Sjogren's syndrome
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Chapter 1
General introduction
General introduction

The historical development of what currently is defined as Sjögren syndrome (SS) begins with the description of Hadden in 1888 who noted an association between the presence of a dry mouth and dry eyes in a 65-year old female patient who also suffered from loss of taste and smell. When she was treated with a tincture of jaborandi (pilocarpine) three times a day, her mouth became much more moist. (1) Also in 1888, Mickulicz described a 42-year old farmer with painless, extensive bilateral swelling of parotid and lacrimal glands. The swelling disturbed his vision and interfered with eating. Mickulicz removed the greater part of the swollen lacrymal glands. Unfortunately, a few months after surgery the patient suddenly died, probably due to appendicitis. At that time, the diagnosis was not conclusive. (2) However, the original woodcuts and colour plate of the drawing of a microscopical field of the submandibular gland have been reviewed with our current knowledge and a diagnosis of MALT lymphoma was made, a condition that rather frequently is observed in patients with SS. (3)

In 1925 the French physician Gougerot related dry eyes and dry mouth to an exocrine gland abnormality. (4) However, in 1933 Henrik Sjögren was the first to give a complete description of the clinical and histological findings in patients with rheumatoid arthritis, dry eyes and a dry mouth. In his thesis entitled ‘Zur Kentniss der Keratoconjuntivitis sicca’ he presented clinical and pathological information of 19 cases of patients with such complaints. (5) Sjögren stated that his major contribution has been the recognition of the sicca syndrome as a systemic disease. At first there was a lot of criticism on his thesis and only years later he received more credit for his work. His thesis was translated in English by Hamilton in 1943. (6) The eponym Gougerot-Sjögren’s disease appeared in the literature in the 1930-ies and was reduced to Sjögren’s disease a decade later due to the many cases reported by Sjögren.

In 1965 Bloch described the same condition as a triad of keratoconjunctivitis sicca, xerostomia and a connective tissue disease. (7) Based on this triad several sets of criteria have been introduced in the eighties of the previous century, (8-11) but none of these classification criteria were validated and universally accepted. In 1988 the European Study Group on Classification Criteria for SS began a multicentre study in order to develop a set of criteria. (12;13) This set of criteria received broader acceptance, although criticism was raised as well. Therefore, a joint study of the European Study Group on Classification Criteria for SS and a group of American experts was started. Presently, the revised American-European classification criteria for SS, which were proposed in 2002, are the most widely accepted and validated criteria (table 1). (14) These criteria combine subjective symptoms of dry eyes and dry mouth with objective signs of keratoconjunctivitis sicca and hyposalivation, and with serological and histopathological characteristics. It should be mentioned that the revised American-European classification criteria for SS have not been developed for clinical practice, but as a research tool for performing studies in patients with SS. Nevertheless, they are now widely accepted as diagnostic tools for SS. One should realize, however, that SS can be present in a patient who does not completely fulfil these criteria.
Table 1 Revised international classification criteria and revised rules for classification for SS (14).

I Ocular symptoms: a positive response to at least one of the following questions:
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than 3 times a day?

II Oral symptoms: a positive response to at least one of the following questions:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for a least one of the following two tests:
   1. Schirmer’s I test, performed without anaesthesia (≤5 mm in 5 minutes)
   2. Rose Bengal score or other ocular dye score (≥4 according to Van Bijsterveld’s scoring system)

IV Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue

V Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
   1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes)
   2. Sialectasia on parotid sialography
   3. Abnormal salivary scintigraphy

VI Autoantibodies: presence in the serum of the following autoantibodies:
   1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:
   a) The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (histopathology) or VI (serology) is positive or
   b) The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)

For secondary SS
In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)
Although the first description of SS was given in 1888 and although SS is the second autoimmune disease in prevalence (0.5-2%), only recently knowledge about SS has become more generally recognized and over the last decades an increasing number of studies is performed on SS. The first symptoms of SS usually develop gradually and are hard to recognize without specific knowledge about SS. First symptom in almost all patients is fatigue accompanied by one or more other symptoms such as oral and eye dryness, arthralgia and extraglandular manifestations. Fortunately, SS is diagnosed more and more in an early stage of the disease nowadays. Currently, more patients are within their working age at the time of diagnosis (mean age 45.7±15.7 years).(15) The influence of having SS on patients functioning and daily activity is still underestimated by both the general public and physicians. Most patients with SS report a large impact of the disease on their quality of life.(15) Moreover, related to the limitations patients experience in their daily life, there is a growing request for treatment options, both from doctors and patients. Although, as for other autoimmune diseases, the aetiopathogenesis of SS is still unknown, there are indications that treatment with biological agents applied for other autoimmune diseases might also be of benefit in the treatment of SS. (16) So far, B cell depletion showed the best results amongst the biologicals tested. (17-20)

Before implementation of treatment of SS with biological agents can be realized, approval should be obtained. Treatment with biological agents is expensive and positive impact on socioeconomic status of SS patients should be clear before implementation. Biological agents have to be investigated, first, in small open-label phase I trials to investigate safety and efficacy and, thereafter, in double-blinded placebo controlled phase II trials and larger phase III trials to confirm results found in the open-label trials. Also, research on the aetiopathogenesis of SS is very important to gain more knowledge on the disease.

Although many trials have been performed during the last decades regarding treatment of SS, including trials aimed at reducing disease activity and/or intervening with the progression of the disease, up to now most agents that have been shown to be of some use in the treatment of SS mainly exert a symptomatic effect. The assessment of the effect of biologicals, aimed at reducing disease activity and to slow down progression of SS, is still at a very early stage. Also, much remains unknown regarding the aetiopathogenesis of SS.

Therefore, the main objective of this thesis is the evaluation of existing and new therapeutic strategies for intervention in SS. Furthermore, the impact of SS on quality of life was assessed and a case report is described aiming to deepen the insight in the role of B cells in the aetiology of SS.

Outline of this thesis

This thesis contains the results of various studies concerning (a) quality of life of SS patients, (b) the applicability of tools to evaluate the efficacy of treatment in SS patients, (c) the evaluation of intervention therapy with anti-CD20, a therapy that is focussed on B cell depletion, and (d) a case series to gain more insight into the role of B cells in the aetiology of SS.
The impact of SS on the quality of life and the socioeconomic status of SS patients is described in chapter 2. This study was done to explore whether treatment is necessary for SS patients and why research on this disease should be performed. Next, in chapter 3 a specific overview of the trials performed up to 2006 with biological agents as treatment for SS is given. The main conclusion from that overview is that anti-CD20 in particular seems to be promising. In chapter 4a, a general overview of tools applicable for treatment evaluation of diseases affecting salivary glands, in particular SS, is provided. On the basis of this overview tools to be used in treatment evaluation (chapter 5) were selected. The possibility of indentifying a genomic and proteomic profile of SS patients as a new tool for evaluation is described in chapter 4b. Based on the data published in chapters 2 and 3 and using a selection of the tools provided in chapter 4, several trials with anti-CD20 (rituximab) as intervention treatment for SS were designed. First, an analysis of the efficacy of retreatment and long-term follow up after treatment (chapter 5a) is described. In chapter 5b a study is presented evaluating the effects of rituximab on the histopathology of parotid gland biopsies in patients with SS described in chapter 5a. Thereafter, a placebo controlled double blinded randomized clinical trial of rituximab treatment in SS (chapter 5c) is described. A study related to the direct scope of this thesis, is the description of a case series of 8 patients in which the combination of nodular cutaneous amyloidosis and SS is present. (chapter 6) The type of amyloid was probably AL amyloid in all 8 patients (immunoglobulin light chain-associated amyloid). Therefore, the combination of cutaneous amyloid and SS appeared to be a distinct disease entity reflecting a particular and benign part of the polymorphic spectre of B cell dysfunction in lymphoproliferative diseases related to SS. Chapter 7 contains the summary and general discussion and chapter 8 the Dutch summary.
Reference List


