Treating Sjögren's syndrome: insights for the clinician

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***Abstract*:** Sjögren's syndrome (SS) is a systemic autoimmune disease that affects the exocrine glands, mainly the salivary and lachrymal glands, with consequent persistent dryness of the mouth and eyes. In addition to the clinical manifestations related to the exocrine gland involvement, a consistent prevalence of patients may present systemic manifestations. Some of these can be ascribed to the periepithelial extension of lymphocytic infiltration whilst others are determined by an immunomediated process affecting small- or medium-size vessels. While the use of tear and saliva substitutes and local or systemic stimulation of residual secretions represent the mainstays of the therapy of sicca component, different immunomodulating or immunosuppressive agents are usually required to treat extraglandular features, similarly to what happens in other connective tissue diseases. In the last few years, the advancement in the understanding the pathogenetic mechanisms of this disorder and the availability of new biologic target therapies seem to offer completely new therapeutic options. The use of B cell depleting or modulating therapies has achieved promising results.

***Keywords*:** Sjögren's syndrome, treatment

Introduction

Sjögren's syndrome (SS) is a slowly progressive systemic autoimmune disease, which is primarily characterized by lymphocytic infiltration in the exocrine glands, mainly in the lachrymal and salivary glands, with their consequent impaired secretory function [Kassan and Moutsopoulos, 2004].

The syndrome may also manifest within a large spectrum of clinical manifestations, ranging from a limited involvement of exocrine glands to a systemic disease with widespread autoimmune features and pronounced immunological abnormalities. The systemic nonexocrine manifestations may include constitutional symptoms (fatigue, arthralgia, myalgia and low-grade fever), arthritis, skin lesions, leukocytoclastic vasculitis, Raynaud's phenomenon, central and peripheral neurologic involvement, renal, lung or hepatic involvement and finally lymphoproliferative disorders [Ramos-Casals *et al.* 2005]. The presence of vasculitis, cryoglobulinaemia and low complement levels characterizes a subset of patient with higher morbidity and mortality mainly related to the higher probability to develop lymphoma [Ramos-Casals *et al.* 2005; Theander *et al.* 2004, 2006].

SS may occur as a primary disorder (pSS) or in association with other systemic autoimmune diseases, traditionally defined as secondary SS (sSS), such as rheumatoid arthritis, and systemic lupus erythematosus [Ramos-Casals *et al.* 2007].

The multiple aspects of the syndrome make it difficult to diagnose. As a consequence, SS may remain either undiagnosed, or may be diagnosed many years after the onset of symptoms. As is commonly accepted for any systemic autoimmune disease, early recognition of this disorder is of particular importance to prevent delay in diagnosis, allow appropriate clinical evaluation and optimize therapeutic intervention. [Kassan and Moutsopoulos, 2004].

pSS has an estimated prevalence of 0.1–0.6% [Bowman *et al.* 2004] according to the American European Consensus classification criteria [Vitali *et al.* 2002], and predominantly affects middle-aged women, although it can occur at any age.

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Appropriate care is an important issue in pSS and involves several different specialties, because of the complexity and varying nature of the disease. During the past few years, a growing body of evidence has induced clinicians to distinguish two different variants of the syndrome: an exocrine gland-localized disease, that mainly affects quality of life, and a systemic syndrome, which is characterized by extra-glandular manifestations, and may potentially evolve to lymphoma [Ramos-Casals *et al.* 2005; Theander *et al.* 2004, 2006]. Whereas symptomatic therapy may be enough for most of patients with limited glandular disease, the lack of disease-modifying drugs has an important impact for those patients with systemic manifestations and severe organ involvement. Some of the new biological-target therapies have shown promising results and others could be considered hypothetically useful in the future for this disorder, if directed against crucial biological mediators or cellular actors of the underlying pathogenetic mechanisms.

Management of glandular manifestations

The main therapeutic measures for glandular manifestation pSS are reported in Table 1.

Therapeutic approach of dry eye

Keratoconjunctivitis sicca (KCS) is the classical ocular condition that affects patients with SS [Samarkos and Moutsopoulos, 2005; Kalk *et al.* 2002]. This is the result of the lymphocytic infiltration of the lachrymal glands and of the consequent decreased lachrymal flow and impaired lachrymal composition, which may cause damage of the corneal and conjunctival epithelia. Diagnosis is usually obtained both by measuring tear production and tear-film stability (by performing Schirmer's test and tear-break time, respectively), and by staining of the cornea with Rose Bengal (or other colorants) to evaluate damage to the epithelium. Patients suffering from KCS might complain of foreign-body sensation, irritation, photosensitivity, with increased visual discomfort and possibly impairment. Moreover, KCS may be complicated by the appearance of different features, which include corneal ulceration and scarring, bacterial keratitis and eyelid infections, which require continuous ophthalmologic care and treatment. Blepharitis or inflammation of the meibomian glands, which produce the lipid component of tears, is another frequently encountered complication and can be managed with local antibiotics [Samarkos and Moutsopoulos, 2005; Foulks, 2003].

Nonpharmacologic-general measures such as avoidance of potentially worsening factors including air conditioning, smoky and windy environments, prolonged reading or computer use, are mandatory in the therapeutic approach of dry eye. Drugs that inhibit tear production, such as diuretics, beta-blockers, tricyclic antidepressants and antihistamines should be avoided or used at the minimum effective dosage [Foulks, 2003].

Topical treatment

Replacement of tear volume with artificial tears is the largest employed measure in the treatment of dry eye. Many preparations, including

Table 1. Main therapeutic measures for glandular manifestations in Sjögren's syndrome.

Manifestation	Therapeutic measures
Ocular manifestation (dry eye)	Artificial tears Autologus serum drops* Local immunomodulatory (cyclosporin A drops) Local secretagogues (diquafosol tetrasodium, rebamipide)* Hypotonic 0.4% hyaluronic acid drops Lachrymal duct occlusion
Oral involvement	
Xerostomia	Hydratation Saliva substitutes
Caries	Routine dental care, fluoride
Candidiasis	Local and systemic anti-fungal treatment
Ocular and oral dryness	General measures Avoidance of dry (air conditioned), smoky or windy environment Avoidance of prolonged reading or computer use Medications Systemic stimulation by muscaric agonists (pilocarpine, cevimeline, hydroxychloroquine).

For references see the text *Experimental measure.

preservative-free products and hypotonic solutions, are available on the market. Among these, hypotonic solution containing hyaluronic acid seems to be particularly effective [Troiano and Monaco, 2008]. In the presence of preservatives, a tear-substitute application more than four times daily can be poorly tolerated by the ocular surface. Lubricating emulsions and slow-release methylcellulose inserts can last longer than tear-liquid substitutes but should be reserved for night use, since their application can disturb the vision during the day [Korb *et al.* 2005; Samarkos and Moutsopoulos, 2005; Foulks, 2003].

Autologous serum eye drops are a promising modality in the dry-eye treatment. However, their preparation is quite complex and costly and their use should be limited to selected cases, mainly to patients intolerant to artificial tears or with treatment-resistant KCS [Noble *et al.* 2004]. Serum drops are totally nonallergenic and have biochemical properties similar to those of normal tears. Furthermore, serum drops support conjunctival epithelium with vitamins, fibronectin and growth factors which may stimulate its proliferation and repair [Geerling *et al.* 2008; Kojima *et al.* 2005]. From this point of view, platelet releasate seems to have a better growth factor concentration and seems to be a promising new treatment for dry eye [Liu *et al.* 2006].

New secretagogues, with a specific mucin-secretory action, have also been examined in human studies [Gipson and Argüeso, 2003]. Diquafosol tetrasodium is a uridine nucleotide analogue that promotes fluid and mucin secretion and restores the normal integrity of the ocular surface by acting as an agonist of purinergic receptor P2Y (present on the ocular surface and the conjunctiva). Phase II and III studies showed that diquafosol 2% demonstrated significant efficacy in improving objective parameters of ocular dryness [Tauber *et al.* 2007; Murakami *et al.* 2004].

Rebapamide, a new secretagogue in its ophthalmologic preparation, demonstrated to improve subjective symptoms and objective tests of dry eye and to have a good safety profile, in a randomized, placebo-controlled study [Donshik *et al.* 2005].

Immunoactive drugs have also been tested locally in the attempt to control the inflammatory process over the ocular surface and in the lachrymal glands [Urashima *et al.* 2004].

Cyclosporine A emulsion, at concentrations of 0.05%, was shown to be beneficial, according to both subjective- and objective-outcome measures of dry eye in multiple controlled and uncontrolled trials [Stonecipher *et al.* 2005; Stevenson *et al.* 2000]. However, no study was specifically designed for patients with pSS.

Calcineurin inhibitors, such as tacrolimus or pimecrolimus, in their ophthalmologic preparations seem to be potentially useful for the treatment of KCS, at least in patients with unsatisfying response to cyclosporine A [Nell *et al.* 2005; Ousler *et al.* 2005].

Topical corticosteroids (CSs) have been shown to be effective in controlling or reducing inflammation-induced corneal damage. Their prolonged use can induce intraocular-pressure elevation or cataract. So, their use should be limited to short-term course during the inflammatory exacerbation of KCS [Avunduk *et al.* 2003]. Loteprednol and rimexolone, two steroids with substantially reduced intraocular-pressure-raising potential, have been shown to be useful in the treatment with no increase in the prevalence and type of adverse events [Leibowitz *et al.* 2006; Pflugfelder *et al.* 2004].

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered useful in treating ocular discomfort in KCS, but they should be applied with caution since they can predispose to corneal damage [Aragona *et al.* 2005].

Preservation of tear quantity by punctual occlusion is reserved for patients with very severe disorder and not responsive to other therapies. Punctual plugs are made from either silicone or dissolvable collagen and have shown significant improvement in both subjective and objective parameters of dry eye [Cohen, 1999]. Migration into the canaliculi, infection and extrusion of plugs may sometimes complicate this procedure.

Treatment of dry mouth

Topical treatment

Adequate hydration, avoidance or reduction of anticholinergic drugs, and potential oral mucosal irritants, such as alcohol, coffee or nicotine, are of primarily importance in the therapeutic approach to dry mouth [Silvestre-Donat *et al.* 2004]. Routine or preventive dental care and

use of fluoride preparations, such as gel or toothpaste, are also strongly suggested to avoid or limit dental caries and periodontal disease [Kassan and Moutsopoulos, 2004].

Traditionally, the basic treatment of xerostomia is represented by the use of saliva substitutes. A wide variety of preparations are available for this purpose, in the form of gels, sprays, oils, and all of these can improve lubrication, hydration and protection from noxious environmental agents [Urquhart and Fowler, 2006; Wynn and Meiller, 2000]. Some comfort can also be obtained simply by assuming frequently small quantities of water or other sugar-free fluids. An increase of residual saliva production and secretion can also be achieved by swallowing sugar free, and not easily adherent, chewing gums.

Oral candidiasis frequently occurs in patients with a deficiency of saliva production [Hernandez and Danils, 1989]. Topical and systemic antifungal treatment should be associated in the case of persistent and recurrent episodes. Gels or creams containing nistatin are commonly used, together with systemic treatment with miconazole or similar antifungal drugs. [Ellepola and Samaranayake, 2000].

Systemic treatment of dry mouth

Muscarinic agonists pilocarpine and cevimeline have been successfully tested in patients with SS to stimulate glandular secretion and have been shown to be particularly effective in patients with residual secretory function [Fox *et al.* 2001]. Pilocarpine, at a daily dose of 20 mg (5 mg four times a day), has been demonstrated to improve sicca symptoms and increase saliva production [Vivino *et al.* 1999]. Similarly, cevimeline, which possesses higher affinity for M3 receptors (mainly present in salivary and lachrymal tissues) at the daily dose of 30–60 mg, has been shown to improve sicca symptoms and salivary flow [Ono *et al.* 2004]. Moreover, hydroxychloroquine also seems to have an effect as an anticholinergic agent [Dawson *et al.* 2005]. The most common side effects observed after the use of both muscarinic agonists are flushing, excessive sweating, urinary frequency and headache.

Since a viral aetiology has been recurrently postulated for pSS, the potential efficacy of interferon-α (IFN-α) in this disorder has been assessed. Parenteral IFN-α treatment was shown to be effective in increasing saliva and tear secretion in patients with SS [Ferraccioli *et al.* 1996]. In order to eliminate adverse effects of this systemic treatment, which includes, alopecia, leukopaenia and flu-like symptoms, an oral route of administration of a low-dose regimen (150 IU three times a day) has been tentatively tested. This regimen demonstrated significant improvement of ocular and oral discomfort, salivary flow and histopathological lesions in salivary glands, with a decrease of adverse events [Khurshudian, 2003]. A possible, but not completely convincing explication of the IFN-α efficacy in pSS, is the potential upregulation of aquaporin 5 (AQ5), with consequent increase in fluid transportation outside the exocrine secretory cell [Smith *et al.* 1999]. In contrast with these results, the presence of an IFN-α type I signature has been largely confirmed in the pathological process of pSS [Nordmark, 2006; Båve *et al.* 2005] and, as a consequence of this, the beneficial effects of anti-IFN-α therapy could be postulated and should be confirmed in future therapeutic trials.

Rebamipide has been investigated recently as a systemic therapeutic intervention for oral sicca complaints. Some encouraging, but so far inconclusive results have been obtained, mainly in patients with the primary variant of the disease [Sugai *et al.* 2009].

Treatment of other glandular manifestations

Exocrine glands different from salivary and lachrymal glands can also, although more rarely, be involved in the autoimmune inflammatory process in pSS, particularly those of the upper airways, skin, gastrointestinal system and external gynaecologic apparatus.

Reduced secretions in the upper respiratory tract mucosa may cause dry nose, epistaxis, sinusitis, sore throat and several bronchial problems such as dry cough, recurrent bronchitis and bronchial hyperresponsiveness. Room humidifiers and cyclic treatment with expectorants are indicated, together with antibiotic treatment for sinusitis or bronchitis. Specific vaccination can be useful to prevent pneumococcal infection. Chronic gastritis with vitamin B12 deficiency and pernicious anaemia are also quite rare, but well-known events in the natural course of pSS [Moutsopoulos and Moutsopoulos, 2001]. The possible association with caeliac disease should also be taken into account [Roblin *et al.* 2004].

Dyspareunia, secondary to impaired lubrication, has been described in a large prevalence of postmenopausal women with pSS. Vaginal lubricants or inserts may help in solving this problem. Oestrogen preparations are also indicated [Moutsopoulos and Moutsopoulos, 2001].

Management of extraglandular manifestations

Extraglandular manifestations of pSS can be distinguished in different groups [Ramon-Casals *et al.* 2005]. In addition to constitutional (fatigue, fever) and musculoskeletal manifestations, the other organ-specific features can be subdivided in periepithelial and extraepithelial features. Periepithelial lesions, such as tubulointerstitial nephritis, bronchiolitis or liver disease, usually characterize a more stable chronic disease course [Ramon-Casals *et al.* 2005; García-Carrasco *et al.* 2002]. In contrast, patients with extraepithelial manifestations, such as leukocytoclastic vasculitis, leg ulcers, glomerulonephritis, polyneuropathy and interstitial pneumonitis, present a more variable course with activity flares, and need a more aggressive therapy [García-Carrasco *et al.* 2002; Ioannidis *et al.* 2002]. The patients are also at higher risk of developing lymphoma, a well-identified cause of mortality in pSS. [Ramos-Casals *et al.* 2005; Theander *et al.* 2004, 2006].

Constitutional symptoms

Fatigue affects approximately 50% of patients with pSS and manifests as an increased need for resting hours. In these patients, concomitant hypothyroidism, fibromyalgia, lymphoma or underlying depression should be considered as potentially associated causes [Kassan and Moutsopoulos, 2004].

The presence of fibromyalgia features often requires the prescription of antidepressants. Since tricyclic antidepressants cannot be used because they can exacerbate sicca manifestations, an alternative therapeutic regimen should be chosen to treat depressive state, such as the administration of selective serotonin reuptake inhibitors [Günaydin *et al.* 1999]. Regular exercise and myofascial therapy could be also of some of benefit [Rooks, 2007].

Musculoskeletal manifestations

Musculoskeletal manifestations, such as arthralgias, myalgias and nonerosive polyarthritis affecting mainly the small joints, are rather common in patients with SS; a combination of low-dosage steroid, NSAIDs or analgesics and hydroxychloroquine (200 mg once daily) is the more commonly applied treatment [Manoussakis and Moutsopoulos, 1996]. Methotrexate (MTX) has been empirically used for polyarthritis in pSS, based on the clinical similarities with rheumatoid arthritis features, although conclusive data on its efficacy has not been provided so far.

Raynaud's phenomenon

Raynaud's phenomenon may be present in 25–30% of patients with pSS, and often precedes sicca manifestations by many years. Administration of calcium-channel blockers, or angiotensin-converting-enzyme inhibitors seems to be clinically efficient measures [García-Carrasco *et al.* 2002; Skopouli *et al.* 1990].

Renal involvement

Renal disease in patients with SS can manifest as either a periepithelial tubular disease or an extraepithelial glomerular disease. Hypokalaemic hyperchloremic acidosis, the most serious manifestation of tubular dysfunction, can be treated with oral potassium and sodium bicarbonate [Moutsopoulos and Moutsopoulos, 2001]. Glomerulonephritis, which is commonly associated with cryoglobulinaemia and hypocomplementaemia, is usually treated with medium/high dosage or pulse prednisolone [Goules *et al.* 2000]. The additional use of pulse intravenous cyclophosphamide should be reserved only in cases of treatment-refractory disease, since cytotoxic agents are associated with an additional increase of the incidence of lymphoma in patients with pSS [Linardaki and Moutsopoulos, 1997]. No data are available at moment on the use of mofetil mycofenolate or rituximab in pSS-associated glomerulonephritis.

Liver involvement

The liver can also be affected in about 5% of patients with pSS who have elevated liver enzymes, antimitochondrial antibodies and histopathologic changes indicative of primary biliary cirrhosis. In these patients, ursodeoxycholic acid can be of some benefit [Moutsopoulos and Moutsopoulos, 2001]. Autoimmune hepatitis can also occur, requiring treatment with prednisolone and azathioprine [Matsumoto *et al.* 2005].

Lung involvement

In addition the periepithelial pathological lesions which may involve the mucosa of upper respiratory airway, but also that of medium- and small-size bronchial structures [Papiris *et al.* 1999],

cases of interstitial lung involvement are also described [Parambil *et al*. 2006]. CS administration with or without an immunosuppressive agent (azathioprine or cyclophosphamide) is the most commonly applied therapeutic option.

Neurological involvement

Focal or diffuse central nervous system manifestations have also been described in pSS, although their real presence is still a matter of discussion [Delalande *et al.* 2004]. Acute transverse myelitis may occur in about 1% of patients with this disorder. Pulse intravenous CSs in combination with pulse cyclophosphamide is the currently considered therapeutic regimen of choice in these patients [Rogers *et al.* 2004]. An early therapeutic approach is essential to obtain total, or at least partial, remission of central nervous system manifestations [De Seze *et al.* 2006]. Other immunosuppressive agents, intravenous immunoglobulins and plasmapheresis have also been tested, when cyclophosphamide was poorly tolerated or not effective [Rogers *et al*. 2004; Soliotis *et al.* 2004].

Peripheral neurologic involvement is considered to be quite common in patients with pSS (10–20% of cases), particularly in the form of cranial neuropathy, distal sensory or sensorimotor polyneuropathy, and multineuritis multiplex [Delalande *et al.* 2004]. As in other systemic autoimmune diseases, the clinical course is usually subclinical, this often leading to delay in the diagnostic suspicion and confirmation [Gøransson *et al.* 2006]. This is probably one of the main reasons of the poor response of peripheral neuropathies to the treatment. Sensory neuropathy is particularly resistant to treatment as well as axonal polyneuropathy [Font *et al.* 2003]. Multiple neuropathies, where nerve biopsy often shows a *vasa nervorum* vasculitis, are usually more responsive to early CSs or immunosuppressive therapy. Intravenous immunoglobulins or plasmapheresis are other anecdotally reported therapeutic attempts [Molina *et al.* 1996; Bakchine *et al.* 1987].

Vasculitis. Vasculitis can occur in 10–20% of patients with pSS, as either a cutaneous localized form, manifesting mainly as palpable purpura (leukocytoclastic vasculitis), or as a systemic necrotizing vasculitis involving small- and medium-sized arteries of various organs [Ramos-Casals *et al.* 2004]. Both forms are often associated to the presence of cryoglobulins. After lymphoma, systemic vasculitis is considered the main autoimmune cause of death in this disease. Medium- or high-dose steroids plus eventually intravenous cyclophosphamide as a second-line treatment are the mainstays of therapy [Ferri and Mascia, 2006]. Plasmapheresis and intravenous immunoglobulins are believed to be alternative treatments in refractory forms [Durez *et al.* 1998].

Haematologic manifestations

Haematologic manifestations include mild, or rarely severe, cytopaenias and lymphoproliferative disorders [Ramos-Casals *et al.* 2002]. Autoimmune cytopaenias, such as haemolytic anaemia, leukopaenia and thrombocytopenia, sometimes require treatment with steroids, danazol or immunosuppressive agents [Schattner *et al.* 2000]. Intravenous immunoglobulins are indicated in the case of severe thrombocytopenia.

Treatment of lymphoma in patients with pSS follows the same principles than the therapy for lymphoma in the general population, and is related to its histologic type, location and extension. Most pSS-associated lymphomas are of B-cell origin, low or intermediate grade, and originate in mucosa-associated lymphoid tissue (MALT lymphoma). Histologically aggressive lymphomas, such as diffuse, large B-cell lymphomas, are encountered occasionally [Smedby *et al.* 2008; Zintzaras *et al*. 2005]. The treatment of choice for systemic lymphoma in pSS is rituximab alone or with different combination regimens. The most commonly used rituximab-associated regimen is a combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), which showed to provided a sustained response in small series of patients with aggressive lymphoma and also induce an improvement of both the extraglandular features and the associated immunologic abnormalities [Voulgarelis *et al.* 2004]. However, the treatment of lymphoma should not be performed by rheumatologists and should be chosen and managed by an expert haematologist.

Target therapies: present and future

In the era of biologic agents, targeting molecules or cells that seems to play a pivotal role in the pathogenesis of pSS might be a promising approach. Overexpression of several cytokines has been detected in the glandular lesions of pSS. Tumor necrosis factor-alpha (TNF-α) secreted by glandular T cells may promote apoptosis of

glandular epithelia by inducing Fas expression [Matsumura *et al.* 2000; Fox *et al.* 1994]. On the basis of these data, anti-TNF-α therapy was postulated to be potentially effective in pSS. An initial pilot trial of infliximab, a chimeric anti-TNF-α monoclonal antibody, showed a statistically significant improvement in clinical and functional parameters of patients with pSS [Steinfeld *et al.* 2001]. However, a subsequent larger randomized, double-blind, placebo-controlled trial failed to confirm any benefit of infliximab monotherapy in this disease [Mariette *et al.* 2004]. A subsequent similar trial with another TNF-α inhibitor, etanercept, gave similar negative results, which discouraged any further investigation [Sankar *et al.* 2004].

Since pSS is the autoimmune disorder where B-cell activation is most prominent, B lymphocytes have been indicated as one of the preferable target for an optimal therapeutic approach [Mariette, 2008]. This is particularly true in view of the fact that B-cell activation may begin as polyclonal, but can progress to monoclonal lymphoproliferation [Ioannidis *et al.* 2002]. A relative risk between 16 and 18 of developing lymphoma has been calculated to be present in patients with pSS, this being the highest among the different systemic autoimmune diseases [Smedby *et al.* 2008; Zintzaras *et al.* 2005]. Moreover, B-cell hyperactivity is also proven in pSS by the presence of high levels of gammaglobulins, rheumatoid factor and autoantibodies, and has been suggested to be closely related to the development of the systemic extraglandular manifestations [Gottenberg *et al.* 2005]. B-lymphocyte activating factor (BAFF) or B-lymphocyte stimulator (Blys) appears to be cytokine critical for B-cell survival and maturation, and then to have a major role pathogenesis by regulating B-cell activation and autoantibody production in pSS [Szodoray *et al.* 2004]. In fact, BAFF transgenic mice develop a clinical picture manifested by severe sialadenitis, decreased saliva production and destruction of submaxillary glands [Groom *et al.* 2002]. In addition, BAFF serum levels in patients with pSS are strongly increased [Mariette *et al.* 2003].

Rituximab, a chimeric monoclonal antibody, directed against CD20, a pan-B-cell surface antigen, which has been approved for the treatment of B-cell lymphoma and of anti-TNF-α refractory rheumatoid arthritis, has been tested in small open studies (Table 2) [Isaksen *et al.* 2008; Mariette, 2008]. In addition to the

Table 2. Efficacy and indications of Rituximab reported in previously published studies.

Authors, Years	Number of patients	Indications of rituximab	Efficacy for lymphoma	Efficacy for systemic features	Efficacy for objective dryness	Efficacy for subjective dryness	Adverse events
Gottenberg *et al.* [2005]*	6	Lymphoma (2/6) Systemic features (4/6)	1/2 (50%) –	– 4/4 (100%)	0/2	3/6 (50%)	2/6 (33%) 1 SSD, 1IR
Pijpe *et al.* [2005]	15	Lymphoma (7/15) Early pSS (8/15)**	3/7 (43%)	NR	2/7 (28.6%) 7/7 (100%)	Yes	6/14 (43%) 3 SSD, 2 IR
Voulgarelis *et al.* [2004]	6	Lymphoma (6/6)	6/6 (100%)	3/6 (50%)	–	No	2/6 (33%)
Seror *et al.* [2007]*	16	Lymphoma (5/16) Systemic features (11/16)	4/5 (80%) –	– 9/11 (82%)	2/16 (18%)	5/16 (36%)	4/16 (25%) 2 SSD, 2 IR
Devauchelle-Pensec *et al* [2007]	16	Pain, Dryness and Fatigue	–	1/1 (Lung)	No	Yes	2 IR
Dass *et al.* [2008]	8 (RCT)	Fatigue	–	–	No	?	1 SSD, 2 IR

Abbreviations: IR, infusion reaction; NR, not reported; RCT, randomized controlled trial; SSD, serum sickness-like disease.
*Four patients are common between the two studies.
**Five out of the eight patients with early disease who presented a new flare underwent a second four-infusion cycle of treatment with rituximab which induced a new remission of the disease.

expected effectiveness on the associated lymphoma, which was documented in part of the enrolled cases, rituximab demonstrated a clear effect on parotidomegaly and systemic manifestations, including vasculitis, arthritis, renal and lung disease [Seror *et al.* 2007]. Efficacy for dryness was restricted to patients with early disease [Pijpe *et al.* 2005]. Recently an additional randomized trial, which included a small number of patients without systemic manifestations, has shown a significant decrease of fatigue in patients treated with rituximab. It is worth noting that in these studies 10–20% of treated patients develop serum sickness disease some days after the infusion of rituximab [Dass *et al.* 2008; Isaksen *et al.* 2008; Mariette, 2008]. This is a largely described event after treatment with chimeric antibodies, due to the production of specific autoantibodies (human antichimeric antibodies [HACA]).

Interestingly, rituximab-induced B-cell depletion was shown to further increase serum levels of BAFF [Lavie *et al.* 2007]. This can be only partially ascribed to the disappearance of BAFF-binding B cells, and could also be due to a feedback overproduction of BAFF [Lavie *et al.* 2007; Toubi *et al.* 2007]. Anyway, this may favour the re-emergence of autoreactive B cells and new disease relapse. Thus, BAFF antagonist therapy has been suggested to play a potential additional role in prolonging the period of remission after rituximab infusion in refractory cases.

An alternative target for B-cell depletion may be to use epratuzumab, a monoclonal antibody directed against another B-cell-specific transmembrane protein, CD22, which functions primarily as negative regulator of B-cell receptor (BCR) [Lajaunias *et al.* 2003]. CD22 is present on the B-cell surface only at mature stages of differentiation, being absent in plasma cells and after B-cell activation [Carnahan *et al.* 2003]. Compared with rituximab, which is a cytotoxic antibody, epratuzumab acts as an immunomodulator and provides a modest decrease in B-cell numbers [Carnahan *et al.* 2007]. Since epratuzumab is a humanized antibody, it appears to be less immunogenic, with less potential for HACA induction and serum sickness disease development [Dörner *et al.* 2006]. An open-label trial in pSS suggested that epratuzumab is safe and well tolerated, and a clinical response was observed in about half of patients [Steinfeld *et al.* 2006].

Conclusions

Despite recent advancements in the knowledge of the aetiology and pathogenetic mechanisms, treatment of pSS remains mostly empiric and symptom-based. The different immunosuppressive regimens that have been tested for several years and in different clinical features seem to be unable to modify the course of the disease. B-cell modulation is certainly a very promising therapy for pSS, although a more precise definition of the clinical subsets where this therapy could be really effective should be provided. Randomized controlled studies are absolutely essential to verify this hypothesis. However, obtaining validated disease status indices for this disease appears to be a critical point prior to initiating specifically designed trials. Different studies have been performed, or are currently in progress, to develop valid and reliable outcome measures for this disease [Seror *et al.* 2009; Bowman *et al.* 2007; Vitali *et al.* 2007].

Conflict of interest statement

None declared.

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