PRIMARY SJÖGREN’S SYNDROME New clinical and therapeutic concepts
Manuel Ramos-Casals, Athanasios G Tzioufas, and Josep Font

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PRIMARY SJÖGREN’S SYNDROME

New clinical and therapeutic concepts

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ABSTRACT

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. The spectrum of the disease extends from an organ specific autoimmune disease (autoimmune exocrinopathy) to a systemic process. Recent studies are focused on extending and characterizing the extraglandular expression of primary SS. Although sicca features can be considered the central clinical manifestations of the disease, recent studies have confirmed that primary SS has undeniably a systemic expression, including a large variety of extraglandular manifestations. There is now substantially more data on the outcome of patients with primary SS, which indicates that patients with a predominantly extraepithelial expression (often associated with cryoglobulinemia) should be monitored and managed differently from patients with a predominantly periepithelial or sicca-limited disease. The therapeutic management of patients with primary SS in coming years will be based on muscarinic agonists for sicca features and a key role for immunosuppressive/biological agents in the treatment of extraglandular features.
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 (1). 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) (2) to a systemic process with diverse extraglandular manifestations (3). The increasing amount of SS-related publications in the last five years has 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 will summarize recent work focused on extending and characterizing the extraglandular involvement of primary SS and evaluating new therapeutic approaches.

1. 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 (4). The main characteristics of SS-associated cutaneous vasculitis were the overwhelming predominance of small (leukocytoclastic) versus medium vessel vasculitis, with life-threatening vasculitis being closely related to cryoglobulinemia. Other authors have demonstrated the association of cutaneous purpura with lymphoma development and mortality (5,6). Taken together, these studies show the clinical significance of cutaneous vasculitis in the prognosis and outcome of patients with primary SS.
Patients with primary SS may also present a wide range of non-vasculitic lesions (4). One of the most characteristic are polycyclic, photosensitive cutaneous lesions, previously reported in Asian patients with primary SS (annular erythema) and recently described in Caucasian patients with primary SS (4,7,8). These lesions are clinically identical to those observed in patients with subacute cutaneous lupus erythematosus, suggesting a common cutaneous disease (closely related to anti-Ro/SS-A antibodies) in patients with either primary SS or SLE. Other cutaneous processes described in patients with primary SS are summarized in Table 1 (7-15).

2. Pulmonary involvement

Various studies have recently described the predominance of bronchial/bronchiolar involvement rather than interstitial disease (16,17). Franquet et al (18) described bronchiolar abnormalities in one third of their patients, with a higher frequency of air trapping in lower lobes and Papiris et al (19) described small airway disease as the main functional disorder, while Taouli et al (20) found large/and or small airway disease as the predominant CT scan pattern in more than 50% of their patients. The results of pulmonary functional tests (PFT) often correlated with the CT scan pattern, although no correlation was found in some cases (21), suggesting the need to combine both diagnostic procedures in patients with suspected pulmonary involvement. Subsequent diagnostic procedures may include bronchoscopy with BAL and transbronquial biopsy (19,22). With respect to the natural history of pulmonary involvement in primary SS, Davidson et al (23) found that although lung disease usually occurred early in the course of SS (predominantly in Ro+ patients), most of these patients did not develop a progressive pulmonary disease. Clinically, the frequency of bronchial/bronchiolar disease in SS patients with pulmonary involvement revealed by several studies and the
slow progression and insidious clinical course often observed in these patients, should
be borne in mind.

3. Vascular involvement
Raynaud’s phenomenon (RP) is probably the most frequent vascular feature observed in
primary SS, with a prevalence of 13% (24). The clinical significance of RP in patients
with primary SS is two-fold. On the one hand, RP may be the first feature observed 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. In this latter group, a specific search for anticentromere antibodies
(ACA) should be performed, especially when high titers of ANA with negative
antiRo/La antibodies are present (24-26). This clinico-immunological subset of patients
with SS, RP and ACA need a closer follow-up, paying special attention to the
development of an associated limited form of systemic sclerosis (SSc). These patients
should be considered as having SS associated with SSc rather than SS “secondary” to
SSc, as Moutsopoulos et al (26) have suggested for the case of coexisting SS and SLE.

4. Renal involvement
Although renal involvement in patients with primary SS has usually been considered as
predominantly tubular, several studies have described glomerulonephritis in a
substantial percentage of patients with primary SS and renal disease (27-30) (Table 2).
Of the 27 SS patients with documented renal biopsy, 15 patients showed tubulo-
interstitial nephritis (TIN), 11 glomerulonephritis (GMN) and one had both entities. In
these patients (29,30), the most frequent glomerular diseases were
membranoproliferative GMN in 7 patients, mesangial proliferative GMN in 6 and
membranous GMN in two. Cryoglobulinemia was detected in half of patients and only two finally developed chronic renal failure requiring hemodialysis. These two types of SS-related renal disease (tubular and glomerular) have important pathogenic, clinical and prognostic implications. TIN is considered a specific tubular epithelitis that is usually found in younger patients, and is characterized by an indolent subclinical course without development of renal failure. In contrast, glomerulonephritis should be considered a severe extraepithelial manifestation closely associated with cryoglobulinemia and hypocomplementemia, appearing late in the course of primary SS and associated with higher morbidity and mortality (30). A renal biopsy is probably unnecessary in patients with a suspected TIN, while those with glomerulonephritis require early diagnosis and therapeutic management.

5. Neurological involvement

Although earlier studies described central nervous system (CNS) involvement as a frequent extraglandular manifestation of primary SS, symptomatic CNS involvement is rarely found in large published series (3,5,31,32). Evaluation of the clinical significance of CNS features in patients with primary SS is difficult due, on the one hand, to the broad spectrum of both CNS and psychiatric processes that may be observed 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 multiinfarct dementia. An illustrative example is the clinical significance of the white matter lesions detected in asymptomatic, older patients with primary SS (33). These lesions are often observed in age-sex matched control populations and are also known to increase with age (34). Various studies have described other CNS processes in SS patients (33,35-47) (Table 3).
With respect to the peripheral neuropathies, pure sensory neuropathy (PSN) is recognized as a characteristic neurological complication of primary SS caused by damage of the sensory neurons of the dorsal root and gasserian ganglia. New research has described three differentiated clinical courses for PSN (48): subacute progression in less than one month (7%), late acceleration some years after an initial indolent onset (20%) and a very long-term insidious, chronic evolution (73%). Clinically, PSN usually shows a poor response to treatment with corticosteroids or immunosuppressive agents, although stabilization of symptomatology (spontaneously or after treatment) during very long periods is often observed (48).

6. Autonomic neuropathy

Several studies have described autonomic disturbances in patients with primary SS, including interstitial cystitis-like symptoms (49,50) and autonomic cardiovascular abnormalities (51-54). Andonopoulos et al (51) reported a higher frequency 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. 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 to 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.

7. Muscular involvement
Two studies have analyzed the prevalence and clinical significance of muscular involvement in patients with primary SS, with a predominance of subclinical myositis (55) rather than other types of myopathies such as inclusion body myositis (56). Lindvall et al (55) 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. 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 observed in patients with primary SS and that, in nearly 50% of cases, histological evidence of myositis may be detected in asymptomatic patients.

8. Sensorineural hearing loss
Since 1997, several studies have evaluated hearing loss in primary SS, describing sensorineural hearing loss (SHL) in 38 (27%) out of 140 patients studied (57-60) (Table 4). Some of these studies suggested an association with immunologic parameters such as aPL (57), ANA, Ro or La (57,59). Boki et al (59) found that primary SS is associated with SHL affecting preferentially the high frequencies, 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 (61)

9. Hematologic abnormalities
Various studies have emphasized the prevalence and significance of hematologic manifestations in patients with primary SS (5,62-67) (Table 5). In a series of 400
patients (62), the most frequent hematologic features were cytopenia (33%), raised ESR (22%) and hypergammaglobulinemia (22%). Although usually asymptomatic, some of these hematological features such as Coomb's positive haemolytic anaemia (63), agranulocytosis (63,66) and thrombocytopenia (63), may present symptoms. Due to the high frequency of hematologic features in patients with primary SS and the close relationship with the main immunologic SS features (62), their possible inclusion in a future revision of the current diagnostic criteria, as has happened in SLE, should be considered.

10. Lymphoma

Lymphoma is traditionally being considered as the main complication in the natural history of SS, although cross-sectional studies have reported that only 98 (4%) of 2311 patients with primary SS developed lymphoma (62). Only one study (68) has prospectively analyzed the incidence of lymphoma, which was found in 7 (7%) of 103 patients with primary SS followed over 5 years, while Ioannidis et al (6) recorded 38 diagnoses of lymphoma during 4,384 person-years of follow-up. The main clinical characteristics of B-cell lymphoma in primary SS are well described in a recent multicenter European study, including 33 patients followed up in 9 centers (69). Lymphadenopathy, skin vasculitis, peripheral nerve involvement, fever, anemia and lymphopenia were observed significantly more frequently 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 significantly worse survival rate, with high-to-intermediate grade lymphoma, B symptoms (fever, night sweats, and weight loss) and a large tumor diameter (>7 cm) being independent risk factors for death (69).
11. Evolution and outcome

The last five years have led to much greater knowledge of the outcomes 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 (70). 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 (glomerulonephritis, polineuropathy, purpura and vasculitis) present higher morbidity and mortality (4,5,6). Cryoglobulinemia probably plays a central etiopathogenic role in this latter group of patients, contributing to the development of the main extraepithelial manifestations. These features are associated with a highest risk of developing life-threatening situations (5), with these patients requiring high doses of corticosteroids and immunosuppressive agents and a 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.

In contrast to other autoimmune diseases such as SLE, there is little analytical data of clinical primary SS activity, although several studies have proposed markers such as total serum IgG levels (71,72), monoclonal Igs (73), beta-2 microglobulin (74) or Blys (BAFF) (75). In addition, various studies have described a close association between extraglandular involvement and positive antiRo/La antibodies (3,76,77), suggesting that this subset of patients represents the most active presentation of primary SS.
Few studies have analysed the causes and rates of mortality in patients with primary SS. Compared to the general population, Skopouli et al (5) found that the overall mortality of patients with primary SS increased only in patients with adverse predictors, while Martens et al (78) reported an increased mortality in patients with SS associated with other systemic autoimmune diseases, mainly RA. Ioannidis et al (6) recorded 39 deaths (7 due to lymphoma) in a cohort of 723 consecutive patients with primary SS, with a standardized mortality ratio of 1.15 compared with the general population of Greece. These studies suggest that associated processes (vasculitis, other autoimmune diseases, lymphoma) are the main causes of the excess age and sex-matched mortality observed in SS patients.

12. New therapeutic agents

At present, there is no treatment capable of modifying the evolution of SS. Local treatments such as artificial tears or oral sprays are limited in their effects, whereas systemic treatment offers the advantage of addressing a wider range of symptoms (79). New therapeutic approaches include muscarinic agonists and biological agents (Table 6).

a) 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 (80). Vivino et al (81) reported that administration of 5-mg
pilocarpine tablets 4 times daily (20 mg/d) was well tolerated and produced significant improvement in sicca symptoms, including dry mouth, dry eyes and other sicca features. Recently, Tsifetaki et al (82) published a 12 week randomized study in which 29 SS patients were treated with a lower dose of oral pilocarpine (10mg/day). Compared with controls, patients receiving pilocarpine showed a significant subjective improvement of dry eye 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 (83), in a double-blind, randomized, placebo-controlled trial in the United States, reported that therapy with cevimeline, 30 mg 3 times daily, was well tolerated and to provided substantial relief of xerostomia symptoms, while Petrone et al (84) reported improvement of saliva and tear flow rates, as well as improving subjective sicca symptoms. Further controlled studies of these muscarinic agonists at different dosages 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 (85).

b) Biological agents

Recent studies have analyzed the role of biological agents for the treatment of primary SS. In a single-center, open-label pilot study, Steinfeld et al (86) found an improvement in clinical and functional parameters in 16 patients with primary SS treated with 3 infusions of infliximab (3 mg/kg) at 0, 2, and 6 weeks. In one-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 (87). Although treatment was
generally well tolerated, the main side effect was a mild, self-limiting infusion reaction in 4 (40%) patients (one of them presenting with generalized rash, fever and arthralgia), while 2 (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 (88) reported improved salivary secretion in 4 patients with RA and associated SS treated with infliximab, while Caroyer et al (89) recently reported the successful treatment of a severe sensory neuropathy with infliximab. However, the results of a multicenter randomized, double-blind study of infliximab versus placebo, involving 103 primary SS patients, clearly showed a lack of efficiency of infliximab in primary SS (90). In addition, an uncontrolled study of 15 patients with primary SS treated with etanercept showed no effect on sicca features, glandular function or histological findings (91). Anti-TNF agents might play a role in the treatment of specific severe refractory extraglandular features, but in the light of these recent studies, they should not be considered as a first-line option for the treatment of primary SS.

Three studies have analyzed the safety and efficacy of IFN-α in primary SS (92-94). Ship et al (92) reported improved salivary output and reduced xerostomia with no significant adverse medical events, while Shiozawa et al (93) reported increased salivary production accompanied by decreased lymphocytic infiltration. Recently, Cummins et al (94) presented the results of a combined phase III study of 497 patients with primary SS receiving 150 IU of human IFN-α vs placebo 3 times daily by the oromucosal route, with improvement of 7 out of 8 sicca symptoms, although no significant increment of the stimulated whole salivary flow was observed.

A promising treatment for primary SS is rituximab (anti-CD20). CD-20 is considered 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 (95). 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, hemolytic anemia and mixed cryoglobulinemia (96). In primary SS, recent reports suggested a role for the treatment of associated lymphoma (97-99). The specific target of rituximab (B-cells) might suggest a role in modifying the etiopathogenic events of patients with primary SS, a disease specifically characterized by B-cell hyperactivity.

c) Other therapies

The role of corticosteroids and antimalarials in the treatment of SS is being reevaluated. Zandbelt et al (100) 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 (101) treated 20 patients with prednisolone, with a significant decrease in serum IgG, anti-Ro/SS-A, anti-La/SS-B antibodies and RF levels and partial decreases of IgA and IgM levels. In an experimental study, Izumi et al (102) found that local corticosteroid irrigation significantly increased the salivary flow rate in patients with SS. However, Tishler et al (103) found a significant reduction of some salivary inflammatory markers in patients treated with 200 mg/day of hydroxychloroquine, which has previously been shown to be effective for treating SS-related arthralgias, myalgias and asthenia (104,105). 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 (106-109).
CONCLUSION

The increasing amount of published data 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 last five years (Table 7), with understanding of the involvement of some organs and systems being expanded. There is now substantially more data on the outcome of patients with primary SS, which indicates that patients with a predominantly extraepithelial expression (often associated with cryoglobulinemia) should be monitored and managed differently from patients with a predominantly periepithelial or sicca-limited disease. The therapeutic management of patients with primary SS in coming years will be based on muscarinic agonists for sicca features and a key role for immunosuppressive/biological agents in the treatment of extraglandular features.
REFERENCES


TABLE 1. Cutaneous involvement of patients with primary SS.

a) Cutaneous vasculitis

a1. SS-associated small vessel vasculitis (4)
   - Cryoglobulinemic vasculitis
   - Urticarial vasculitis
   - Other leukocytoclastic vasculitis

a2. SS-associated medium vessel vasculitis (4,9)

b) Other cutaneous processes

- Ro-associated polycyclic, photosensitive cutaneous lesions (7,8)
- Erythema nodosum (4)
- Livedo reticularis (4)
- Thrombocytopenic purpura (4)
- Lichen planus (4)
- Vitiligo (4)
- Nodular vasculitis (4,10)
- Cutaneous amyloidosis (4,11-14)
- Annular granuloma (4)
- Granulomatous panniculitis (15)
TABLE 2. Renal involvement in patients with primary SS: altered renal parameters and renal biopsy results.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Total patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered renal parameters (27-29)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Proteinuria</td>
<td>55</td>
<td>198</td>
<td>28%</td>
</tr>
<tr>
<td>- Distal RTA</td>
<td>31</td>
<td>237</td>
<td>13%</td>
</tr>
<tr>
<td>- Low creatinine clearance</td>
<td>29</td>
<td>182</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Renal biopsy (29,30)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tubulo-interstitial nephritis</td>
<td>16*</td>
<td>27</td>
<td>59%</td>
</tr>
<tr>
<td>- Glomerulonephritis</td>
<td>12*</td>
<td>27</td>
<td>44%</td>
</tr>
<tr>
<td>*Membranoproliferative</td>
<td>6**</td>
<td>12</td>
<td>50%</td>
</tr>
<tr>
<td>*Mesangial-proliferative</td>
<td>5</td>
<td>12</td>
<td>42%</td>
</tr>
<tr>
<td>*Membranous</td>
<td>1</td>
<td>12</td>
<td>8%</td>
</tr>
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*One patient had coexisting tubulo-interstitial nephritis and glomerulonephritis

**Five of them had associated cryoglobulinemia
<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Multiple-sclerosis like disease (33,35,36)</td>
</tr>
<tr>
<td>Myelopathy</td>
</tr>
<tr>
<td>Acute myelitis (37,38)</td>
</tr>
<tr>
<td>Chronic myelopathy (39)</td>
</tr>
<tr>
<td>Central pontine myelinolysis (40)</td>
</tr>
<tr>
<td>Parkinsonism (41)</td>
</tr>
<tr>
<td>Painful tonic/dystonic spasms (42)</td>
</tr>
<tr>
<td>Bell’s palsy (43)</td>
</tr>
<tr>
<td>Optic neuritis (44)</td>
</tr>
<tr>
<td>CNS vasculitis (45)</td>
</tr>
<tr>
<td>CNS T-cell lymphoma (46)</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy (47)</td>
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<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hearing loss</th>
<th>ANA</th>
<th>Anti-Ro/SS-A</th>
<th>Anti-La/SS-B</th>
<th>aCL</th>
</tr>
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<tbody>
<tr>
<td>Tumiatti et al (57)</td>
<td>30</td>
<td>14 (46%)</td>
<td>14 (100%)</td>
<td>14 (100%)</td>
<td>12 (86%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Ziavra et al (58)</td>
<td>40</td>
<td>9 (23%)</td>
<td>9 (100%)</td>
<td>7 (78%)</td>
<td>3 (33%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Boki et al (59)</td>
<td>48</td>
<td>7 (15%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hatzopoulos et al (60)</td>
<td>22</td>
<td>8 (36%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>140</td>
<td>38 (27%)</td>
<td>23 (100%)</td>
<td>21 (91%)</td>
<td>15 (65%)</td>
<td>10 (43%)</td>
</tr>
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TABLE 5. Hematological abnormalities in patients with primary SS: recent studies.

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>References</th>
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<tr>
<td><strong>a) Red blood cell count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normocytic anemia</td>
<td>118/641 (18.4%)</td>
<td>5,62</td>
</tr>
<tr>
<td>- Hemolytic anemia</td>
<td>Isolated cases</td>
<td>62,63</td>
</tr>
<tr>
<td><strong>b) White blood cell count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Leukopenia</td>
<td>116/628 (18.5%)</td>
<td>5,62,64</td>
</tr>
<tr>
<td>- Lymphopenia</td>
<td>23/268 (8.6%)</td>
<td>62</td>
</tr>
<tr>
<td>- Neutropenia</td>
<td>19/268 (7.1%)</td>
<td>62</td>
</tr>
<tr>
<td>- Eosinophilia</td>
<td>31/268 (11.6%)</td>
<td>62</td>
</tr>
<tr>
<td>- Chronic agranulocytosis</td>
<td>Isolated cases</td>
<td>62,63,65,66</td>
</tr>
<tr>
<td><strong>c) Platelet count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Thrombocytopenia</td>
<td>55/479 (11.5%)</td>
<td>62,64</td>
</tr>
<tr>
<td><strong>d) Other abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Raised ESR (&gt; 50mm/h)</td>
<td>82/380 (21.6%)</td>
<td>62</td>
</tr>
<tr>
<td>- Hypergammaglobulinemia</td>
<td>191/585 (32.6%)</td>
<td>5,62,67</td>
</tr>
<tr>
<td>- aPL</td>
<td>24/184 (13%)</td>
<td>62</td>
</tr>
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TABLE 6. New therapeutical agents for the treatment of patients with primary SS.

<table>
<thead>
<tr>
<th></th>
<th>Dosage</th>
<th>Number of patients treated</th>
<th>References</th>
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<tr>
<td><strong>Muscarinic agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pilocarpine</td>
<td>5mg/6h po</td>
<td>127 (primary + associated SS)</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>5mg/12h po</td>
<td>27 (primary SS)</td>
<td>82</td>
</tr>
<tr>
<td>- Cevimeline</td>
<td>30mg/8h po</td>
<td>25 (primary + associated SS)</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62 (primary + associated SS)</td>
<td>84</td>
</tr>
<tr>
<td><strong>Biological agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Infliximab</td>
<td>3mg/kg ev</td>
<td>4 (SS associated with RA)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>5mg/Kg ev</td>
<td>1 (primary SS + neuropathy)</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 (primary SS)</td>
<td>86,87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 (primary SS)</td>
<td>90</td>
</tr>
<tr>
<td>- Etanercept</td>
<td>25 mg/12h sc</td>
<td>15 (primary SS)</td>
<td>91</td>
</tr>
<tr>
<td>- Rituximab</td>
<td>375mg/m² ev</td>
<td>1 (primary SS + lymphoma)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (primary SS + lymphoma)</td>
<td>99</td>
</tr>
<tr>
<td>- INFA</td>
<td>150IU/8h po</td>
<td>300 (primary SS)</td>
<td>94</td>
</tr>
<tr>
<td><strong>Other therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prednisolone</td>
<td>15mg/d po</td>
<td>20 (primary SS)</td>
<td>101</td>
</tr>
<tr>
<td>- Octreotide</td>
<td>30 mg im</td>
<td>1 (primary SS)</td>
<td>107</td>
</tr>
<tr>
<td>- 2-chloro-2’deoxyr</td>
<td>0.12mg/kg ev</td>
<td>2 (primary SS + lymphoma)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (primary SS + MC)</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 7. Current concepts in the extraglandular expression of primary SS.

a) Cutaneous involvement
   - Prognostic significance of cryoglobulinemia and cutaneous purpura (4-6)
   - Ro-associated polycyclic, photosensitive lesions (SCLE-like) (4,7,8)

b) Pulmonary involvement
   - High frequency of bronchial/bronchiolar disease (30-50%) (18-20)
   - Insidious and slow progression of pulmonary involvement (23)

c) Renal involvement
   - Indolent subclinical course of TIN (30)
   - Demonstration of glomerulonephritis in 44% of patients biopsied (29,30)
   - Key role of cryoglobulinemia in SS-related glomerulonephritis (29,30)

d) Neurological involvement
   - Increased cerebral white matter lesions (33)
   - Long-term insidious course and poor response to treatment of PSN (48)
   - Autonomic disturbances (abnormal responses to cardiovascular tests) (51-54)

e) Lymphoproliferative disease
   - Prevalence of 4% of lymphoma in cross-sectional studies (62)
   - Lymphadenopathy, purpura and neuropathy as clinical markers of lymphoproliferation (69)
   - Anemia, lymphopenia, cryoglobulins and mIgs as analytical markers (69)
   - Salivary glands as the main site of lymphoma (69)
   - Higher prevalence of extranodal involvement (69)

f) Miscellaneous
   - Subclinical muscle inflammation (53)
   - Interstitial cystitis associated with severe urological symptoms (49,50)
   - Sensorineural hearing loss in nearly 25% of patients (57-60)
   - Rare occurrence of symptomatic cytopenias (62,63,66)
   - Autoimmune myocarditis (110,111)
   - Fatigue (112-116)
Primary Sjögren's syndrome: new clinical and therapeutic concepts

Manuel Ramos-Casals, Athanasios G Tzioufas and Josep Font

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