenia. Finally, several studies performed in small series of patients have analysed the efficacy of other therapeutic agents, including 2-chloro-2'-deoxyadenosine, octreotide, AZT, or azathioprine.
CONCLUSION
The increasing amount of published information on primary SS has contributed to a better understanding of the extraglandular expression of the disease and has changed the therapeutic management of these patients. A wide spectrum of extraglandular features has been studied in the past 5 years (table 7), and understanding of the involvement of some organs and systems has been expanded. Substantially more information on the outcome of patients with primary SS is now available, which indicates that patients with a predominantly extraorbital involvement (often associated with cryoglobulinaemia) should be monitored and managed differently from patients with a predominant ocular or uveitis+signa+systemic+features. Long-term management of patients with primary SS in coming years will be based on mucocutaneous antigens for sicca features and a key role for immunosuppressive/biological agents in the treatment of extraglandular features.

References
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