Drugs 1998 Sep; 56 (3): 345-353
0012-6667/98/0009-0345/$09.00/0

Rational Drug Therapy Recommendations for the Treatment of Patients with Sjögren's Syndrome

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Abstract

The aetiology of Sjögren's syndrome (SS) is unknown, and consequently curative treatments are not available. The immunopathogenesis of SS is partly clarified and immune-regulating drugs (IR) may therefore be of therapeutic value. However, the present understanding of SS is still too unclear to allow an exact and evidence-based algorithm for therapeutic decision making. Rational drug recommendations for the therapy of SS must, therefore, rely mostly on empirical data.

Several IR drugs have been shown to be able to downregulate the immunopathological activity of primary SS, but it is not certain whether the diagnostic and cardinal manifestations from the eyes and mouth can be improved. In primary SS the disease-modifying qualities of IR and cytotoxic drugs, therefore, largely apply to the treatment of severe internal organ involvement, inflammatory vascular disease and malignant B lymphocyte disease. In secondary SS the IR therapy is directed against the basic immunoinflammatory connective tissue disease. Symptom-modifying therapies include drugs to stimulate and substitute for exocrine functions, and drugs to treat complications of the exocrine disease manifestations and to improve the various nonexocrine disease manifestations.

The main drugs available for increasing lacrimal and salivary gland output are bromhexine and pilocarpine, respectively. However, exocrine substitutes, and in

particular eye drops, are still the most important means of alleviating the sicca symptoms. They are also indispensable local treatment measures which may help to prevent mucosal complications.

1. Introduction

Sjögren's syndrome (SS) belongs to the chronic immunoinflammatory connective tissue disorders (ICTD). It has been designated an autoimmune exocrinopathy[1] and (more lately) an autoimmune epitheliitis.[2] The two descriptive terms emphasise the primary pathobiological characteristic of SS, that is, immune-mediated destruction of exocrine epithelia. The corresponding clinical key feature is desiccation of body surfaces, in particular the ocular and oral surface.

SS may (secondary SS) or may not (primary SS) be associated with another ICTD. Primary SS is a disease mostly affecting women (90%) and assumed to be almost as prevalent (0.5 to 1%) as rheumatoid arthritis.[3,4] In addition to the exocrine disease involvement, primary SS patients display a broad spectrum of nonexocrine manifestations. Secondary SS affects 20 to 30% of patients with rheumatoid arthritis and systemic lupus erythematosus, and may complicate most other ICTD as well. Nonexocrine manifestations in patients with secondary SS are usually categorised with the concomitant ICTD.

The clinical multiformity of SS necessitates the use of a stringent and rational attitude towards diagnostic procedures and patient management. This implies the need for functional means of classifying and assessing the disease status, as well as relevant measures for the outcome. With this in mind, this article outlines the theoretical and practical basis for recommendations on the pharmacological treatment of patients with SS.

2. Disease Classification

In order to act rationally on the recommendations for drug treatment of SS patients, as given in the literature, it is necessary to be fully aware of the differences in applied terminology and disease classification. Unfortunately, there is still no international consensus about the diagnostic criteria for SS (reviewed in Daniels[5]). Since 1977 we have used the 'Copenhagen criteria' (fig. 1),[6] and classification criteria for diagnosing SS were recently developed by collaborating European SS centres (fig. 1).[7] Although the EEC criteria have gained wide acceptance, but this very first attempt to create classification criteria for SS must await international validation.

For many years there has been fairly reasonable agreement about the terminological hierarchy (primary and secondary SS), but the nomenclature and classification for single disease manifestations and their groups and subgroups have been very inconsistent (see the review in Oxholm et al.[8]). In figure 2 we summarise a recently published proposal for the main disease manifestations and their groups and subgroups (the Copenhagen Classification Wheel).[9] This model forms the skeleton for the following overview of drug treatment recommendations.

3. Disease Assessment

Rational drug therapy is based on a detailed assessment of disease status (activity and damage) and is directed towards clinically meaningful outcome variables. Unfortunately, there is neither a 'golden standard' nor any expert consensus regarding activity measures for SS. We concluded in a recent literature survey[10] that the clinical means to assess disease manifestations in primary SS are unsuited for selectively measuring disease activity. Moreover, there is currently no evidence to suggest that disease activity in primary SS can be accurately estimated by measuring only one or a few soluble immune activation products.

Outcome criteria are of multidimensional origin and define the overall impact of the disease. Outcome measures are absolutely necessary tools in clinical trials, but may also assist the routine management of the patients. However, guidelines for

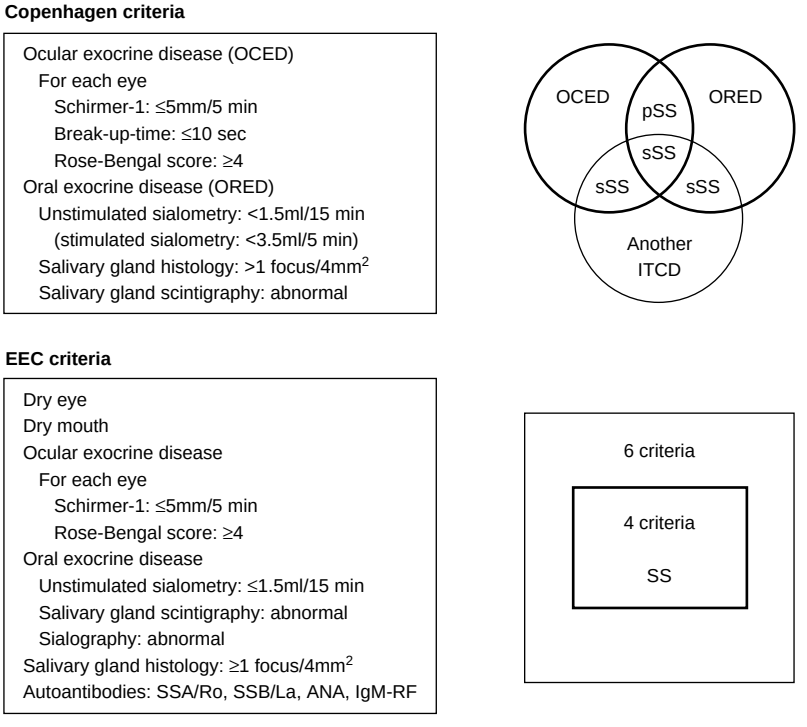

Fig. 1. The Copenhagen and EEC criteria for Sjögren's syndrome. In the Copenhagen criteria, ocular and oral exocrine disease both require that 2 of 3 tests give abnormal results. In the EEC criteria, ocular and oral exocrine disease as well as the presence of autoantibodies require just one test for each manifestation to be abnormal. **ANA** = anti–nuclear antibodies; **ICTD** = immunoinflammatory connective tissue disease; **IgM-RF** = immunoglobulin M rheumatoid factors; **pSS** = primary Sjögren's syndrome; **SS** = Sjögren's syndrome; **SSA/Ro** =anti SSA/Ro antibodies; **SSB/La** = anti-SSB/La antibodies; **sSS** = secondary Sjögren's syndrome.

choosing well recognised and easily measurable outcome variables in SS patients, so far as we know, have not been published.

4. Rational Drug Therapy Recommendations

As appears from the above, present understanding of SS does not allow an exact and evidence-based algorithm for therapeutic decision making. Clinical practice, however, requires rational guidelines, and these therefore need to be based mainly on empirical data. Another problem is that the recommendations given in the literature for treating SS are often directed towards a single, or at most a few, disease manifestations and only seldom towards the entire disease. One explanation may be that complete management of SS requires a collaboration between several specialities, and this can be difficult to accomplish. Given the above limitations, we present here a systematic overview of disease- and symptom-modifying drug therapies in use for SS.

4.1 Disease-Modifying Therapy

The aetiology of SS is largely unknown, and curative treatments are consequently not available. The pathogenesis of the disease, however, has to some extent been clarified and is supposed to be fundamentally immune mediated (see Price and Venables[11]). The evidence for exocrine autoimmunity is based on the findings of activated B and T lymphocytes and of autoantibody production in structurally and functionally damaged glands. Exocrine lymphoproliferation refers to the B lym-

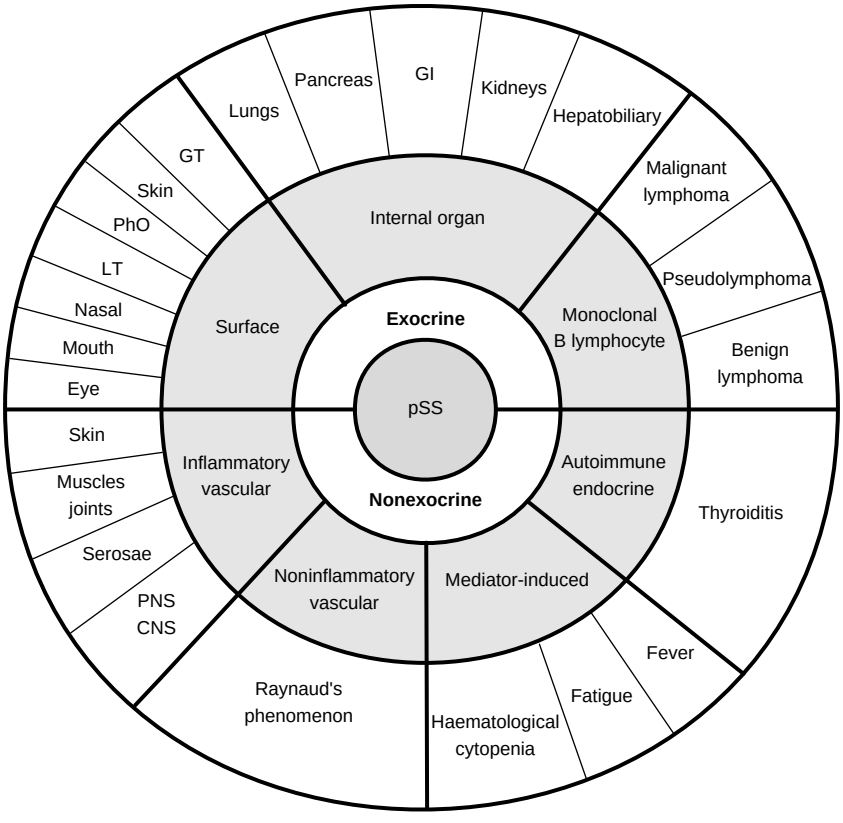

Fig. 2. The Copenhagen Classification Wheel for classifying the clinical disease manifestations of primary Sjögren's syndrome (pSS). **CNS** = central nervous system; **GI** = gastrointestinal; **GT** = genital tract; **LT** = laryngotracheal; **PhO** = pharyngo-oesophageal; **PNS** = peripheral nervous system; **pSS** = primary Sjögren's syndrome.

phocytes, and is assumed to be a highly selective process where transition in some patients from polyclonal to monoclonal activity ultimately may result in non-Hodgkin's lymphoma. Evidence for exocrine immunoinflammation is given by infiltration of the glands by activated lymphocytes, plasma cells and other inflammatory cells and by the production and expression of a number of cytokines and other immunoinflammatory mediators. Disease-modifying therapies with systemic immune-regulating (IR) or cytotoxic agents, directed towards suppressing the pathological autoimmune, lymphoproliferative and immunoinflammatory disease processes, may therefore be considered.

In brief, systemic IR therapy has been shown capable of controlling some of the essential immunopathological variables, but it is still uncertain whether this is followed by improvement in the cardinal manifestations of exocrine disease. In primary SS the disease-modifying drugs, therefore, largely apply to the treatment of severe internal organ exocrine disease, inflammatory vascular disease and malignant B lymphocyte disease[12] (see sections 4.1.2, 4.1.3 and 4.1.4). However, new drugs are continually under investigation,[13] and as an example, interferon-α_2 was recently shown in an open pilot trial[14] to improve lacrimal and salivary function.

4.1.1 Surface Exocrine Disease

Whether surface exocrine disease, including the diagnostic and cardinal manifestations of SS, may

or may not benefit from IR therapy is at present unclear. Table I shows results from reported clinical trials, in which key markers of surface exocrine disease and immunopathological status have been the subject of follow-up examination. The data suggest that several IR drugs are able to downregulate B lymphocyte activity, but it is uncertain whether the objective clinical status can be improved.

Hydroxychloroquine is the IR drug which has attracted most attention, probably because of its ability to influence primary immunopathological variables (table I)[17-19] and because of its effectiveness against certain nonexocrine manifestations (see section 4.1.4), while displaying only mild adverse effects. A placebo-controlled trial by Kruize et al.[18] could not demonstrate clinical effects on ocular and oral exocrine disease, while a retrospective, open-label study by Fox et al.[19] reported improvements in both exocrine and nonexocrine variables. Study design supports the conclusions by Kruize et al.,[18] while size of material and study length are in favour of Fox et al.[19]

Differences in selection of patients may also be an important factor as the San Diego criteria,[23] used by Fox et al.,[19] are weighted towards patients with provable immunopathological activity. In our opinion, the evidence is not yet sufficient to recommend hydroxychloroquine, or any other IR drug, as a routine treatment of the surface exocrine disease manifestations of SS patients. However, whether immunopathological active primary SS patients may benefit from long term treatment with hydroxychloroquine should be investigated further. Patients with painful recurrent parotid swellings, not due to infections or stone formation, may on an empirical basis be treated with low dose prednisolone. In order to aid the tapering of corticosteroid dosages, and with the same reservations as given above, hydroxychloroquine may be added.

IR drugs may also be used locally in the target organs. Thus, suppression of exocrinopathy in the ocular mucosa with topical cyclosporin is a promising new therapeutic approach,[24] which warrants further investigation.

4.1.2 Internal Organ Exocrine Disease

Immunopathologically active primary SS patients with severe or progressive manifestations from internal organ exocrine disease are candidates for systemic IR therapy. Unfortunately, recommendations cannot be based on controlled trials, but must rest on general clinical experience. Pancreatic, hepatobiliary and renal disease manifestations are usually subclinical or only display mild symptoms.

Table I. Reported clinical trials in which key markers of surface exocrine disease and of the immunopathogenesis of primary Sjögren's syndrome have been the subject for follow-up examination (reproduced from Oxholm and Asmussen;[10] with permission)

Drug	Dosage (mg)	Study design	No. of pts	Treatment period (mo)	Treatment-related changes					Reference
					clinical measures		immunopathological measures			
					ocular	oral	lymphocyte infiltration	autoantibody level	Ig level	
Prednisolone	40 qod	nc	7	6	Sch↑, RB↓		LSG↑			15
	30 qod	pl	8	6	Sch↔, RB↔	SF↔	LSG↔	↔	↓	16
Hydroxychloroquine	200/day	c	10	12	Sch↔	SF↔		↓	↓	17
	400/day	pl, co	19	12	Sch↔, RB,BuT↔	ScG↔	Gallium scan↔	↔	↓	18
	6-7/kg/day	nc	40	>24	Sch↑, RB↓	SF↑			↓	19
Cyclosporin	5/kg/day	pl	7	6			LSG↑			20
			10	6	Sch↔	SF↔	LSG↔	↔		21
Methotrexate	0.2/kg/wk	nc	17	12	Sch,BuT RB↔	SF↔		↔	↔	22

BuT = break-up time; **c** = control group; **co** = crossover; **Ig** = immunoglobulin; **LSG** = labial salivary gland; **nc** = no controls; **pl** = placebo group; **qod** = every other day; **RB** = Rose-Bengal score; **ScG =** salivary gland scintigraphy; **Sch** = Schirmer-1 test; **SF** = salivary flow; ↑ = improvement; ↓ = deterioration; ↔ = unchanged.

IR drug therapy is therefore seldom required. Pulmonary SS involvement is more likely to progress and, thus, to be the target of systemic IR therapy. Patients with interstitial lung disease are usually treated initially with moderate to high doses of prednisolone 0.5 to 1 mg/kg/day and azathioprine 1 to 2 mg/kg/day may be added, dependent on the effect and the ability to taper the corticosteroid. Alkylating cytotoxic drugs should be avoided because of the risk of the development of lymphoma.[12] If long term treatment with hydroxychloroquine could be shown to improve surface exocrine disease in immunopathologically active patients, mild to moderate manifestations due to internal organ involvement might be found to be responsive as well.

4.1.3 Malignant B Lymphocyte Disease

Malignant B lymphocyte disease requires specialised oncological treatment and is based on the histological grading and extent of the disease. Details are not within the scope of this article, but have been reviewed elsewhere.[25]

4.1.4 Inflammatory Vascular Disease

Mild inflammatory manifestations from skin, muscles and joints are generally regarded as the main indication for treating primary SS patients with hydroxychloroquine. The antirheumatic drugs penicillamine (D-penicillamine) and gold compounds cannot be recommended for primary SS patients because of an increased risk of adverse effects and because beneficial effects have not been proven. Experience with sulfasalazine in the treatment of primary SS is lacking. Except for cases of mild leukocytoclastic vasculitis in the skin, the vasculitic manifestations of primary SS often require systemic IR therapy (glucocorticosteroids and cytotoxic drugs) following the same recommendations as for other types of vasculitis. Anecdotal reports of rare case studies displaying various non-exocrine manifestations suggest a therapeutic role for other IR drugs as well, e.g. intravenous pulse cyclophosphamide[26] for myositis, plasmapheresis for acute transverse myelopathy[27] and high dose intravenous immunoglobulins for arthritis.[28]

4.2 Symptom-Modifying Therapy

The symptom-modifying therapies have a key role in the management of SS patients, especially because the cardinal exocrine disease manifestations appear to be inaccessible to pharmacotherapeutic disease modification. Criteria for assessing symptom-modifying drug therapies should be defined within the key measures of clinical status, primarily within the subjective target variables.

4.2.1 Exocrine Stimulation

Ocular Exocrine Disease

Bromhexine has a proven secretagogue effect when given systemically.[29] However, a certain amount of functional glandular tissue appears to be necessary. Thus, patients with some residual secretory function are those who benefit from treatment with bromhexine. An oral dosage of 16mg 3 times daily is recommended. If only a minor effect is observed after 3 weeks' treatment, an increase to 24mg 3 times daily should be tried. A soluble modification of bromhexine has recently shown effect *in vitro*.[30] Topical application of this drug might also be effective in patients, because high drug concentrations may be reached in the tear glands. Attempts to stimulate the tear glands with androgens have been promising.[31]

Oral Exocrine Disease

A low unstimulated sialometry with normal or moderately reduced stimulated sialometry suggests that there is some remaining functional capacity of the salivary glands. Such cases should be treated primarily with sugarfree chewing gum, and systemic stimulation of salivary flow. Pilocarpine, a parasympathomimetic drug, may be used for the systemic treatment of xerostomia/hyposalivation in SS patients. A dosage of 5mg 3 times daily leads to an increase in salivary output.[32] Adverse effects due to pilocarpine include sweating, frequent urination and gastrointestinal upset. The drug is contraindicated in patients with a history of gastrointestinal ulcer or uncontrolled asthma, and in those with acute iritis or narrow-angle glaucoma. Furthermore, pilocarpine should be used with caution

in patients with arterial hypertension or when used concomitantly with β-adrenergic antagonists.

4.2.2 Exocrine Substitution

Ocular Exocrine Disease

Frequent use of tear substitutes, in some rare cases as frequent as every 10 minutes, is the most important pharmacological modality for treating dry eyes. Many formulations are available.[33] A balanced composition of ions, mucomimetics and pH at or close to physiological levels appears to be important for optimum effect. The use of mucomimetics with growth factor has recently proven effective in the treatment of severe dry eye.[34]

Oral Exocrine Disease

Patients with low unstimulated and stimulated sialometry should preferably be treated with saliva substitutes. Mucin-containing substitutes are more satisfactory to the patients than preparations without mucin.[35]

Other Surface Exocrine Manifestations

Topical treatment of skin dryness with creams is often helpful. Vaginal dryness may be treated with lubricants and postmenopausal women may benefit from estrogen suppositories.

Internal Organ Exocrine Disease

Acidosis secondary to interstitial nephritis may need correction with oral potassium and sodium bicarbonate (1 to 2g 3 times daily). Expectorant drugs are useful to help symptoms of bronchitis.

4.2.3 Treatment of Exocrine Complications

Ocular Exocrine Disease

The consequences of longlasting dry eyes include the formation of corneal filaments composed of desquamated epithelial cells, mucins and debris adherent to intraepithelial nerve endings. This very painful condition may be treated with a combination of tear substitutes and topical mucolytics like acetylcysteine (*N*-acetylcysteine). Immediate improvement in patient comfort can be achieved by applying a thin bandage contact lens; however, this should only be used until the filaments have disappeared with treatment. Persistent corneal epithelial defects may lead to permanent reduction in visual acuity due to stromal scarring. Frequent use of tear substitutes may not be sufficient to prevent this, and the addition of topical antibiotics should be considered.

Severe dry eye in SS is not solely the consequence of reduced tear production. All epithelia of the eye region are involved in the immunoinflammatory process. In cases of severe keratoconjunctival inflammation permanent scarring, shrinkage and formation of symblepharon may be the result. In such cases topical steroids should be applied until the inflammation is controlled.

If topical tear substitutes, applied very frequently, are unable to prevent the conditions described above, occlusion of the tear drainage system should be considered. Closure may be performed reversibly with collagen or silicon plugs in the tear puncta. If sufficient effect is achieved, permanent closure is performed surgically.

Oral Exocrine Disease

The consequences of longstanding dry mouth include atrophic oral mucosa, oral candidiasis and dental caries. Oral candidosis of the erythematous (atrophic) type occurs in 25 to 30% of patients with primary SS. Topical treatment includes antifungal drugs such as miconazole gel or amphotericin B lozenges. Nystatin vaginal tablets may also be used as lozenges, but this drug dispensed as a mixture is not recommended in dentate patients because of the high sugar content in the vehicle. In the case of angular cheilitis a nystatin ointment may be used. Severe oral candidosis including the pseudomembranous type may be treated with fluconazole.

SS patients require frequent control of oral hygiene by their dentist, and topical fluoride treatment should be added in order to increase resistance to dental decay.

4.2.4 Treatment of Nonexocrine Disease Manifestations

Arthralgia and myalgia often benefit from symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).

Raynaud's phenomenon is difficult to treat, but calcium channel blockers such as nifedipine or α_1-

adrenoceptor antagonists such as prazosin may be effective and should be tried.

Fatigue is a common and most incapacitating complaint in primary SS patients, but until now has been resistant to any drug therapy. The fatigue, sometimes present along with sleeping disturbances, pain syndromes and depression, may, in these cases, benefit from antidepressant medications. However, the adverse effect of oral and ocular dryness from antidepressants should be borne in mind.

Intermittent fever can be treated symptomatically with salicylates or NSAIDs.

The haematological cytopenias rarely require medical therapy. If severe cytopenia is found, systemic lupus erythematosus (SLE) should be considered. Occasional severe thrombocytopenia can be treated with systemic IR drugs.

Both hyper- and hypofunction of the thyroid gland, requiring suppression/substitution therapy, may be associated with primary SS.

5. Conclusions

SS is an ICTD in which disease progression usually occurs during the early years after onset, and most patients will then experience a lifelong steady clinical status. In some cases, however, progressive development of multiorgan involvement occurs, and a few individuals eventually develop malignant lymphoproliferation. Although the immunopathogenesis behind this clinical scenario is partly clarified, the evidence which should recommend IR therapy is still sparse and empirical. To date, IR drugs have not been proved to be effective in the treatment of the cardinal exocrine manifestations from eyes and mouth. Consequently, symptom-modifying drugs, and in particular the tear substitutes, still have a key role in the treatment of SS patients.

On an empirical basis, IR drugs can be used in cases of severe or progressive manifestations from internal organs, as well as in cases of inflammatory vascular disease, mostly affecting skin, muscles and peripheral nerves. Malignant B lymphocyte disease requires specialised oncological treatment. Future directions for rational drug therapy of SS should evolve from the increasing insight into the fundamental immunopathogenetic disease processes, and should be documented in controlled long term clinical trials involving patients diagnosed and assessed in a standardised and validated fashion.

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