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Clinical aspects of primary and secondary Sjögren's syndrome

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Rada Moerman

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A word aptly uttered or written cannot be cut away by an axe.

Nikolai Gogol

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Introduction

Introduction

Sjögren's syndrome (SS) is a systemic rheumatologic disorder which primarily affects salivary and lacrimal glands, but also is accompanied by other manifestations with involvement of many tissues and organs of the human body.¹ SS can be present as single auto-immune disease, called primary SS. SS can also be associated with another auto-immune disease, like systemic lupus erythematosus (SLE), systemic sclerosis, myositis or dermatomyositis, mixed connective tissue disease or rheumatoid arthritis (RA), called secondary or associated SS. Due to lacrimal and salivary gland involvement, patients experience complaints of dryness of eyes and mouth, called keratoconjunctivitis sicca and xerostomia, or sicca symptoms. Next to multiple other well-defined organ manifestations, profound fatigue and diffuse pain are frequent symptoms of the disease.

The severity of the disease varies tremendously ranging from very mild disease without any organ involvement to lethal manifestations. It has been demonstrated that patients with SS have increased risk of cardiovascular and cerebrovascular disease.^{2,3} Furthermore, patients with SS are at increased risk of malignancies, especially the development of hematological cancer.⁴ Although several studies did not demonstrate the increased overall risk of all-cause mortality compared to general population in several cohorts with SS patients^{5,6} there is a distinct group of SS patients who are certainly at increased risk of mortality. This concerns the group with severe disease, requiring aggressive treatment and close follow-up.⁶ Several factors have been identified to determine which patients are at increased risk. These are male patients, especially those with extraglandular manifestations, patients with vasculitis, persistent parotid gland enlargements, low complement levels, high levels or increasing levels of rheumatoid factor and IgG and cryoglobulinemia.⁷

Because fatigue and pain are almost always present, the burden of the disease is high, even if there are no life-threatening complications. Patients experience brain fog (i.e. confusion, forgetfulness and lack of focus and mental clarity). Furthermore, patients with SS have significantly decreased health-related quality of life and socio-economic status.^{8,9,10} Moreover, patients with SS have also a diminished quality of life compared to patients with other rheumatic diseases, such as rheumatoid arthritis or fibromyalgia, and have comparable level of disability to patients with SLE despite of a much higher frequency of organ involvement in SLE.^{11,12}

Epidemiology

Originally, in the beginning of the 20th century when little was known about SS, the disease was considered as rare. However, in the beginning of the 1990s, awareness of SS

increased, more research in the SS area was performed, the ability to diagnose SS was improved, resulting in an increase in reported prevalence. Nowadays, the prevalence and incidence of primary and secondary SS have been investigated in multiple studies. The results of epidemiological studies show large variation, probably due to different populations investigated (general population vs. population from a tertiary centre), classification criteria used, different research methods and differences in geographic and ethnical distribution of SS. The estimated prevalence of primary SS is 0.04–1%.^{13,14} A recent systematic review and meta-analysis reported pooled prevalence rates of 19.5% for secondary SS associated with RA and 14.0% for SS associated with SLE.¹⁵ The peak incidence of primary SS is at age 40–55 years.

Although there is a clear predominance of women with SS over men, with an estimated female to male ratio of 9–14 to 1^{13,16,17}, it is important to mention that men have more frequently and more severe extraglandular manifestations and therefore usually suffer from a more severe form of disease, regardless of lower risk to develop SS.¹⁸

Although the onset of SS is uncommon in children, there are more than 200 cases of pediatric SS reported in the literature. The age at SS diagnosis in children ranges from 4 to 16 years (mean age 9.8 years). Female to male ratio is 5:1.¹⁹

There are conflicting results on prevalence of SS in elderly patients. Botsios et al.²⁰ found the disease onset after 65 years in 6% of the patients while Ramos-Casals et al.²¹ reported higher onset of SS in the elderly of 15%. A study from Norway reported the prevalence of SS approximately seven times higher in the elderly population compared to middle aged patients.²² The researchers all agree that the age at diagnosis plays an important role in the clinical manifestations of SS and that SS is being recognized better and earlier nowadays also in the elderly.

Geographic and ethnical differences in epidemiology of SS are reported as well. In the Big Data Sjögren Project Consortium analysis is found that SS was diagnosed 7 years earlier in African-American than in Caucasian patients, the female-to-male ratio was highest in Asian patients (27:1) and lowest in African-American patients (7:1). Asian patients had lowest prevalence of sicca symptoms.²³

Pathogenesis and histopathology of SS

The etiopathogenesis of SS is very complex and still not fully understood. Genetic, epigenetic, gender-related and environmental factors (e.g., virus infections) are suggested to play a role in the development of the disease.²⁴ Both the innate and adaptive immune systems are involved. Evidence for involvement of innate immune system in the

etiopathogenesis of SS comes from the interferon-signature.²⁵ Activation of IFN type I promotes production of chemokines and cytokines and adaptive immune response through activation of T and B cells. Chemokines, such as CXCL10, are the driving force of initial recruitment of lymphocytes towards the glandular tissue. Chemokines such as CXCL12, CXCL13, CCL19 and CCL21 play an important role in expansion and perpetuation of the local inflammatory infiltrate. Therefore, the histopathological findings of lacrimal and salivary glands comprise periductal focal mononuclear infiltrates composed of T and B cells, plasma cells, macrophages and dendritic cells.²⁶

Although there are many different kinds of immune cells involved in the pathogenesis of SS, the hallmark of SS appears to be B-cell hyperactivity, as reflected by multiple serological manifestations of the hyperactive B-cells, like high serum IgG levels, elevated rheumatoid factor, autoantibodies, like anti-SSA/SSB and ANA, elevated levels of polyclonal or monoclonal free light chains, β 2-microglobulin, cryoglobulins and increased risk of the development of hematologic malignancies, for example non-Hodgkin B-cell lymphoma.²⁶ Furthermore, the epithelium of the lacrimal and salivary glands plays an important role, and therefore the disease is also named 'autoimmune epithelitis'. The epithelial cells, in particular the ductal cells, are not only an important source of autoantigens and target of the disease but also has immunological functions, including cytokine and chemokine production (like BAFF, IL1, IL6, TNF alpha, IL22, CXCL10, CXCL13, and many others) and antigen presentation (their surface express major histocompatibility complex (MHC) class II molecules, and co-stimulatory molecules).²⁷

In salivary gland tissue, and predominantly in the parotid glands, there is development of lymphoepithelial lesions, formed by hyperplastic and multilayered epithelium in association with infiltrating lymphocytes. There is also an increased number of IgG instead of IgA producing plasma cells in the salivary and lacrimal glands, as a reflection of aberrant B-cell activity. Furthermore, in the course of the disease, the size of the infiltrates increases, and may develop to ectopic lymphoid tissue and the presence of germinal centers.²⁸ As a result of all these above described processes, progressive infiltrates develop in salivary and lacrimal glands along the striated ducts and impair their function due to destruction of glandular tissue.

When diagnosing a SS patient, the clinician expects from the pathologist a report of salivary gland histology with respect to (1) the presence (or absence) of the focus score (FS), (2) a shift of IgA to IgG producing plasma cells, (3) lymphoepithelial lesions and (4) germinal centers. A focus is defined as a cluster of 50 or more mononuclear lymphoid cells located around the striated ducts, while the tissue surrounding the foci is composed mainly of unaffected salivary tissue. The focus score is the number of foci per 4 mm² salivary gland tissue. A FS ≥ 1 (one or more foci) is a histopathologic criterion for

SS.²⁹ The FS is included in the most recent classification criteria of SS.³⁰ It is important to mention that FS is often confused with the older scoring method proposed by Chisholm and Mason (score 0-IV).³¹ In this scoring system ≥ 50 lymphocytes per 4 mm^2 is still called focus, but the report gives score 0: absence of infiltration; score 1: slight infiltration; score 2: moderate infiltration less than one focus; score 3: one focus; 4: more than one focus.

The foci are composed mainly of T- and B- lymphocytes and several other mononuclear cells which may develop organized ectopic lymphoid structures, containing all components to carry out immune responses. Besides FS there are lymphoepithelial lesions (LELs) and shift of IgA positive to IgG positive plasma cells characteristic for SS. Lymphocytic infiltrates are arranged around striated ducts. The interaction of lymphocytes and the ductal epithelial cells results in formation of LELs that are composed of proliferative epithelial cells and lymphocytes. These LELs are predominantly present in parotid glands rather than in labial glands.³² Furthermore, there is still no consensus about clear definition of a germinal center. Staining with CD21, CD20, CD3 and Bcl-6 is required as relying only on CD21 staining overestimation of germinal centers can occur.^{33,34}

A sufficient area of salivary gland tissue has to be examined, as different sections taken from the same salivary gland specimen can show different results.³² Therefore, the minimum amount of tissue assessed by the pathologist to make a good evaluation whether SS is present or not, is 8 mm^2 .³³

Classification criteria and diagnosis of SS

Despite of tremendous improvements in the field of SS research, the diagnosis of SS stays a difficult diagnosis. The mean time between the onset of symptoms and the diagnosis of SS is often several years. There is no single diagnostic test for SS, on the contrary, an experienced, dedicated multidisciplinary team is requested to establish the diagnosis of SS. The required specialists are a rheumatologist, an ophthalmologist (to assess ocular involvement), an oral and maxillofacial surgeon or specialist in oral medicine (to assess salivary glands involvement) and a pathologist (to assess the salivary gland biopsy). Rheumatologist (preferably with ultrasound skills) evaluates all signs, symptoms, serologic parameters and clinical manifestations of the disease and finally diagnoses SS based on the collected data. In addition, heterogeneity of clinical presentations with different and often age- and gender-dependent manifestations of the disease further complicates the diagnostic work up.

The clinical features of SS are characterized by three distinct disease manifestations: glandular features, extraglandular organ manifestations and fatigue and pain. The differential diagnosis is broad and includes medication-related dryness, radiation injury, infections (Hepatitis C, HIV), other auto-immune diseases, including IgG4 and sarcoidosis, amyloidosis, graft versus host disease, metabolic diseases and fibromyalgia.

To help the physicians in the violence of clinical struggle and to perform uniform scientific research, more than 12 classification criteria for SS were introduced since 1965. The AECG criteria proposed by the American-European Consensus Group in 2002 were until recently most widely used in studies and clinical practice (Table 1).³⁵ The AECG criteria can be used to classify primary and secondary SS. Criteria for primary SS contain subjective ocular and oral symptoms (I-II), objective oral and ocular signs of keratoconjunctivitis sicca and xerostomia (III,V), histopathology findings and serological parameters (IV,VI). Patients can be classified as having SS if four of six criteria are met, including a positive biopsy or the presence of auto-antibodies. Another possibility to classify patient as having SS according to AECG criteria is the presence of any three of the four objective items (III-VI). Criteria for secondary SS are the presence of an associated well-defined connective tissue disease and any one of I and II plus any two of items III, IV and V. The exclusion criteria for primary and secondary SS are listed in table 1.

In 2012 ACR criteria were developed (Table 2), citing 'The need for new classification criteria is clear considering the current lack of standardization inherent to the use of multiple older criteria in the field, and the emergence of biological agents as potential treatments'.³⁶ These criteria contain only objective items including a serological presence of rheumatoid factor and ANA titer $\geq 1:320$. Furthermore, compared to AECG criteria, ocular staining score was added and in the exclusion criteria the addition of IgG4-related disease and amyloidosis and the exclusion of the use of anticholinergic drugs was performed. The ACR criteria did not contain any sicca symptoms evaluation and made no distinguishing remarks concerning primary and secondary SS.

These 2012 ACR criteria were still not embraced by the Sjögren's community, as the subjective items were not included and the ocular staining score needed involvement of trained expert ophthalmologists. Therefore, the American College of Rheumatology and the European League Against Rheumatism developed the international consensus on classification criteria, the 2016 ACR/EULAR classification criteria of SS (Table 3).³⁰ Patients with a single sicca complain from 2002 AECG questionnaire or patients with any possible extraglandular manifestation as defined by EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)³⁷ can enter the classification criteria analysis. The ocular staining score threshold is increased from 3 to 5 compared to 2012 ACR criteria. Serological criterion is changed from SSA/SSB positivity to only SSA positivity as anti-SSB positive

and anti-SSA negative patients have other phenotypic features of SS.³⁸ Furthermore, ACR/EULAR SS criteria are validated only for primary SS and it is still a question if these criteria are applicable to secondary SS patients. These criteria should still be validated in cohorts with secondary SS patients. The sensitivity (96%) and specificity (95%) of the 2016 ACR/EULAR classification criteria of SS are high, tested against the expert opinion of well-trained clinicians as golden standard.

The main purpose of developing classification criteria was to define a homogenous population of SS patients for clinical trials. Therefore, classification criteria should always be used with caution when diagnosing a single patient as these are not diagnostic criteria. The golden standard for diagnosis of SS still remains the clinician's expert opinion. A patient can clinically be diagnosed as suffering from SS, while he or she does not fully comply with the classification criteria. Possibly ultrasound of salivary glands can give additional clinical value to make the accurate diagnosis of SS, as the B-mode ultrasound of the major salivary glands was found a reliable imaging technique for patients with clinically suspected SS.³⁹ The salivary glands of patients with SS can be evaluated with respect to the glandular size (i.e., normal, increased, decreased), parenchymal echogenicity, parenchymal inhomogeneity and posterior border (visible/non-visible). The specificity and sensitivity of these findings are 90% and 69% respectively.^{40,41,42}

Assessing the disease activity of SS

As mentioned earlier, the clinical features of SS are characterized by three distinct disease manifestations: glandular features, extraglandular organ manifestations and fatigue and pain.

Assessment of glandular features includes anamnesis of sicca symptoms, using questions from sicca questionnaire from the AECG 2002 classification criteria (Table 4), measurement of the production of unstimulated whole saliva (UWS) and ophthalmological evaluation, including Schirmer's test and ocular staining score (OSS). Ultrasonography is a promising diagnostic examination to assess salivary glands in SS and is under current research in order to determine the place of this simple and broad available tool in daily clinical practice.⁴³ Furthermore, glandular tissue biopsy is an important part in assessing the disease activity.

Regarding to extraglandular manifestations important steps were taken in the past decade with the development of a systemic disease activity index of primary SS by the EULAR task force, the ESSDAI.⁴⁴ ESSDAI assesses the systemic disease activity by evaluating 12 domains or organ systems (cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, haematological,

glandular, constitutional, lymphadenopathic and biological). Each organ system should be evaluated and weighted into the levels of activity (0: no activity; 1: low activity; 2: moderate activity; 3: high activity). According to ESSDAI, a patient has low activity of SS if total score <5; moderate activity of SS if score 5-13; and high activity if score ≥ 14 . ESSDAI is developed as a golden standard to assess the disease activity and as a primary outcome measure in clinical trials. ESSDAI showed a good sensitivity to change in independent cohorts in clinical trials with rituximab.⁴⁵ But, there is still no registered effective therapy for SS, and in the absence of an effective therapy it is challenging to assess the sensitivity to change of the ESSDAI and therefore doubtful if the ESSDAI is the right instrument.

However, ESSDAI is also an important tool in the daily clinical practice, providing systematic approach for assessment of SS patient. In 2016 ClinESSDAI was developed, representing the same domains of ESSDAI, but without biological domain, as immunological tests are not always available.⁴⁶ ClinESSDAI can also be used in clinical trials to evaluate clinical responses after biological therapies, as many therapies influence biological domain, lowering the total ESSDAI score, but not necessary giving clinical improvement.

Furthermore, to assess the systemic disease activity several biomarkers are used in daily clinical practice. These biomarkers are serum IgG levels, rheumatoid factor, serum cryoglobulins, anti-SSA/SSB, ANA autoantibodies, low serum complement C4 and lymphopenia.²⁶ These parameters are considered as risk factors for the development of high systemic disease activity and/or the development of MALT lymphoma.

For the assessment of fatigue and pain, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) was developed.⁴⁷ ESSPRI is a very simple and patient centered tool consisting of only 3 questions, designed to assess patient symptoms of dryness, physical fatigue and pain in primary SS patients using a single 0-10 numerical scale for each domain. Although ESSDAI and ESSPRI correlated poorly to each other in clinical studies, these two are still important to assess simultaneously, as these tools measure two different components of the disease and are complementary to each other.

Table 1. The American-European classification criteria for SS.³⁵

- 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 at 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. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts
 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
- VI. Autoantibodies: presence in the serum of the following autoantibodies: 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 (Ocular signs), IV (Histopathology), V (Salivary gland involvement), or VI (Serology)).

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)

Table 2. 2012 American College of Rheumatology classification criteria for SS.³⁶

1. Positive serum anti-SSA and/or anti-SSB or positive rheumatoid factor and ANA $\geq 1:320$;
2. Keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years);
3. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with focus score ≥ 1 focus/4mm ² .

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the 3 features.

Exclusion criteria:

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency disease (AIDS)
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Table 3. 2016 ACR-EULAR classification criteria for SS.⁴⁸

Entry criterium: sicca symptoms (at least one positive answer on the questions in Table 4) or EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) ≥ 1

Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm ²	Score 3
Anti-Ro/SSA positive	
Score 3	
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	Score 1
Schirmer test ≤ 5 mm/5 minutes in at least one eye	Score 1
Unstimulated whole saliva flow rate ≤ 0.1 mL/minute	Score 1

The classification of primary SS applies to any individual who meets the entry criterium, does not have any of the conditions listed as exclusion criteria, and has a score ≥ 4 when the scores from the five criteria items are summed.

Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness.

Exclusion criteria:

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency disease (AIDS)
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Table 4. Patient questionnaire for the assessment of xerostomia and ocular dryness based on sicca questionnaire from the AECG 2002 classification criteria.³⁵

1. Did you have 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?
4. Did you have daily feeling of dry mouth for more than 3 months?
5. Did you have recurrently or persistently swollen salivary glands as an adult?
6. Do you frequently drink liquids to aid in swallowing dry food?

Table 5. The difference of AECG and ACR-EULAR exclusion criteria.

AECG	ACR-EULAR
Past head and neck radiation	Same
Acquired immunodeficiency	Same
Sarcoidosis	Same
Graft versus host disease	Same
Pre-existing lymphoma	Deleted
Current use of anticholinergic drugs	Evaluation after stopping these drugs
Hepatitis C infection	Restricted to patients with positive PCR
	New: IgG4-related disease

Treatment of SS

SS is a chronic disease. Until now there is no curative treatment available. As there are three main domains in disease activity: the sicca domain, the systemic manifestation domain, the pain and fatigue domain, treatment of these three domains will be discussed separately.

Treatment of sicca domain is mainly symptomatic with local lubricating agents.⁴⁹ If there is inflammation of the mucous membrane or cornea, anti-inflammatory agents can be used. If patients have rest function of salivary or lacrimal glands, pilocarpine and cevimeline can be used to stimulate the production of saliva and tears.⁵⁰ There are still no systemic drugs to completely restore the function of salivary or lacrimal glands. Several trials with rituximab were performed to evaluate the salivary gland function after treatment. Two studies showed significant improvement in unstimulated salivary flow after rituximab treatment, however, other trials were not able to confirm this effect.^{51,52,53,54}

Regarding to the treatment of systemic manifestations, there are synthetic disease modifying antirheumatic drugs (sDMARD) therapies available as well as biological DMARD therapies. Depending on the organ manifestations several sDMARDs can be used, like prednisolone, hydroxychloroquine, methotrexate, cyclophosphamide, azathioprine and mycophenolate mofetil.⁵⁰ No single biological DMARD has yet been approved for the treatment of SS. Although several trials with rituximab showed a significant decrease of

ESSDAI score following the treatment, a substantial heterogeneity is observed regarding the effect of rituximab on systemic manifestations.^{51,52,54,55} Other biological DMARDs like anti-tumor necrosis factor inhibitors (anti-TNF), belimumab and abatacept have been evaluated. Anti-TNF agents were not effective in pSS.^{56,57,58} Belimumab was evaluated in an open-label study with 30 pSS patients and found a modest reduction of dryness and improvement in parotid enlargement, arthritis and arthralgia.⁵⁹ Abatacept showed promising results regarding to safety, tolerability and possibly had effect on extraglandular manifestations in two small open-label studies.^{60,61} Phase III trial investigating abatacept has recently been published, but showed negative result on primary end point.⁶²

Fatigue and pain are often seen by a physician as relative benign features of SS and are often underestimated and not discussed with the patient. However, these features of SS are the cause of significant patient's disability. There is still too little understanding of the real impact of fatigue and pain on SS patients. The pathogenesis of fatigue and pain are also not yet clarified. Therefore, there is less attention to the treatment of fatigue and pain in daily clinical practice. The first step in the treatment of fatigue and pain are self-care measures, including advices about physical exercises to reduce these symptoms.⁶³ According to expert opinions and a retrospective trial,⁶⁴ fatigue and pain are sometimes treated with hydroxychloroquine. Treatment of fatigue and pain in SS is investigated in clinical trials with rituximab. Although the effect size was small, most studies showed improvement of fatigue, but no improvement of pain and tendinomyalgia.^{54,65,53,66}

Aim of this thesis

The overall aim of the research reported in this thesis was to assess major clinical manifestations and potential biomarkers of primary and secondary SS in order to make a step forward to a better understanding of the disease and to improve care for SS patients.

Chapter 2 focuses on general aspects of SS with emphasis on elderly patients. Several diagnostic and therapeutic challenges in elderly patients with SS are discussed. The paper provides a detailed, clinically orientated guide to the etiology, diagnosis and management of elderly patients with SS.

Chapter 3 evaluates the performance of ESSDAI score in patients before and after rituximab treatment. The study described in this chapter was a sub study of the randomized controlled rituximab trial of Meijer et al.⁵¹ In 2010 ESSDAI score has not been developed yet, but the analysis of the trial showed a significant improvement of extraglandular manifestations after rituximab treatment. Therefore, in request of the EULAR task force, we retrospectively calculated the ESSDAI score to evaluate the usefulness of ESSDAI for clinical studies and assessed responsiveness of ESSDAI after

rituximab treatment. Our sub study was the first study assessing the responsiveness of ESSDAI in patients with pSS in a randomized controlled trial.

As discussed earlier, there is no uniform treatment for all SS manifestations available. Therefore, several extraglandular manifestations can be evaluated and treated separately. Articular involvement is the most frequent extraglandular manifestation in pSS.^{21,67} The ESSDAI score makes it possible to assess the systemic disease activity of pSS patients for clinical trials and daily practice. However, it is difficult to show the effect of treatment on a single domain or organ manifestation, e.g. arthritis, in clinical trials due to the composed nature of the ESSDAI. There is need for a validated tool to evaluate the articular involvement in pSS. In **Chapter 4** we used the Disease Activity Score of 28 joints (DAS-28) to assess the effect of rituximab and abatacept treatment on the articular domain of the ESSDAI in pSS patients.

Levels of FLC reflect the actual activity of the antibody secreting compartment, and elevated levels may be indicative for B-cell hyperactivity. In **Chapter 5** the possible biomarker to evaluate systemic disease activity of SS with serum immunoglobulin free light chains (FLC) was assessed. Furthermore, we evaluated FLCs as possible biomarkers for evaluation of MALT lymphoma and response to the treatment.

Daily fatigue and pain are important limiting factors of the daily activities in patient with SS.^{9,8,10} In the study described in **Chapter 6** patient's experience regarding the importance of fatigue was evaluated in relation to other symptoms as well as the effect of rituximab treatment on fatigue in 28 pSS patients treated with rituximab in our open-label rituximab trial. Symptoms of physical fatigue, pain and mental fatigue were scored and analyzed (according to ESSPRI questionnaire and MFI).

There are only a few studies available, focusing on sicca complaints and SS in patients with an associated connective tissue disease. **Chapter 7** describes a prospective cohort of rheumatoid arthritis patients with 10 years follow-up with respect to sicca complaints and occurrence of secondary SS. The recognition of SS in RA patients might have implications for treatment choices.

In **Chapter 8** the current therapies available for SS were reviewed with respect to the safety of symptomatic treatment, systemic stimulation of tears and saliva and the effectiveness and safety of synthetic and biological agents in the treatment of SS.

Chapters 9 provides a general discussion based on the results of these studies and future prospectives are made.

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2

Sjögren's Syndrome in Older Patients: Aetiology, Diagnosis and Management

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Abstract

Sjögren's syndrome (SS) is a systemic autoimmune disease, characterized by chronic inflammation of exocrine glands that results in development of xerostomia and keratoconjunctivitis sicca. The disease activity of SS is not restricted to exocrine glands, and many other organs and organ systems can be involved. Diagnosis of SS in the elderly population can be challenging because xerostomia, dry eyes, symptoms of fatigue, weight loss and muscle pain are also common features of old age. Delay between clinical onset and diagnosis of SS in the elderly may be due to the shared features of SS and old age. The 2002 revised American–European Consensus Group (AECG) classification criteria for SS are the preferred tool used to confirm diagnosis of SS, but recently alternative criteria have been put forward by the American College of Rheumatology (ACR). The AECG criteria set combines subjective symptoms of dry eyes and dry mouth with objective signs of keratoconjunctivitis sicca, salivary gland dysfunction and histopathological (salivary gland biopsy) and serological (autoantibodies against SSA/Ro and SSB/La antigens) features. Treatment of SS in the elderly does not differ from that in younger patients. The aims of the treatment of SS are to control glandular and extraglandular manifestations, to prevent damage to organ systems and loss of function, and to decrease morbidity and mortality. Treatment of the elderly can be complicated by co-morbidities, an increased rate of adverse events related to therapeutic agents, and polypharmacy. Therefore, careful follow-up of the treatment is required.

Introduction

Sjögren's syndrome (SS) is a systemic rheumatic disease characterized by progressive focal lymphocytic cell infiltration and destruction of exocrine glands. In particular, salivary and lacrimal glands are affected by SS, leading to dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS is in many cases a primary, idiopathic condition of unknown aetiology [primary Sjögren's syndrome (pSS)]. The syndrome may, however, also be secondary to other connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma and mixed connective tissue disease. In these cases, the condition is designated as secondary Sjögren's syndrome (sSS).^{[1][2][3][4,5]}

In the elderly, clinical presentation of SS can be atypical, and in some cases, it is difficult to distinguish SS from SLE-SS or SLE. The autoantibody profile of both diseases is similar. For example, autoantibodies to SSA/Ro and SSB/La and rheumatoid factor (RF) are also found in patients with SLE.^[6] Furthermore, SS is associated with organ-specific autoimmune diseases such as thyroid disease, primary biliary cirrhosis (PBC) and autoimmune gastritis.^[7,8] The disease course results in a significant morbidity, limiting patients' daily activities, participation in society and quality of life.^[9]

There are several diagnostic and therapeutic challenges in elderly patients with SS. Clinical manifestations can be atypical and prognosis and treatment of SS varies with age.^{[10][11]} Especially in the elderly, besides other autoimmune diseases, several conditions may result in sicca complaints: dehydration, polypharmacy, chemotherapy, and head and neck radiation.^[12-15] Moreover, with age, salivary secretion may reduce and salivary composition may undergo chemical changes. Furthermore, malnutrition and diabetes mellitus play a role in hyposalivation and are more frequent in the elderly.^[16-19] Finally, impaired cholinergic stimulation of muscarinic salivary receptors may lead to xerostomia in the elderly as well.^{[20][21]}

In this paper, we provide a detailed, clinically orientated guide to the aetiology, diagnosis and management of elderly patients with pSS or sSS.

Search Strategy

A review of the literature search for the MESH terms 'elderly' AND 'Sjögren*' matched with the terms 'management,' 'treatment,' 'saliva*' and 'lacrimal' was performed using PubMed, MEDLINE, EMBASE, Cochrane and Ovid databases. No language restriction was applied. All relevant articles between January 2000 and January 2012 were reviewed.

Prevalence

The prevalence of pSS is estimated to be between 0.5 and 1 %, with some studies reporting prevalence rates of up to 5 %^[12,22-26], primarily affecting females. The prevalence of sSS is estimated to be 9–19 % in patients with SLE, 4–31 % in patients with rheumatoid arthritis and 14–20 % in patients with systemic sclerosis.^[27] Although SS can occur in patients of all ages, it mainly manifests in the fourth and fifth decade of life (female-to-male ratio 9:1, or even 14:1^[3]). The most obvious explanation for the variation in prevalence rates is the differences in age of the study populations, the differences in sample sizes and the use of different classification criteria for SS. For the same reason, there are no exact data on the prevalence of SS in the elderly. Haugen et al.^[26] found a prevalence of pSS of 1.4 % in adults aged 71–74 years, using revised European classification criteria from 1996.^[28] The prevalence in the elderly population was higher than in the younger population. Another study by Thomas et al.^[29], based on European Community criteria from 1993^[30], estimated the prevalence of pSS in the elderly as 3–4 %. Botsios et al.^[11] reported a 6 % rate of onset of pSS in a cohort of 336 Italian patients older than 65 years. Garcia-Carrasco et al.^[31] showed that, in the elderly, onset of SS is not uncommon and onset of SS occurred in their study population in 14 % of the patients older than 70 years. The 1993 and 1996 European classification criteria were less strict than the currently most commonly used criteria, the 2002 American–European Consensus Group (AECG) criteria, and may thus have resulted in a higher prevalence of SS being reported.^[32]

Pathogenesis

SS is a complex multifactorial autoimmune disease characterized by infiltration of the salivary and lacrimal glandular tissue with predominantly CD4+ T lymphocytes, B lymphocytes and dendritic cells by epithelial cell proliferation and apoptosis.^{[33][34][35]} In salivary glands, saliva, and serum, there are increased levels of proinflammatory cytokines, including interleukin (IL)-1 β , IL-2, IL-6, interferon- γ (IFN γ), tumour necrosis factor- α (TNF α) [T helper-1 cell (T_h1)-response], and antibody-stimulating cytokines, such as IL-4, IL-5 and IL-13 (T_h2-response).^[36] The presence of SSA/Ro and SSB/La antibodies, RF, type-2 cryoglobulins, and hypergammaglobulinaemia, the formation of ectopic lymphoid structures, and a fivefold increased risk of B-cell lymphoma, all reflect B-lymphocyte hyperactivity observed in patients with SS.^[33]

Innate immunity seems to play a critical role in the pathogenesis of SS. Salivary gland biopsies of patients with SS contain relatively high levels of IFN type I (IFN α and IFN β) and IFN type I-producing cells, like plasmacytoid dendritic cells, suggesting a role of IFN α in the induction of SS.^[37,38] Furthermore, patients with SS have an IFN type I signature, indicating that IFN type I inducible genes are upregulated. One of these

genes encodes for B-lymphocyte activating factor (BAFF). BAFF over-expression results in B-lymphocyte hyperactivity and prolonged B-cell survival.^[39] With age, both innate and adaptive immune systems undergo changes; there is an increase in the level of oxidative damage, insufficiency of signalling of particular toll-like receptors (TLRs) and T-cell receptors, age-related changes in dendritic cell function, and accumulation of functionally exhausted memory B cells.^[40]

Viruses have been proposed to be involved in the pathogenesis of pSS, as might be indicated by the type I IFN signature. There are different viral infections whose clinical manifestations share some features of SS. For example, hepatitis C virus infection can cause mild sialadenitis with type II mixed cryoglobulinaemia and production of RF.^{[41][42]} Other viruses that have been supposed to play a role in pathogenesis of SS include the Epstein–Barr virus, cytomegalovirus, HIV virus and human herpes virus-6.^[42,43]

Sarcoidosis also shares some features of SS and thus is considered an exclusion criterion for SS.^[44,45]

Given the predominance of SS in females, there is a hypothesis that hormonal influence, in particular, oestrogen deprivation, is a risk factor for the development of sicca symptoms. Possible oestrogen deficiency might result in the activation of innate immunity. However, a placebocontrolled, double-blind study of dehydroepiandrosterone (DHEA) treatment in pSS patients disproved a beneficial effect of DHEA over placebo.^[46]

Familial predisposition to SS suggests the presence of genetic factors influenced by environmental factors, contributing to the pathogenesis of SS. Several studies demonstrated the association of pSS with an increased frequency of HLA-DR3 (DRB1*03).^[47,48] Although disease susceptibility seems to be best associated with major histocompatibility complex (MHC), there are non-HLA genes suspected of increasing the risk of SS.^[49]

Further research is needed to better understand the pathogenesis of this multifactorial disease.

Salivary Flow and Composition in the Elderly

Salivary dysfunction in SS is of significant clinical and diagnostic importance. It is also known that xerostomia is a common feature of elderly patients. Up to 30 % of patients aged over 65 years' experience the sensation of dry mouth.^[50] With aging there is a decrease in the number of acinar cells, while the amount of fatty and fibrous tissue increases. Although the loss of the acinar cells per se does not lead to clinically significant

decrements in the output of stimulated salivary flow, because of secretory overcapacity of the salivary glands, unstimulated (resting) whole saliva has been reported to decline first with age.^{[17][51,52][53-55]} The sensation of xerostomia probably becomes manifest when the salivary output has been reduced by about 50 %.^[56-58]

A variety of factors affect salivary flow. An intact autonomic regulation mechanism is required for an appropriate salivary flow. Drug-induced xerostomia is the most common cause of dry mouth in the elderly.^[20] In particular, anticholinergic drugs (like tricyclic antidepressants), some sedatives and tranquilizers, antihypertensives (α - and β -blockers, diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors), antiparkinson drugs, antiseizure drugs and cytotoxic agents have a great influence on saliva production.^[59-62] In the case of medication-induced xerostomia, unstimulated salivary flow rate is substantially reduced, while stimulated flow rate is (sub)normal. Nutritional changes and deficiencies occur more often in the elderly and can influence salivary function as well.^[60]

Lacrimal Flow and Composition in the Elderly

There are few reports about lacrimal flow in elderly patients. Hay et al.^[63] demonstrated a weak association between self-reported symptoms of dry eyes and objective measures of lacrimal impairment. Patients with SS have impaired tear production, as detected by the Schirmer's I test (≤ 5 mm/5 min). Elderly individuals with ocular complaints have an abnormal Schirmer's I test less frequently, probably because their ocular symptoms often result from other causes than keratoconjunctivitis sicca, such as blepharitis.^[63] Composition of the tears in SS is changed, with increased sodium, chloride and protein concentrations due to destruction of lacrimal epithelial cells.^[64]

Classification Criteria of Sjögren's Syndrome

Since the Polish–Austrian surgeon Johann Mikulicz in 1892^[65], the French dermatologist Henri Gougerot in 1925^[66] and the Swedish ophthalmologist Henrik Sjögren in 1933^[67] described clinical and histological findings of SS, several classification criteria for SS have been proposed.^{[30][68][69][70]} The revised AECG criteria for SS from 2002^[32] are the most widely accepted and validated criteria (Table 1). These classification criteria are also often used as diagnostic criteria, in particular, for research purposes. Recently the American College of Rheumatology (ACR) proposed alternative classification criteria for SS^[68] (Table 2). In contrast to the AECG criteria (see below) the provisional ACR criteria are solely based on objective tests. Compared to the AECG criteria the provisional

Table 1 The AECG criteria for Sjögren's syndrome (SS)^[32]**Revised international classification criteria for SS**

- 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 at least one of the following two tests:
 1. Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 min)
 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 sialadenitis, 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 min)
 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts
 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
 1. Antibodies to SSA/Ro or SSB/La antigens, or both

Revised rules for classification**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
- b. The presence of any 3 of the 4 objective criteria items (that is, items III [Ocular signs], IV [Histopathology], V [Salivary gland involvement], or VI [Autoantibodies])
- c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

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 fourfold the half-life of the drug)

ACR criteria have higher sensitivity and similar specificity, but these results need to be replicated in other datasets. Furthermore, it is currently being considered whether alternative criteria should be added to the AECG and/or ACR criteria sets or even can replace criteria within these sets.^[174]

The AECG criteria combine subjective symptoms of dry eyes and dry mouth with objective signs of keratoconjunctivitis sicca and salivary gland dysfunction. The subjective ocular and oral symptoms are obtained by history taking. Reduced tear production can be evaluated by performance of the Schirmer's I test, rose bengal test or lissamin-green staining. Positive histopathological findings from the lip salivary glands with a focus score of ≥ 1 (a focus is defined as an accumulation of more than 50 lymphocytes per 4 mm^2), impaired unstimulated whole salivary flow ($\leq 1.5\text{ mL}$ in 15 min) and presence of serum autoantibodies (SSA/Ro and/or SSB/La) are other objective criteria of SS.

Regarding lip gland biopsy, according to our experience, a parotid biopsy might serve as a proper alternative in the diagnosis of SS. The morbidity of parotid biopsy is less than that of lip biopsy, and parotid biopsy is more sensitive and is able to detect marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)/non-Hodgkin's lymphoma (NHL) in the parotid gland. In addition, parotid biopsies can be used to monitor the therapy effect, since the same gland can be biopsied more than once.^[71]

Recently, Theander et al.^[72] showed that the presence of germinal centre-like lesions in lip gland biopsies is also highly predictive for development of NHL during the course of SS.

Table 2. Provisional American College of Rheumatology (ACR) classification criteria for Sjögren's syndrome (SS)^[68]

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least two of the following three objective features:	
1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titre $\geq 1:320$)	
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score of ≥ 1 focus/ 4 mm^2	
3. Keratoconjunctivitis sicca with ocular staining score of ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)	
Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:	
History of head and neck radiation treatment	
Hepatitis C infection	
Acquired immunodeficiency syndrome	
Sarcoidosis	
Amyloidosis	
Graft versus host disease	
IgG4-related disease	

ANA anti-nuclear antibodies

Table 3. Useful investigations for the diagnosis and assessment of Sjögren's syndrome^[173]

	Systemic	Oral	Ocular
Essential	Blood tests: FBC, electrolytes, Ur, Cr, liver enzymes, CK, TSH, ESR, CRP, glucose, Ig & EPS, C3, C4, ANA, RF, SSA/Ro, SSB/La, anti-dsDNA. Urine: dipstick analysis. Imaging: chest radiograph	UWS, salivary gland biopsy	Schirmer's I test, tear film break-up time, ocular surface staining (e.g. lissamin green, fluorescein or rose bengal staining)
If indicated	Serology for hepatitis A, B, C, EBV & HIV; sACE, ENA, ACPA, AMA, cryoglobulins, amylase, HbA1c, haemolytic screen	Sialography	
Optional		SWS, selective sialometry, sialochemistry, ultrasound salivary glands, MRI salivary glands, scintigraphy	

ACPA anti-citrullinated peptide antibodies, *AMA* anti-mitochondrial antibodies, *ANA* anti-nuclear antibodies, *anti-dsDNA* anti-double-stranded DNA antibodies *SSA/Ro* and *SSB/La* antibodies, *CK* creatinine kinase, *Cr* creatinine, *CRP* C-reactive protein, *ENA* extractable nuclear antigen, *ESR* erythrocyte sedimentation rate, *EBV* Epstein-Barrvirus & *FBC* full blood counts, *HbA1c* glycosylated haemoglobin, *HIV* human immunodeficiency virus, *Ig* & *EPS* immunoglobulins and electrophoresis, *MRI* magnetic resonance imaging, *RF* rheumatoid factor, *sACE* serum angiotensin converting enzyme, *SWS* stimulated whole saliva, *TSH* thyroid stimulating hormone, *Ur* urea, *UWS* unstimulated whole saliva

Diagnostic Work-Up

Diagnosis of SS in the elderly is a new challenge for physicians, considering the increasing number of elderly, as patients with SS are frequently misdiagnosed and physicians treat each symptom individually, unaware of underlying systemic disease. Such an approach is due to a lack of knowledge regarding the manifestations and treatment of SS and to the fact that the presentation of autoimmune diseases in the elderly is usually atypical. Early, accurate diagnosis of SS can prevent complications associated with the disease and improve the patient's well-being.^[1]

Investigations for the diagnosis and assessment of Sjögren's syndrome include the following:

Systemic

- Essential investigations are:
 - blood: full blood counts, electrolytes, urea, creatinine, liver enzymes, creatinine kinase, thyroid stimulating hormone, erythrocyte sedimentation rate, C-reactive protein, glucose, immunoglobulins and electrophoresis, C3, C4, anti-nuclear antibodies, RF, SSA/Ro, SSB/La, and anti-doublestranded DNA;
 - urine: dipstick analysis;
 - imaging: chest radiography.

- If indicated, investigations should also include:
 - serology for hepatitis A, B, C, Epstein–Barr virus and HIV, serum angiotensin converting enzyme, extractable nuclear antigen, anti-citrullinated peptide antibodies, anti-mitochondrial antibodies, cryoglobulins, amylase, glycosylated haemoglobin (HbA1c), and haemolytic screen.

Oral

- Essential investigations are:
 - unstimulated whole saliva, salivary gland biopsy.
- If indicated:
 - sialography.
- Optional tests include:
 - stimulated whole saliva, selective sialometry, sialochemistry, ultrasound salivary glands, magnetic resonance imaging of salivary glands, and scintigraphy.

Ocular

- Essential investigations are:
 - Schirmer's I test, tear film break-up time, and ocular surface staining (e.g. lissamine green, fluorescein or rose bengal staining).

Glandular Manifestations

Ocular Involvement

Dry eyes, photosensitivity or photophobia, erythema, eye fatigue, decreased visual acuity, discharge in the eyes and the sensation of a film across the visual field are all symptoms of ocular manifestations of SS. Patients also commonly complain of a 'sandy' feeling in the eyes. These symptoms can be exacerbated by low-humidity environments like air-conditioned or centrally heated buildings, dry climates or irritants such as cigarette smoke and dust. A sensation of dry eyes is an early complaint in patients with SS.^[73]

The composition of certain proteins in the tears of SS patients is changed and there is an elevated osmolarity due to increased sodium ion concentrations in tears.^[74] Increased osmolarity of the tears damages the corneal epithelium and activates a cascade reaction leading to the inflammation and apoptosis of the corneal cells.^[75] Patients with SS have decreased concentrations of certain proteins in tear fluid, including lactoferrin and epidermal growth factor, that correlate with severity of corneal damage.^[76] On the other hand, levels of proinflammatory cytokines/chemokines like IFN γ , IL-1, IL-6, IL-8, CCL3/MIP-1 α and CXCL-10/IP-10 are increased in tears and these cytokines/chemokines promote inflammation and apoptosis of corneal epithelium.^{[64][77]}

Punctate conjunctival and corneal damage can be detected with rose bengal staining. A rose bengal score of ≥ 4 according to the van Bijsterveld scoring system is considered abnormal.^[78] As a result, filamentary keratitis develops by accumulation of thick rope-like strands (mucus filaments) with signs of ocular discomfort ranging from foreign-body sensation to severe pain or loss of vision. Other complications due to insufficient tear secretion include corneal ulceration, eyelid infections, and dilation of the bulbar conjunctival vessels.

In the elderly with a presumption of SS, differential diagnosis of the ocular symptoms include blepharitis, hypovitaminosis A, ocular pemphigoid, cranial nerve V dysfunction or an impaired lid function.

Oral Involvement

As a result of autoimmune destruction and the resulting hypofunction of the salivary gland, SS patients experience xerostomia or complications such as dysphagia, denture problems, difficulties with speech, hypersensitivity of the oral mucosa, burning sensations of the oral mucosa, a high risk of developing dental caries, nocturnal discomfort and change in taste. Patients with advanced salivary gland hypofunction as a result of SS have signs of mucosal dryness, cracked and atrophic lips, pale buccal mucosa, and a smooth and reddened tongue with loss of some of the dorsal papillae or a fissured tongue. Despite of good oral hygiene, patients with SS have oral infections more often than patients without SS, particularly oral candidiasis, which develops in 30–70 % of the patients with SS.^[79,80] Fungal lesions of the corners of the mouth (angular cheilitis) may also occur more frequently in patients with SS.^[81,82]

At the onset of SS, salivary flow can still be relatively normal, because the inflammation has not yet destroyed the salivary glands to a significant level, although loss of salivary function can be prominent in early disease. Often, both healthy elderly and the elderly with SS have a decline in secretory capacity of the submandibular and sublingual salivary glands first, while parotid glands have a longer-lasting secretory capacity. Patients with long-standing disease are characterized by severely reduced secretions of the parotid, submandibular and sublingual glands.^[83]

Sialochemistry may be a useful tool to distinguish xerostomia underlying SS from xerostomia as a result of other causes.^[84,85] In patients with SS, there are significant changes in salivary composition, with increases in sodium and chloride concentrations and lower phosphate concentration. Total protein concentration in parotid saliva is higher in patients with SS than in healthy controls.^[17,86] When patients still have a reasonable salivary flow, the changes in composition may give a clue to the underlying diagnosis.

Salivary and Lacrimal Gland Enlargement

Lacrimal gland enlargement is rare and should prompt a work-up for MALT lymphoma.^[1] Enlargement of salivary glands, in particular, of the parotid and submandibular glands, occurs in up to 50 % of patients with SS.^[87,88] Enlargement can be either chronic or episodic and is most often present on both sides. Persistent glandular enlargement with hard or nodular gland may be due to lymphoma development, in most cases, in the parotid gland. The most common are MALT lymphomas, but other NHLs may also develop.^[1] Patients with low levels of C4 and monoclonal cryoglobulinaemia are at particular risk of progression to lymphoma.^[89]

Differential diagnosis of bilateral parotid gland enlargement are endocrine disorders, like hyperthyroidism, hypothyroidism, diabetes mellitus, gonadal hypofunction, chronic pancreatitis or viral infections like HIV infection or hepatitis C.

Extraglandular Manifestations

Disease activity of SS is not restricted to exocrine glands. Many other organs and organ systems can be involved. Moreover, elderly patients with SS seem to have a more benign disease course with less renal involvement, thrombocytopenia and lymphadenopathy.^[6] Furthermore, the symptoms of fatigue, weight loss and muscle pain are common features of old age, which may explain the long delay between clinical onset and diagnosis of SS.

Cutaneous Involvement

Cutaneous manifestations are multiple in SS and consist of xerosis, angular cheilitis, eyelid dermatitis, pruritus, Raynaud's phenomenon, cutaneous vasculitis, and erythema annulare. The prevalence of skin involvement is up to 50 %. Xerosis and angular cheilitis are the most frequent skin diseases in SS.^[90]

The aetiology of xerosis in patients with SS is not fully understood, but seems to be similar to that of xerosis in the elderly. Patients with SS have probably no inflammatory atrophy of sweat glands of the skin, but there are biochemical alterations in the epidermis (increased epidermal proliferation and perturbation of epidermal differentiation), which are most prominent on dorsal and lateral surfaces of the extremities.^[91,92]

Raynaud's phenomenon is a common manifestation of SS, with a prevalence of about 30 %. Raynaud's phenomenon can manifest many years before the diagnosis of SS.^[93-95] Cutaneous vasculitis is found in about 10 % of SS patients and appears as purpura, urticarial lesions, macules, papules and small ulcers. Annular erythema appears similar to subacute cutaneous lupus erythematosus, and there are common pathophysiological mechanisms, mainly the presence of SSA/Ro or SSB/La antibodies.^[96]

Respiratory Involvement

Airway involvement and interstitial lung disease are frequent manifestations of respiratory tract involvement in SS.^[97] Involvement of the mucosal surfaces of the upper airways leads to xerotrachea and is a cause of persistent hoarseness and a chronic, nonproductive cough. Up to 20 % of SS patients have recurrent bronchial and pulmonary infections and otitis media.^[98] Interstitial lung disease affects 8–38 % of patients with SS, with non-specific interstitial pneumonia as a most common pattern, characterized by interstitial infiltration with polyclonal lymphocytes and plasma cells. It has a favourable prognosis. Severe interstitial disease in SS is rare.^[98]

Pleural involvement, such as thickening and effusions, is uncommon in SS. Patients with onset of dyspnoea should be evaluated for pulmonary vascular disease like pulmonary thromboembolic disease or pulmonary arterial hypertension.^[99,100] Patients with SS have an increased risk of developing a pulmonary lymphoma, usually B-cell NHL from mucosal sites of the lung, with a prevalence of 1–2 %.^[101]

Sarcoidosis can coexist with SS and can also mimic SS by presenting with lacrimal and salivary gland involvement, such that they share clinical, pathological and immunological features.^[45]

Neurological Involvement

Neurological manifestations of SS include peripheral and central nervous system involvement. Peripheral neuropathies are more common than central nervous system neuropathy and include sensory or pure sensory neuropathies, painful sensory neuropathy, multiple mononeuropathy (mononeuritis multiplex), polyradiculopathy, autonomic neuropathy and multiple cranial neuropathies.^[102]

The prevalence of peripheral neuropathy in SS patients varies from 20 to 60 % and can precede the diagnosis of SS.^[103–105] Govoni et al.^[105] and Gemignani et al.^[106] reported that peripheral nervous system involvement occurs more often than central nervous system disease in the elderly (age >50 years). Age could be a risk factor for developing peripheral nervous system complications in patients with SS because of the development of age-related microangiopathic alterations.

The range of central nervous system involvement includes focal or diffuse neurological processes. Among others, these processes include diffuse brain lesions, spinal cord involvement, subacute aseptic meningitis, chorea, optic neuritis, and subtle changes in cognitive function, with poor memory and concentration. The prevalence of central nervous system involvement is difficult to estimate because of selection bias and the use of different diagnostic criteria; estimates range from 8 to 40 %.^{[105,107][108]}

Renal Involvement

There are several manifestations of kidney involvement in SS. The most common is interstitial nephritis, characterized by an interstitial infiltrate, leading to tubular damage. About 30 % of patients with SS have interstitial nephritis, but only in 5–10 % of patients does it lead to clinical symptoms.^[109] Because of tubular damage, patients may develop distal renal tubular acidosis, which may result in clinical symptoms such as compromised renal function, proteinuria, nephrocalcinosis, kidney stones, hypokalaemia, hypophosphataemia, polyuria and nephrogenic diabetes insipidus.^[110–112] Glomerulonephritis is less common than interstitial nephritis and is histologically characterized by membranoproliferative glomerulonephritis or membranous glomerulopathy, leading to clinical findings such as hypertension, proteinuria (mild to nephrotic syndrome) and to an active urinary sediment with erythrocytes and casts. Glomerular disease is associated with cryoglobulinaemia and hypocomplementaemia, suggesting deposition of circulating immune complexes.^[113]

Arthritis

Articular manifestations occur in about 50 % of patients with SS.^[114,115] Elderly patients seem to have a lower frequency of articular involvement.^[114] The arthropathy can precede the development of sicca syndrome.^[116] The most common symptoms are arthralgia and intermittent symmetrical non-erosive polyarthropathy, affecting both small and large joints. Synovitis is uncommon and synovial biopsies have shown non-specific infiltration with mononuclear cells.^[117]

Muscular Involvement

Patients with SS experience chronic pain, muscle stiffness and weakness, accompanied by increased tenderness at tender points, meeting criteria for fibromyalgia. Lindvall et al.^[118] found that 17 % of patients with SS experienced muscle pain, and that 27 % of patients also fulfilled diagnostic criteria for fibromyalgia, a higher prevalence of fibromyalgia than observed in general population. About 4 % of the patients were found to have polymyositis, defined as clinical symptoms combined with inflammatory cell infiltrates on muscle biopsy. Patients with significant muscle weakness and elevated muscle enzymes should be evaluated for an overlap connective tissue disease.

Gastrointestinal Involvement

Dysphagia is described in patients with SS due to motility abnormalities, reduced oesophageal sphincter pressure and decreased contractility. Nutcracker oesophagus and achalasia are also associated with SS.^[119] Patients complain of dyspepsia, nausea and epigastric pain, and these symptoms can be associated with gastritis, reduced acid production and antiparietal cell antibodies, also called autoimmune gastritis. When gastritis is suspected, a diagnostic test for *Helicobacter pylori* infection should

be performed. Treatment of *H. pylori* does not reduce gastric lymphocytic infiltration, gastric atrophy, or dyspepsia in SS patients.^[120] Pancreatitis and pancreatic insufficiency are rare manifestations of SS.

SS is associated with PBC, but the mechanism of this association is not clear. A significant number of patients with PBC have sicca symptoms. In both diseases, epithelial cells are likely to participate in the pathogenesis of the diseases, and in both diseases, SSA/Ro and SSB/La antibodies are produced. Environmental factors like infectious agents could play a role in pathogenesis of both diseases, causing salivary or biliary cell apoptosis.^[121]

Fatigue

Up to 70 % of patients with SS have disabling fatigue with reduced quality of life, social activities and lower employment rates.^[9] The pathogenesis of fatigue is poorly understood. Several factors seem to play a role in the development of fatigue. These factors are disease activity of SS (systemic inflammation, circulating cytokines and immune dysregulation); sleep disturbances due to dryness, pain and irritable bladder, depression, anxiety, restless legs, and nocturia from over-hydration during the day; fibromyalgia; dysregulation of the hypothalamic-pituitary-gonadal system; hypothyroidism; anaemia; celiac disease; vitamin deficiencies (B₁₂, D); pulmonary and renal dysfunction (rare); and autonomic dysfunction.^[122] A reduced physical capacity due to inactivity, a sedentary lifestyle and kinesiphobia can also contribute to the development of fatigue.

Lymphoma

Patients with SS have a higher risk of developing MALT lymphoma and NHL, which is about 5–7.5 %.^[123] Risk factors for lymphoproliferative disease are persistent parotid gland enlargement, lymphadenopathy, cryoglobulinaemia, low C4 complement levels, purpura, neutropenia and splenomegaly.^[124] Pollard et al.^[125] showed that SS patients with MALT lymphoma and high disease activity of SS are at risk for progression or recurrence of MALT lymphoma and deterioration of SS during follow-up (Fig. 1). Recently, Theander et al.^[72] showed that the presence of germinal centre-like lesions in the lip biopsies of pSS patients detected by light microscopy is a highly predictive and easy-to-obtain marker for NHL development.

Urogenital Involvement

Female SS patients experience vaginal dryness, pruritus, dyspareunia and increased frequency of vaginal candidiasis. In addition, they have, more frequently, complaints of polyuria, nocturia, and urge incontinence due to irritable bladder.^[126]

Fig. 1 Progression free survival of mucosa-associated lymphoid tissue (MALT) lymphoma according to initial high or low Sjögren's syndrome (SS) disease activity. Reproduced from Pollard et al.,^[125] with permission.

Management of Sjögren's Syndrome

Treatment of SS in the elderly does not differ from that in younger patients. The aims of the treatment are to control glandular and extraglandular manifestations, to prevent damage to organ systems and loss of function, and to decrease morbidity and mortality. Treatment of the elderly can be complicated by co-morbidities, an increased rate of adverse events related to therapeutic agents, and polypharmacy. Therefore, careful follow-up of the treatment is required.

Management of Glandular Manifestations

Preventive Measures

Preventive measures for ocular dryness include avoidance of exacerbating factors like low-humidity atmospheres such as air-conditioned areas, centrally heated buildings, airplanes, and windy locations. Cigarette smoke and dust can irritate eyes and upper airways. Prolonged reading or computer use can provoke tear film instability. Caution is required when using antidepressants, antihistamines, anticholinergics, antihypertensive and neuroleptic drugs. Other medical conditions like ectropion and meibomian gland disease should be treated.

Preventive management of oral complications include regular dental visits (usually every 3–4 months), guidance from a team of oral health professionals, and fluoride mouth rinse 0.1 % (weekly to daily in case of severe hyposalivation) or up to daily application of a neutral sodium fluoride gel with a custom-made carrier.^[127] Remineralizing solutions can help against demineralization and the consequent loss of tooth structure. Patients should be given diet advice, including an instruction to avoid cariogenic food like fermentable carbohydrates and beverages. Chronic use of alcohol and caffeine needs to be minimized. Of importance, avoidance of drugs that may worsen sicca symptoms is recommended. Other disorders like endocrine and metabolic diseases and viral infections should be excluded and treated.

Symptomatic Treatment

Substitution of saliva and tears is recommended. Patients are advised to use eye drops three to six times a day. Ophthalmic gels and ointments may be used at night. Acetylcysteine 5 % eye drops can be used if patients have mucus secretions or sticky eyes. Dexamethasone drops are advised as a short treatment to suppress the associated inflammatory process. Punctum occlusion can be surgically performed to preserve the tears. Patients often wear occluding glasses.

Sugar-free gums or mints are recommended for patients with dry mouth. Combined gustatory and masticatory stimulatory techniques, such as the use of candies, assuming they are sugar free, are easy to implement and generally harmless. Frequent sips of water during the day and with meals prevents dry mouth sensation, but this moisture is not prolonged.^[128] There are numerous oral rinses, mouthwashes, gels and saliva substitutes available.^[129] Whether saliva substitutes will be accepted by a patient is heavily depending on proper instruction being given to the patient. The following advice on the general use of oral mucosal lubricants is extracted from Regelink et al.^[130]

If severe xerostomia, the application of a saliva substitute with gel-like properties may provide relief during the night and when daily activities are at a low level. During daytime, a saliva substitute with less viscous properties resembling natural saliva based on e.g. polyacrylic acid, xanthan gum or mucin may provide relief. If moderate xerostomia, saliva substitutes with a rather low viscoelasticity, such as substitutes based on carboxymethylcellulose, hydroxypropylmethylcellulose, mucin or low concentrations of xanthan gum and polyacrylic acid are indicated, supplemented by a gel to provide relief during night or other periods of severe oral dryness. At slight xerostomia little alleviation is to be expected from the use of saliva substitutes.

Systemic Tear and Saliva Stimulation

Pilocarpine and cevimeline are effective in the treatment of dry eyes and dry mouth. Both drugs are muscarinic agonists and can be used in patients who have residual functional gland tissue.^[131-134] Common adverse effects include sweating, flushing, urinary urgency and gastrointestinal discomfort, but are rarely severe. These drugs are contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, and acute iritis and should be used with caution in patients with significant cardiovascular disease, Parkinson's disease or chronic obstructive pulmonary disease. Therefore, the use of pilocarpine and cevimeline is limited in the elderly.

Treatment with IFN α has been tried via the oromucosal route. Initial studies were promising, but later studies were less convincing.^[135,136] Furthermore, flu-like adverse effects and high costs make this treatment option less attractive.

Topical cyclosporin use appeared to be an effective treatment in patients with keratoconjunctivitis sicca.^[137]

Prevention and Treatment of Oral Candidiasis

Secondary infection with *Candida albicans* is common in patients with SS and may require prolonged treatment.^[138] As mentioned before, oral candidiasis has been reported to occur in 30–70 % of SS patients, especially after use of corticosteroids or antibiotics.^[79,80] Infection should be treated with topical or systemic antifungal drugs. Patients should not wear dentures overnight and the dentures should be soaked in chlorhexine solution to prevent reinfections. Among others, nystatin or clotrimazole cream can be used to treat angular cheilitis.

Systemic Treatment

Relief of ocular and oral symptoms has been reported with the use of biologicals. Patients treated with anti-CD20 (rituximab) showed improvement of subjective and objective measures.^[139-144] These and other systemic medications are discussed more extensively in Sect. 9.2.

Management of Dry Surfaces Other than Mouth and Eyes

The use of humidifiers is helpful for nasal, pharyngeal and vaginal dryness. Nasal sprays should be used frequently, because nasal blockage increases mouth breathing and exacerbates oral dryness.

Management of Extraglandular Disease

Anti-inflammatory and Disease-Modifying Drugs

No special contraindications with regard to the use of disease-modifying anti-inflammatory drugs are known in elderly patients. Nonsteroidal anti-inflammatory drugs can be used in patients with constitutional symptoms and musculoskeletal pain. On the other hand, these drugs are associated with cardiovascular, gastrointestinal and renal adverse effects and should be used carefully, especially in the elderly population.

The treatment of SS patients with hydroxychloroquine is mostly used in patients with cutaneous, musculoskeletal and constitutional symptoms. There is no evidence of improvement in objective measures of sicca symptoms, but it has been reported to improve systemic features, especially arthritis and skin involvement.^[145,146] Retina damage is a well-known adverse effect of hydroxychloroquine, especially in renal failure, which increases drug toxicity. Older age is also a risk factor for developing a retinopathy, so patients should be monitored by the ophthalmologist for eye complications.^[147] In the case of inefficacy of hydroxychloroquine, corticosteroids may be used as an alternative. Low-dose prednisone (up to 10 mg/day) may relieve joint symptoms, pruritus and mild leukocytoclastic vasculitis. A moderate dose of steroids (up to 30 mg/day) can be used in cases of necrotic or ulcerating vasculitis. High-dose corticosteroids (1 mg/kg/day) are used in combination with cyclophosphamide to treat severe manifestations of SS, like life-threatening central nervous system manifestations or renal involvement.^[148] In a controlled trial, corticosteroids had no significant effect on salivary and lacrimal function.^[149]

There is no evidence that methotrexate is useful for treatment of articular manifestations of SS. In a small open-label study, no improvement of objective parameters was reported, but it improved subjective sicca symptoms.^[150] There is no clinical trial of toxicity of methotrexate in elderly patients with SS, but this drug has been tested in patients with rheumatoid arthritis who were older than 65 years. Age had no influence on the efficacy of methotrexate, but the renal dysfunction was related to the occurrence of more adverse effects.^[151]

Azathioprine and sulfasalazine were not effective in patients with SS. A high prevalence of adverse events was reported.^[152,153]

Leflunomide showed a modest improvement of salivary and lacrimal gland function, but no systemic improvement of the disease.^[154] In several cases, an exacerbation of leukocytoclastic vasculitis was seen. The adverse effects of leflunomide in the elderly did not significantly differ from those in younger patients.^[155]

Other Systemic Drugs

DHEA was evaluated in patients with SS because of the female predominance in pSS, decreased serum levels of dehydroepiandrosterone and the finding that quality of life in pSS correlates with circulating levels of DHEA-sulfate. However, in a controlled trial, no evidence of DHEA efficacy was found, except for subjective improvement of dry mouth.^[46]

Biologicals

Several biologicals have been used in patients with SS in clinical trials. At this moment, no biological has been approved for the treatment of SS, but treatment with rituximab showed promising results in phase II studies (see Sect. 9.2.3.3).

Interferon- α As mentioned in Sect. 4, patients with SS have an “IFN type I signature”. Therefore, anti-IFN α therapy should be theoretically effective. Clinical trials with monoclonal antibodies to IFN α in patients with SLE and dermatomyositis/polymyositis are underway. To our knowledge, no trials have been performed with these monoclonal antibodies in pSS patients yet.

Surprisingly, IFN α therapy itself has been used in pSS patients in a phase III randomized controlled trial in 497 patients. Cummins et al.^[135] showed a significant increase in unstimulated whole saliva in patients treated with IFN α , but there was no significant effect on the primary end-points [visual analogue scale (VAS) for oral dryness and stimulated whole salivary flow]. There is no clear explanation why IFN α therapy increases salivary flow. Further research is needed to clarify the effects of IFN α and anti-IFN α on salivary gland tissue.

Anti-tumour Necrosis Factor Biologicals There are five biologicals targeting TNF: the chimeric monoclonal antibody infliximab, the receptor fusion protein etanercept, the fully human monoclonal antibody adalimumab, the pegylated humanized antibody Fab’ fragment of TNF α monoclonal antibody certolizumab, and the human monoclonal antibody golimumab. In a double-blinded, placebo-controlled, randomized clinical trial, infliximab showed no evidence for the efficacy of this treatment on clinical or functional parameters.^[156] Etanercept was evaluated in a small pilot trial with 15 patients. No reduction of sicca symptoms or signs was seen.^[157] To our knowledge, no trials of adalimumab, certolizumab or golimumab treatment in pSS have been reported in the literature.

Anti-CD20 Monoclonal Antibodies Rituximab is a chimeric monoclonal antibody specific for the B-cell surface molecule CD20, which is expressed on the surface of B lymphocytes. In phase II trials, it has been shown that rituximab is effective for at least 6–9 months in patients with active pSS, improving both subjective symptoms and objective signs of the disease.^[140,142-144,158,159] Retreatment with rituximab resulted in a similar good clinical response. In pSS patients with longer disease duration and

Fig. 2 Management of mucosa-associated lymphoid tissue (MALT) type lymphoma of parotid gland and associated Sjögren's syndrome (SS). Reproduced from Pollard et al.,^[125] with permission. CT computed tomography, FNA fine-needle aspiration, IgM-RF immunoglobuline M-rheumatoid factor, MRI magnetic resonance imaging, R-CP intravenous rituximab, intravenous cyclophosphamide and oral prednisone, NSAID nonsteroidal anti-inflammatory drugs. *Extraglandular disease: polyarthritis/myositis, glomerulonephritis, nervous system involvement, cryoglobulinaemic vasculitis, other severe organ involvement, serological abnormalities: cryoglobulinaemia, C4 <0.10 g/L, ** Six intravenous infusions of 375 mg/m² of rituximab and 6–9 cycles of cyclophosphamide, given every 3 weeks.

lacking residual salivary gland function, anti-CD20 treatment seemed to be effective for systemic features, but no recovery of salivary flow was observed in patients with no or almost no residual salivary flow at baseline.

Anti-CD22 Monoclonal Antibodies Epratuzumab is a humanized monoclonal antibody specific for the B-cell surface molecule CD22, which is expressed on the surface of B lymphocytes. In an open-label, phase I–II study, the safety and efficacy of epratuzumab were investigated in 16 pSS patients.^[160] The results were promising, with improvements in Schirmer’s I test scores, the level of unstimulated whole salivary flow, and the VAS scores for fatigue. Randomized, placebo-controlled clinical trials with epratuzumab are needed to confirm these promising results.

Management of MALT Lymphoma

In elderly patients with asymptomatic MALT lymphoma restricted to the salivary glands and low SS activity, a ‘wait-and-see’ policy can be chosen.^[140,161] For a symptomatic localized MALT lymphoma and low SS activity, local low-dose radiotherapy (2×2 Gy) is a good treatment option. Patients with MALT lymphoma and high SS activity (vasculitis, kidney involvement, polyneuropathy, low C3 and C4, cryoglobulinaemia) may be treated with 6–8 cycles of R-CP [intravenous (IV) rituximab, IV cyclophosphamide and oral prednisone]. Fig. 2 shows a guideline for management and treatment of patients with MALT-SS.^[125]

Monitoring Disease Activity

In order to detect the disease activity of SS and the effect of the therapy on the disease course, there have been a couple of attempts to develop a disease activity index: the Sjögren’s Syndrome Disease Activity Index (SSDAI) and the Sjögren’s Systemic Clinical Activity Index (SCAI).^[162,163] Recently, the efforts of the European League Against Rheumatism (EULAR) led to the development of two new indices, viz. a patient-administered questionnaire to assess patient symptoms, the EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI), and a disease activity index to evaluate systemic complications, the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI). These indices have been found to be sensitive enough to measure changes in disease activity after treatment with rituximab, and these results favour the use of these indices in future clinical trials.^[139,164–167]

Future Perspectives

New biological therapies can potentially be effective in the treatment of SS. BAFF is a positive regulator of B-cell function and expansion.^[168,169] Two human BAFF antagonists have been developed (belimumab and atacicept) and should be tested in clinical trials. Other potential targets include cytokines such as IL-6, adhesion molecules and chemokines. Furthermore, the use of parotid gland evaluation may be preferable to using lip gland evaluation, because it causes less morbidity, repeated biopsies are possible and malignant lymphoma may be located in the parotid gland.^[171] Salivary biomarkers are still potential clinical tools to diagnose SS noninvasively and at low cost.^[170,171] Gland-specific sialometry and sialochemistry are also useful methods to determine the cause of hyposalivation and to select the most effective treatment of xerostomia in the individual patient.^[172]

Conclusions

Diagnosis and treatment of elderly patients with SS is challenging. Since there are numerous conditions mimicking manifestations of SS, the range of differential diagnoses is wide. The revised AECG criteria for SS from 2002 are the preferred tool to confirm diagnosis; however, these are in fact classification criteria, and some patients do not have enough criteria for diagnosis. Those who are suspected of having SS should be approached as having SS. When the AECG criteria are revised, how to deal with elderly patients suspected as having SS should be emphasized. The AECG criteria and also the recently introduced provisional ACR classification criteria unfortunately do not specifically address which guidelines to follow in the elderly. Furthermore, treatment of SS in the elderly does not differ substantially from that recommended in younger patients, but it can be complicated by co-morbidities and an increased rate of adverse events. Careful monitoring of elderly patients is therefore essential.

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3

EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial*

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Abstract

Background: The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) has been developed to measure clinical disease activity in patients with primary Sjögren's syndrome (pSS), but its value in measuring changes in disease activity in randomized controlled trials has to be assessed.

Objective: To assess the responsiveness of the ESSDAI in pSS patients treated with rituximab or placebo.

Methods: 30 pSS patients were randomly assigned to rituximab (1000 mg; n=20) or placebo infusions (n=10) on days 1 and 15. Follow-up was conducted at 5, 12, 24, 36 and 48 weeks after treatment. At baseline and during all follow-up visits, disease activity measures were scored by the primary investigator who was blinded for the treatment the patients had received. The change of ESSDAI scores over time was analyzed with generalized estimating equations. Responsiveness of ESSDAI was assessed using standardized response means (SRM) and effect sizes (ES). SRM and ES <0.5 was interpreted as small, between 0.5 and 0.8 as moderate and >0.8 as large.

Results: In the rituximab group, ESSDAI scores were decreased significantly up to 36 weeks after treatment, while in the placebo group significance was found only at week 5, probably due to high dose corticosteroids given with infusions. SRM and ES for ESSDAI in the rituximab group were large at weeks 5, 12, and 24, moderate at week 36 and small at week 48. In the placebo group SRM and ES were moderate at week 5 and small at all other time points.

Conclusion: ESSDAI is a sensitive tool to measure disease activity changes in pSS patients. The results favor the use of ESSDAI in future clinical trials.

Introduction

Primary Sjögren's Syndrome (pSS) is a systemic rheumatic disease characterized by progressive focal lymphocytic cell infiltration and destruction of exocrine glands. In particular, salivary and lacrimal glands are affected by pSS resulting in keratoconjunctivitis sicca and xerostomia. Patients with pSS may have involvement of many organs beyond the exocrine glands, for example arthritis, polyneuropathy or respiratory tract involvement. All these changes result in a significant morbidity limiting patients' daily activities and quality of life.¹

Until recently, there was no effective treatment for pSS and symptomatic therapy was the only option. As B-cell hyperactivity seems to be one of important pathogenetic factors in pSS,² B-cell depleting therapy with anti-CD20 (rituximab, Mabthera) has been presumed to be a promising treatment.^{3,4,5,6} Rituximab treatment was shown to result in improvement of fatigue, quality of life and salivary secretion, particularly in patients with shorter disease duration, as well as in a reduction of extra-glandular manifestations.^{7,8}

Although several studies described a good efficacy of rituximab therapy on fatigue, quality of life and extraglandular manifestations, there is no uniform outcome measure so far to compare the effect of the therapy in these studies.

In order to monitor the disease activity, disease progression and treatment efficacy in pSS there have been several attempts to develop a disease activity index: pSS disease activity index (SSDAI) and the Sjögren's systemic clinical activity index (SCAI).^{9,10} Recently, the effort of the European League Against Rheumatism (EULAR) has led to a development of a consensus disease activity index, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), based on expert opinion, and aiming for measuring disease activity in patients with systemic complications of pSS.¹¹ ESSDAI has been tested for sensitivity to detect changes (responsiveness) in disease activity in a number of vignettes of real patients by Serró et al.¹² That study revealed that ESSDAI was able to detect changes in disease activity more accurately than SSDAI and SCAI. In addition, ESSDAI correctly detected patients with stable disease.

Next, the ESSDAI was tested in a prospective open label study by Meiners et al.¹³ They demonstrated that ESSDAI is able to detect the effect of intervention treatment with anti-CD20 (rituximab) in pSS subjects.

The aim of the current study was to assess the responsiveness of the ESSDAI after rituximab treatment in a randomized, double-blind, placebo-controlled trial with pSS patients.

Materials and methods

Study design and patients.

Between August 2006 and September 2007, 30 patients were included in a prospective, single-center randomized, double-blind, placebo-controlled trial.⁸ Patients were older than 18 years and fulfilled the American-European Consensus Group criteria for pSS. Eligibility criteria were a stimulated whole salivary flow rate of ≥ 0.15 ml/minute and positivity for autoantibodies rheumatic factor (≥ 10 kIU/L) and anti-SSA and/or anti-SSB autoantibodies. In addition, results from a salivary gland biopsy performed within 12 months before inclusion and showing the characteristic features of pSS had to be available. During the study, patients were asked to use reliable methods of contraception. Patients who had been treated previously with other biological disease-modifying antirheumatic drugs (DMARDs) were excluded. Treatment with prednisone and hydroxychloroquine had to be discontinued at least 1 month before baseline, and treatment with methotrexate, cyclophosphamide, cyclosporine, azathioprine, and other traditional DMARDs had to be discontinued at least 6 months before baseline. Patients were allowed to use artificial tears and artificial saliva, but the regimen had to remain identical during follow-up. The use of these substitutes had to be stopped 1 day prior to each assessment. All patients underwent electrocardiography and chest radiography at baseline. Patients with a history of any malignancy or with underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases, or immune deficiency were excluded.¹³

Patients received intravenous infusions with either 1000 mg rituximab (n=20) or placebo (n=10) on days 1 and 15. All patients were treated with methylprednisolone (100 mg i.v.), acetaminophen (1,000 mg orally), and clemastine (2 mg i.v.), and received 60 mg oral prednisone on days 1 and 2, 30 mg on days 3 and 4, and 15 mg on day 5 after each rituximab infusion.

As the principal investigator (HB) was involved in the development of ESSDAI, the database was prospectively completed according to the 12 ESSDAI domains: the cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathy and biological domains. The ESSDAI scores were assessed using the medical records of all pSS patients by an independent and blinded researcher (RM) at baseline, and at 5, 12, 24 and 48 weeks after treatment.

Statistical analysis

Evaluation of change over time in ESSDAI scores was analyzed using generalized estimating equations (GEE) analysis. Responsiveness of the ESSDAI was assessed using standardized response means (SRM) and effect sizes (ES). SRM was calculated as the mean change in score between two visits divided by the standard deviation (SD) of the change in score. ES was calculated as the mean change in score between two visits divided by the SD of the baseline score. SRM and ES <0.5 were interpreted as small, 0.5-0.8 as moderate and >0.8 as large. SRM or ES close to zero point towards an unchanged disease activity and indicates a stable clinical situation. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA). P Values <0.05 were considered statistically significant.

Results

Median (range) ESSDAI scores at baseline were 8.0 (4-13) and 6.5 (2-13) in the rituximab and placebo group, respectively. In rituximab treated patients, ESSDAI scores improved significantly compared to baseline up to 36 weeks after treatment and had returned to baseline values by week 48. In placebo treated patients, a significant decrease in ESSDAI scores was found only at week 5 (figure 1). From 5 to 24 weeks, the evolution of ESSDAI scores over time was significantly different between rituximab and placebo treated patients. ESSDAI scores were significantly lower in the rituximab group compared to the placebo group at weeks 12 and 24, which demonstrates the effectiveness of rituximab in reducing disease activity.

Figure 1. Median ESSDAI scores of pSS patients treated with rituximab (n=20) or placebo (n=10). * p <0.05 versus baseline. † p <0.05 rituximab versus placebo.

In the rituximab group, SRM and ES for ESSDAI scores were large at weeks 5-24, moderate at week 36, and small at week 48 (table 1). This indicates that ESSDAI scores adequately reflects the transient effect of the rituximab with decreasing disease activity up to week 24 and relapse of the disease activity at week 48. In the placebo group, SRM and ES were moderate at week 5 and small at all other time points.

Table 1. Responsiveness of ESSDAI in pSS patients treated with rituximab (n=20) or placebo (n=10). SRM and ES <0.5 were interpreted as small, 0.5-0.8 as moderate, and >0.8 as large.

	Standardized response mean (SRM)				
	Time point				
	Week 5	Week 12	Week 24	Week 36	Week 48
ESSDAI rituximab	-1.11	-0.97	-1.04	-0.44	-0.20
ESSDAI placebo	-0.60	-0.39	0.07	0.15	-0.18

	Effect size (ES)				
	Time point				
	Week 5	Week 12	Week 24	Week 36	Week 48
ESSDAI rituximab	-1.09	-1.04	-1.15	-0.50	-0.26
ESSDAI placebo	-0.60	-0.37	0.06	0.10	-0.18

Discussion

The present analysis of the data of our randomized double-blind, placebo-controlled trial demonstrates that the ESSDAI is able to show significant changes in disease activity in patients with pSS treated with rituximab compared to placebo. These findings confirm the usefulness of ESSDAI for clinical studies as suggested previously in the patient profile study by Seror et al.¹² and in the prospective open label study by Meiners et al.¹³

The high responsiveness at weeks 5, 12, and 24 matches the results of the changes in the other clinical and laboratory values as reported by Meijer et al.,⁸ showing a beneficial effect up to 24 weeks after treatment followed by a gradual return to baseline values. These laboratory values returned to baseline values within the same timeframe as ESSDAI after rituximab treatment. The significant decrease in ESSDAI as well as the moderate SRM and ES in the placebo group at week 5 are likely due to steroids (100 mg intravenous methylprednisolone, followed by an oral tapering of 2 days 60 mg, 2 days 30 mg and 1 day 15 mg prednisone), administered to minimize side effects of rituximab infusions.⁸

The large differences in responsiveness of ESSDAI between rituximab and placebo groups show that ESSDAI is a sensitive instrument to assess changes in disease activity over time. Based on the present data, ESSDAI at week 24 seems to be a good endpoint to assess treatment efficacy of rituximab. Overall, these results support the usefulness of ESSDAI in future clinical trials.

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4

Detailed analysis of the articular domain in patients with primary Sjögren syndrome

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Abstract

Objective: We used the 28-joint Disease Activity Score (DAS28) and the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) articular domain to assess the effect of rituximab (RTX) and abatacept (ABA) on articular involvement in primary Sjögren syndrome (pSS).

Methods: Patients with pSS treated with RTX (n = 18) or ABA (n = 13) and having a DAS28 erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) level ≥ 3.2 at baseline were selected. Generalized estimating equations were used to analyze the DAS28 and ESSDAI articular domain over time.

Results: In the RTX group, DAS28-ESR/CRP decreased significantly up to 48 weeks. In the ABA group, DAS28-ESR/CRP decreased significantly up to 24 weeks. DAS28 correlated significantly with ESSDAI articular domain.

Conclusion: DAS28 is useful to evaluate the effect of biologicals on articular involvement in patients with pSS.

Introduction

Arthralgia and arthritis are common features of disease activity in patients with primary Sjögren syndrome (pSS), with prevalence rates of 45%–50% and 15%–35%, respectively^{1,2}.

In a large cohort study of 921 Spanish patients, articular involvement was found to be the most prevalent extraglandular manifestation of pSS³.

The Disease Activity Score of 28 joints (DAS28) has been developed and validated to monitor disease activity including swollen joint count (SJC) and tender joint count (TJC) in patients with rheumatoid arthritis (RA)⁴. Although the DAS28 is validated for RA only, it is also used in other autoimmune diseases⁵. Patients with pSS with articular involvement could benefit from the therapies used in patients with RA. Therefore, it is clinically relevant to have a disease activity index that can be used in both diseases, to compare treatment effects.

The European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) has been developed and validated to measure systemic disease activity in patients with pSS⁶. The ESSDAI includes 12 domains, of which the articular domain is based on arthralgia in combination with morning stiffness and on the SJC from DAS28, but includes only 3 activity levels⁷.

In our study, we used the DAS28 and ESSDAI articular domain to assess the effect of rituximab (RTX) and abatacept (ABA) treatment on articular involvement in patients with pSS.

Materials and methods

Patients with pSS who received either RTX or ABA within our previously reported prospective open-label studies^{8,9} were selected based on DAS28-erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) ≥ 3.2 at baseline, to allow assessment of improvement in disease activity after treatment. Of the 28 patients treated with RTX (1000 mg, days 1 and 15)⁸, 18 had baseline DAS28-ESR ≥ 3.2 , and 11 patients had DAS28-CRP ≥ 3.2 . These patients were evaluated at baseline and at weeks 16, 24, 36, 48, and 60 after treatment. Of the 15 patients treated with ABA (infusions ~ 10 mg/kg of body weight, days 1, 15, and 29 and every 4 weeks thereafter)⁹, 13 had baseline DAS28-ESR ≥ 3.2 , and 11 DAS28-CRP ≥ 3.2 . These patients were evaluated at baseline and at weeks 4, 12, 24 (while taking treatment), and 36 and 48 weeks (while not taking treatment).

The patients with pSS with DAS28-ESR/CRP < 3.2 at baseline were excluded from this analysis because those patients had no articular involvement at baseline and thus could not show improvement from RTX or ABA treatment (of note: none of those patients developed articular involvement when receiving RTX or ABA treatment).

All patients fulfilled the revised American-European Consensus Group criteria for pSS¹⁰ and were negative for anticitrullinated protein antibodies.

At all visits, the number of swollen joints (SJC; range 0–28), number of tender joints (TJC; range 0–28), ESR, CRP, and patient visual analog scale (VAS) regarding general health were routinely recorded to calculate the DAS28-ESR and DAS28-CRP.

The articular domain of the ESSDAI (range 0–3) was scored as 0 (no activity: absence of currently active articular involvement); 1 (low activity: arthralgias in hands, wrists, ankles, and feet accompanied by morning stiffness > 30 min); 2 (moderate activity: 1–5 synovitis of 28 SJC); or 3 (high activity: ≥ 6 synovitis of 28 SJC)^{6,7}.

For this study, ethics board approval was not required.

Statistical analysis

Generalized estimating equations (GEE) were used to analyze the DAS28-ESR, DAS28 components, and ESSDAI articular domain over time within both treatment groups. In the RTX group, followup data up to 60 weeks were used to assess change over time compared to baseline. In the ABA group, on-treatment data up to Week 24 were used to assess change over time compared to the baseline and off-treatment data up to Week 48 that were used to assess change over time compared to Week 24. Further, the correlation between DAS28 and the ESSDAI articular domain over time was analyzed using GEE.

Internal responsiveness analysis was performed for DAS28-ESR at Week 24 in both RTX and ABA treatment groups using standardized response mean (SRM) as described by Husted, et al¹¹. SRM was calculated as the mean change in score between baseline and Week 24 divided by the SD of the change in score. SRM < 0.5 was considered small, 0.5–0.8 moderate, and > 0.8 large^{12,13}.

The same methodology was used to perform the additional analysis of DAS28-CRP in the RTX (n = 11) and ABA (n = 11) treatment groups. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS). P < 0.05 was considered statistically significant.

Figure 1. Changes over time of DAS-28_{ESR} in patients with either rituximab (A; N=18) or abatacept (B; N=13) treatment and of DAS-28_{CRP} with either rituximab (C; N=11) or abatacept (D; N=11) treatment. Box-and-whisker plots (Turkey); boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 1.5 times the interquartile distances; • indicate outliers; * p<0.05. DAS28: 28-joint Disease Activity Score;

Results

At baseline, the median DAS28-ESR scores were 3.7 [interquartile range (IQR) 3.4–5.0] and 4.5 (IQR 3.9–5.9) in the selected patients from the RTX and ABA treatment studies, respectively. Patients' baseline characteristics are shown in Supplementary Table 1, available with the online version of this article.

In the RTX group, no patients were taking additional disease-modifying antirheumatic drug therapy during the study period. In the ABA group, 2 patients were briefly treated with prednisolone because of photosensitivity of the skin. One of them had to start with hydroxychloroquine to control the skin manifestations.

Following RTX treatment, DAS28-ESR decreased significantly up to 48 weeks and had returned to baseline values at Week 60 (Figure 1A). In ABA-treated patients, DAS28-ESR

Figure 2. Changes over time of tender joint counts (TJC) and swollen joint counts (SJC) in patients with either rituximab (A and B; N=18) or abatacept (C and D; N=13) treatment. Box-and-whisker plots (Turkey); boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 1.5 times the interquartile distances; • indicate outliers; * p<0.05.

decreased significantly up to 24 weeks and had returned to baseline values at Week 36 (Figure 1B). Comparable results were found for DAS28-CRP (Figure 1C and 1D). The decrease of disease activity assessed with SJC and TJC was significant over time in both RTX and ABA treatment groups, with maximum effect at Week 24 (Figure 2).

Regarding the other components of the DAS28, ESR showed a significant decrease over time in the RTX group, again with maximum effect at Week 24. In the ABA group, there was no significant decrease of ESR over time. VAS general health decreased significantly over time until Week 60 in the RTX group, whereas no significant change over time was found for VAS general health in the ABA group.

Table 1. Proportion of pSS patients per category of ESSDAI articular domain during treatment with rituximab (n=18) or abatacept (n=13).

Rituximab group	Week 0	Week 16*	Week 24*	Week 36	Week 48	Week 60
No activity	11 (61)	17 (94)	17 (94)	13 (72)	14 (78)	12 (71)
Low activity	2 (11)	0 (0)	1 (6)	4 (22)	2 (11)	2 (12)
Moderate activity	4 (22)	1 (6)	0 (0)	0 (0)	1 (6)	1 (6)
High activity	1 (6)	0 (0)	0 (0)	1 (6)	1 (6)	2 (12)

Abatacept group	Week 0	Week 4*	Week 12*	Week 24	Week 36†	Week 48†
No activity	1 (8)	4 (31)	7 (54)	10 (77)	5 (38)	3 (23)
Low activity	5 (38)	5 (38)	5 (38)	2 (15)	3 (23)	4 (31)
Moderate activity	2 (15)	4 (31)	0 (0)	1 (8)	3 (23)	2 (15)
High activity	5 (38)	0 (0)	1 (8)	0 (0)	2 (15)	4 (31)

Values are presented as number (%) of patients.

* p<0.05 compared to baseline, † p<0.05 compared to week 24.

The articular domain of the ESSDAI decreased significantly over time with maximum effect at Week 24 in both treatment groups (Table 1). The proportion of patients with ESSDAI articular domain score ≥ 1 decreased significantly from 38.9% at baseline to 5.6% at Week 24 after RTX treatment and from 92.4% at baseline to 23.1% at Week 24 during ABA treatment.

During RTX or ABA treatment, there were no patients with an increase in DAS28-ESR/CRP or ESSDAI articular domain score between baseline and Week 24.

GEE analysis over time revealed that DAS28 was significantly associated with the articular domain of the ESSDAI in the RTX group [0–48 weeks: B (regression coefficient) = 1.203, $p < 0.001$] and in the ABA group (0–24 weeks: B = 0.942, $p < 0.001$; 24–48 weeks: B = 0.853, $p < 0.001$).

SRM for DAS28-ESR and DAS28-CRP at Week 24 versus baseline were large: 1.45 and 1.83 in the RTX group, respectively, and 1.37 and 1.81 in the ABA group.

Discussion

To our knowledge, this is the first analysis using DAS28 to assess the articular involvement in patients with pSS. These patients have several clinical and laboratory characteristics that are also rather common in RA, such as arthralgia and arthritis, vasculitis, pulmonary involvement, peripheral neuropathy, and decreased complement levels. These are important components of disease activity and should be considered in the clinical assessment and followup of patients with pSS and RA. The ESSDAI is a validated tool to evaluate these systemic disease manifestations and responses to treatment in pSS. However, there is a need to assess in more detail several specific extraglandular manifestations and individual domains or groups of domains of the ESSDAI, e.g., articular involvement, to provide target therapies. It will be impossible to develop and validate new diagnostic tools for each extraglandular manifestation of pSS. Therefore, some tools used outside of pSS can be validated for clinical trials in patients with pSS. We showed that DAS28-ESR and DAS28-CRP are sensitive enough to show the effect of treatment over time with biological therapies. Therefore, we propose to use DAS28 as an additional tool to assess articular involvement in pSS in clinical trials and to extrapolate the dosages of therapeutics from RA treatment experiences to pSS, because RA is a model disease in the development of new treatments for autoimmune diseases.

It is important to mention that the improvement in articular involvement in our patients with pSS, measured by DAS28, was dependent not only on ESR/CRP or VAS global health. SJC and TJC components of DAS28 contributed most to the change over time. Moreover, the DAS28 has comparable course and significant correlation over time with the articular domain of the ESSDAI. Baseline characteristics of our 2 open-label studies were different, mainly because of differences in inclusion criteria^{8,9}. In the RTX study we found less articular involvement than in the ABA study. Nevertheless, as in the ABA group, the decrease in articular involvement was statistically significant in the RTX group, but VAS and ESR/CRP also contributed to the decrease of DAS28 over time. Therefore, we suggest that DAS28 should be interpreted in patients with pSS in the same way as in patients with RA. Patients with pSS without arthralgia or arthritis should not be evaluated with DAS28, because DAS28 is meaningless in that setting (TJC and SJC will not be evaluated, only VAS and ESR).

The DAS28 is useful not only in patients with RA but also in patients with pSS to evaluate the effect of biological therapies on articular involvement.

Supplementary Table 1. Baseline characteristics of the pSS study population.

	Rituximab, N=18	Abatacept, N=13
Age (years)	40 (32-57)	41 (32-50)
Female gender (%)	17 (94)	11 (85)
Disease duration (months)	59 (37-90)	11 (7-37)
IgG (g/l)	21 (17-27)	20 (18-28)
RF (kIU/L)	107 (32-223)	62 (22-190)
Anti-Ro / SSA positive (%)	18 (100)	13 (100)
Anti-La / SSB positive (%)	13 (72)	10 (77)
ACPA positive (%)	0 (0)	0 (0)
UWS (ml/min)	0.09 (0.03-0.30)	0.13 (0.06-0.23)
SWS (ml/min)	0.30 (0.15-0.54)	0.39 (0.20-0.62)
Schirmer's I test (mm/5 min)	7 (1.5-11)	8 (4-16.5)
Tear break-up time (sec)	5 (3-7)	8 (4-10)
DAS-28ESR	3.7 (3.4-5.0)	4.5 (3.9-5.9)
SJC	2 (0-3)	2 (0-8)
TJC	4 (0-7)	8 (2-13)
ESR	34 ± 14	31 ± 18
VAS	69 ± 17	60 ± 16
DAS-28CRP*	4.3 (3.5-5.2)	4.9 (4.0-5.4)
ESSDAI	8.5 (5-11.5)	11 (8-15)
Cutaneous domain (%)	2 (11)	4 (31)
Respiratory domain (%)	3 (17)	2 (15)
Renal domain (%)	0 (0)	0 (0)
Articular domain (%)	7 (39)	12 (92)
Muscular domain (%)	0 (0)	0 (0)
PNS domain (%)	2 (11)	1 (8)
CNS domain (%)	0 (0)	0 (0)
Hematological domain (%)	8 (44)	2 (15)
Glandular domain (%)	11 (61)	9 (69)
Constitutional domain (%)	8 (44)	5 (38)
Lymphadenopathy domain (%)	0 (0)	1 (8)
Biological domain (%)	17 (94)	11 (85)
ESSPRI	7.3 (6.3-8.3)	7.3 (6-7.9.0)
Parotid biopsy characteristics		
Focus score ≥1	17 (94)	13 (100)
Lymphoepithelial lesions	8 (44)	9 (69)
Shift IgA to IgG	15 (83)	12 (92)
Germinal centres	5 (28)	0 (0)

Values are presented as number (%) of patients, mean ± SD or median (interquartile range).

* Selected patients from rituximab (N=11) or abatacept (N=11) groups with DAS-28CRP ≥3.2.

RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; UWS, unstimulated whole salivary flow rate; SWS, stimulated whole salivary flow rate; DAS-28ESR, Disease Activity Score in 28 joints, including erythrocyte sedimentation rate (ESR); DAS-28CRP, Disease Activity Score in 28 joints, including C-reactive protein; SJC, swollen joint count; TJC, tender joint count; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index.

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5

Serum immunoglobulin free light chains are sensitive biomarkers for monitoring disease activity and treatment response in primary Sjögren's syndrome

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Abstract

Objectives: Serum immunoglobulin free light chains (FLCs) are frequently elevated in B-cell-mediated autoimmune diseases, including primary SS (pSS). The objective of this study was to assess if serum FLCs can contribute to classification, mucosa-associated lymphoid tissue (MALT) lymphoma detection, monitoring of disease activity and treatment response in pSS.

Methods: Serum samples of 100 consecutive patients suspected of pSS were included. Forty-five patients fulfilled ACR-EULAR criteria for pSS. Additionally, samples of 17 pSS patients with MALT lymphoma and longitudinal samples of pSS patients treated with rituximab (n=20), placebo (n=10) or abatacept (n=15) were included. Serum FLC κ /FLC λ was measured by nephelometry or turbidimetry.

Results: At diagnosis, FLC κ and FLC λ serum levels were significantly higher in pSS compared with non-SS sicca patients. The FLC κ /FLC λ ratio was abnormal in 11% of pSS patients. In established MALT-pSS patients, without recent rituximab treatment (n=12), 50% had abnormal FLC κ /FLC λ ratios. FLC measurement had no additional value for pSS classification, compared with IgG and anti-SSA. FLC levels correlated significantly with systemic disease activity, assessed by EULAR SS Disease Activity Index (ESSDAI) and clinical ESSDAI, both cross-sectionally and longitudinally following treatment. Treatment with rituximab or abatacept significantly lowered FLC levels. FLCs show a large sensitivity to change and relative changes induced by treatment were higher compared with IgG.

Conclusion: Serum FLCs are elevated in pSS, and abnormal FLC κ /FLC λ ratios may be indicative for the presence of MALT lymphoma. FLC levels can be used as a biomarker for systemic disease activity and monitoring treatment responses. FLCs are sensitive to change and have more favorable kinetics than IgG.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease which characteristically affects the salivary and lacrimal glands. B-cell hyperactivity is a major contributor to the pathology of pSS [1]. The involvement of B-cells in pSS pathogenesis is among others reflected by the presence of hypergammaglobulinemia and autoantibodies, such as anti-SSA/Ro, anti-SSB/La and rheumatoid factor (RF). The elevated intracellular levels of Bruton's tyrosine kinase in naive and memory B-cells further reflect their intrinsic, more activated state [2]. Also, pSS patients have an enhanced risk of developing mucosa-associated lymphoid tissue (MALT) lymphoma, a subclass of malignant B-cell lymphoma [1,3]. In line with this role for B-cells in pSS pathogenesis, B-cell depletion therapy with rituximab shows favorable effects on salivary gland architecture and extraglandular manifestations of pSS [4]. However, not all patients benefit from this treatment, as shown by two large randomized controlled trials [5,6]. Validated biological markers for monitoring clinical response to therapy and/or disease activity in pSS are lacking. Promising markers are serological parameters of B-cell activity, including BAFF (B-cell Activation of the TNF Family, also named BLyS), CXCL13, β 2-microglobulin and immunoglobulin free light chains (FLC). These markers are fairly associated with systemic disease activity in pSS patients [7,8].

Primary SS (pSS) is a chronic, systemic autoimmune disease that characteristically affects the salivary and lacrimal glands. B cell hyperactivity is a major contributor to the pathology of pSS [1]. The involvement of B cells in pSS pathogenesis is reflected by, among others, the presence of hypergammaglobulinaemia and autoantibodies, such as anti-SSA/Ro, anti-SSB/La and RF. The elevated

FLC comprise kappa (κ) and lambda (λ) light chains, which are produced in excess compared to heavy chains during immunoglobulin synthesis by B-cells, plasmablasts and plasma cells. The surplus of light chains is secreted as FLC into serum [9]. The half-life of FLC in serum is very short (2-6 hours) compared to complete immunoglobulins and therefore the presence of FLC may reflect actual B-cell activity. FLC may have specific biological functions, which include binding to antigens on antigen-presenting cells and inhibition of apoptosis of neutrophils [10–12]. FLC serum levels correlate positively with other serological markers of B-cell activity and most strongly with serum IgG [13]. Levels of polyclonal FLC are not only elevated in pSS compared to healthy controls, but also in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [13–15]. In patients with SLE, FLC levels correlate with disease activity and are elevated in urine prior to relapse of symptoms [14,16]. However, the clinical relevance of serum FLC levels as a biomarker in pSS is unclear. The objectives of this study were to assess if serum FLC can contribute to classification, MALT-lymphoma detection, monitoring of disease activity and treatment response in pSS.

Methods

Study population

Consecutive patients (n=129), referred to the Sjögren Expertise Center of the University Medical Center Groningen (UMCG) for suspicion of pSS, were screened for eligibility. Exclusion criteria were age < 18 years, an incomplete diagnostic work-up, diagnosis of another systemic auto-immune disease, hepatitis C positivity and renal impairment (eGFR < 60 mL/min, MDRD formula), which influences serum FLC levels [9]. Patients that fulfilled 2016 ACR-EULAR criteria for pSS were classified as pSS patients [17], and the remaining patients as non-SS sicca patients. Serum samples of 18 pSS patients diagnosed with salivary gland MALT-lymphoma, who were enrolled as a subgroup in our Registry of Sjögren syndrome in UMCG-Longitudinal (RESULT) cohort, were also screened for eligibility. Of these 18 patients, one patient was excluded from FLC analysis because of renal impairment. The remaining 17 pSS-MALT patients were divided in a treatment group (patients who were treated for MALT lymphoma < 1 year before inclusion) and a no-treatment group (untreated patients and patients who were treated for MALT lymphoma > 1 year before inclusion). Informed consent was obtained from all patients according to the Declaration of Helsinki and the studies were approved by the Medical Research Ethics Committee of the UMCG (METc2013.066/METc2014.491).

Additionally, longitudinal serum samples of pSS patients that participated in our previously reported double-blind, randomized controlled trial with rituximab (1000 mg, days 1 and 15, n=30 with 2:1 randomization for rituximab and placebo) and open-label study with abatacept (~10 mg/kg of body weight, days 1, 15 and 29 and every 4 weeks thereafter, n=15) were included [18,19]. One patient in the placebo-arm of the rituximab study was lost to follow-up after week 12 and therefore no samples were available from this patient at week 24, 36 and 48. To minimize the risk of infusion reactions and serum sickness, all patients in the rituximab- and placebo-arm were treated with methylprednisolone (100 mg IV), acetaminophen (1000 mg orally) and clemastine (2 mg IV) prior to each infusion, and received oral prednisone (60 mg on days 1&2, 30 mg on days 3&4 and 15 mg on day 15). Except for these precautionary medications, treatment with concomitant immunosuppressants, including hydroxychloroquine and glucocorticoids, was discontinued during the study. All patients that participated in the rituximab and abatacept studies also fulfilled, retrospectively, the ACR-EULAR criteria.

The EULAR Sjögren's syndrome disease activity index (ESSDAI) and clinESSDAI (ESSDAI without the biological domain) were completed in all pSS patients [20,21].

FLC measurement

FLC (κ and λ) were measured in stored serum by quantitative turbidimetry using the Freelite assay and the Optilite analyzer (Binding Site, UK). The Freelite assay estimates FLC κ and FLC λ by two separate immunoassays that are based on affinity purified polyclonal antibodies coated onto latex particles. Samples from the MALT-lymphoma group and the rituximab study were measured by quantitative nephelometry using the Freelite assay and the BNProSpec analyzer (Siemens AG, Germany), as part of the diagnostic work-up. Reference intervals were 3.3–19.4 mg/L for FLC κ , 5.7–26.3 mg/L for FLC λ , and 0.26–1.65 for the κ/λ ratio, according to the 95% percentile range provided by the manufacturer. An abnormal FLC level was defined as an abnormal kappa and/or lambda level and/or abnormal κ/λ ratio.

Statistical analysis

Continuous data are presented as medians and interquartile ranges. Mann-Whitney U test was used to compare FLC levels between different groups. Predictor analyses of pSS classification were performed using binary logistic regression. Multivariate analysis was performed using the forward Wald method for inclusion of predictors that had a P-value <0.05 in the univariate analysis. The explained variance is presented as Nagelkerke's R square (R^2). Cross-sectional correlations between serum FLC and clinical and biological parameters (i.e., ESSDAI, clinESSDAI, IgG) were evaluated with Spearman's correlation coefficient. Longitudinal correlations between FLC and clinical parameters were analyzed with generalized estimating equations (GEE). GEE were used to analyze changes in FLC levels over time, namely during B-cell depletion (week 0–24), B-cell repopulation (week 24–48), during abatacept treatment (week 0–24) and after cessation of abatacept treatment (week 24–38). For the placebo group, identical time points were analyzed as for the rituximab group. To evaluate sensitivity to change, the standardized response mean (SRM) was calculated as the mean change score divided by the SD of the change score, between baseline and each consecutive time point. SRM <0.5 were interpreted as small, 0.5–0.8 as moderate, and >0.8 as large [22]. P-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, USA).

Results

From the diagnostic cohort, 100 out of 129 patients were included in the analyses. Reasons for exclusion were an incomplete diagnostic work-up (n=8), presence of another systemic auto-immune disease (n=12), missing serum samples (n=5), hepatitis C

Table 1. Baseline characteristics of different study cohorts.

Characteristic	Diagnostic cohort (n=100)		MALT-lymphoma cohort (n=17)	Rituximab trial (n=30)		Abatacept trial (n=15)
	pSS (n=45)	non-SS sicca (n=55)		RTX (n=20)	Placebo (n=10)	
Age, median (IQR), years	54 (46-63)	50 (40-56)	60 (50-64)	42 (32-53)	37 (32-60)	43 (32-51)
Female gender, n (%)	43 (96)	47 (86)	16 (94)	19 (95)	10 (100)	12 (80)
ESSDAI, median (IQR)	4 (1-9)	-	2 (1-12)	8 (6-11)	7 (5-9)	11 (8-14)
clinESSDAI, median (IQR)	4 (0-10)	-	2 (0-12)	7 (5-11)	5 (5-8)	11 (9-17)
IgG (g/L), median (IQR)	16 (12-20)	10 (9-12)	13 (9-17)	22 (19-26)	23 (16-27)	20 (15-27)
Anti-Ro/SSA positive, n (%)	34 (76)	3 (6)	16 (94)	20 (100)	10 (100)	15 (100)
Anti-La/SSB positive, n (%)	19 (42)	0 (0)	6 (35)	14 (70)	8 (80)	12 (80)
Biologic activity, n (%)	25 (56)	10 (18)	11 (65)	17 (85)	9 (90)	11 (73)
Treatment with corticosteroids, n (%)	2 (4)	2 (4)	2 (12)	0 (0)*	0 (0)*	0 (0)*
Treatment with DMARD, n (%)	7 (16)	3 (5)	7 (41)	0 (0)*	0 (0)*	0 (0)*
Kappa FLC mg/L, median (IQR)	22 (16-36)	15 (11-18)	24 (16-37)	23 (17-45)**	21 (15-27)**	38 (28-44)**
Lambda FLC mg/L, median (IQR)	21 (15-31)	15 (13-18)	15 (10-22)	26 (19-46)**	23 (19-24)**	30 (23-41)**
Ratio kappa/lambda	1.15 (0.89-1.51)	0.97 (0.78-1.20)	1.44 (1.15-1.95)	0.96 (0.75-1.24)**	0.98 (0.74-1.11)**	1.11 (0.86-1.52)**

*Treatment with prednisolone, hydroxychloroquine or other traditional disease-modifying anti-rheumatic drugs (DMARD) had to be discontinued at least 1 month before baseline. **Values at baseline, before start of treatment, are displayed. MALT: Mucosa-associated lymphoid tissue; IQR: Interquartile range; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; clinESSDAI: ESSDAI without the biological domain.

infection (n=2), or renal impairment (n=2). There were no patients with renal impairment in the treatment groups (rituximab, abatacept) at baseline or during follow-up. Baseline patient's characteristics of the different cohorts are summarized in table 1. Detailed clinical characteristics per patient of the MALT-lymphoma group are described in Supplementary Table 2.

Elevated FLC levels and κ/λ ratio in pSS patients at the time of diagnosis

Of the included patients from the diagnostic cohort, 45 (45%) patients were classified as having pSS. Twenty-nine (64%) of these pSS patients had abnormal FLC levels. Both FLC κ and FLC λ levels were significantly increased in pSS compared with non-SS sicca patients (figures 1A and 1B, $P<0.001$). In pSS, FLC κ and FLC λ levels were above the upper reference limits in 58% and 44% of patients, respectively. FLC levels were higher in anti-

Figure 1: Serum levels of FLCκ and FLCλ and the κ/λ ratio in pSS patients and sicca patients. FLC levels in a diagnostic cohort consisting of non-SS sicca patients (n=55) and pSS patients (n=45), classified according to the ACR-EULAR criteria, are displayed. In addition, results from established pSS patients with mucosa-associated lymphoid tissue (MALT)-lymphoma located in the salivary glands, without current or recent (<1 year) B cell depletion therapy, are displayed (n=12). Horizontal lines indicate the median. Dashed horizontal lines indicate the cut-off value(s). Orange triangles represent patients with salivary gland MALT-lymphoma. Mann-Whitney U test was used for statistical comparisons. P-values <0.05 were considered significant. Ns: Not significant.

SSA positive, compared with anti-SSA negative patients (P=0.037 for FLCκ, P=0.064 for FLCλ). In addition to absolute levels of FLC, the κ/λ ratio was assessed. A small but significant increase in the κ/λ ratio was observed in pSS, compared with non-SS sicca patients (figure 1C, P=0.009), indicating a slightly higher production of FLCκ versus FLCλ. There was no significant difference in κ/λ ratio between pSS patients with or without anti-SSA antibodies.

In five (11%) pSS patients and three (5%) non-SS sicca patients, a κ/λ ratio above the upper cut-off value was found. One of these pSS patients was diagnosed with MALT-lymphoma. This patient also presented with abnormal levels of RF (>200 IU/mL), IgG (25 mg/L), and weak type I cryoglobulinemia (polyclonal), but without lymphopenia or low C4. A second pSS patient with an abnormal κ/λ ratio had an IgG level of 32 mg/L and developed urticarial vasculitis and unilateral parotid gland swelling a few months after inclusion. A third pSS patient with an abnormal κ/λ ratio developed progressive neuropathy with lymphopenia, low C4 level and type I cryoglobulinemia (polyclonal) one year later during follow-up. In the other two pSS patients and in the three non-SS sicca patients with an abnormal κ/λ ratio, risk factors for lymphoma such as cryoglobulinemia, lymphopenia or low complement levels were not detected. . Together, these results indicate that an altered κ/λ ratio may indicate or precede severe clinical manifestations of pSS.

Abnormal κ/λ ratios in MALT-lymphoma patients

Because an abnormal κ/λ ratio was observed in a MALT-lymphoma patient in our diagnostic cohort, these ratios were also evaluated in established pSS patients with salivary gland MALT-lymphoma. Seventeen MALT-lymphoma patients were included, and five patients were analyzed separately because of recent or current B-cell depletion therapy. Of the 12 patients who were not treated with rituximab, six (50%) patients had an abnormal κ/λ ratio (figure 1C). In only one of these six patients a weak monoclonal immunoglobulin (M-protein) was detected by immunofixation. Of the five patients who were recently treated with rituximab, only one had an abnormal κ/λ ratio (data not shown). The latter patient with a κ/λ ratio of 6.2 received maintenance treatment with rituximab every half year, because of recurrent symptoms of vasculitis and polyneuropathy in the last three years.

FLC versus IgG measurement for prediction of pSS

We next investigated if FLC κ and FLC λ could predict pSS classification by logistic regression analysis. Univariate logistic regression analysis showed that FLC κ and FLC λ are both significant predictors of fulfilling the ACR-EULAR criteria for pSS (R^2 : 0.374 and 0.254, respectively). However, the explained variances for IgG and anti-SSA positivity were higher (R^2 : 0.521 and 0.605, respectively). After inclusion of the variables FLC κ , FLC λ , IgG and/or anti-SSA positivity in multivariate analysis, IgG and anti-SSA positivity were the only independent predictors of pSS classification (R^2 : 0.696). When only FLC κ , FLC λ and anti-SSA were included in the multivariate analysis, FLC κ contributed significantly to the model (Supplementary Table 3). These results indicate that FLC levels are neither superior nor additional to IgG and anti-SSA positivity as a classification biomarker for pSS.

Association between FLC levels and systemic disease activity at baseline

Previous studies have suggested that FLC levels correlate positively with extraglandular involvement in pSS patients [7,13]. Consistent with this finding, combined data from our diagnostic cohort and baseline data from the rituximab and abatacept trials, in which ESSDAI scores were relatively high (table 1), indicated that FLC κ , and to a lesser extent also FLC λ , correlated significantly with ESSDAI scores (figure 2A). The ESSDAI domain that showed the highest correlation with FLC levels was the biological domain, which can be explained by the strong correlations between IgG and FLC κ and FLC λ ($p=0.685$ and $p=0.621$, respectively). Therefore, also correlations between FLC and clinESSDAI were assessed and only FLC κ was significantly correlated to clinESSDAI scores, although a trend was seen for FLC λ (figure 2B).

Figure 2: Correlations between FLC and systemic disease activity. Correlations between FLC and systemic disease activity, as measured by ESSDAI and clinESSDAI, in 90 pSS patients classified according to ACR-EULAR criteria. Patients with pSS from the diagnostic cohort (n=45) and baseline data from the rituximab (n=30) and abatacept (n=15) cohorts were combined. Correlations were evaluated with Spearman's correlation coefficient (ρ).

FLC levels are affected by immunomodulatory treatment

Rituximab In the group of rituximab-treated and placebo-treated patients, 19 (63%) patients had abnormal FLC levels at baseline, which is comparable to the diagnostic cohort. None of the patients had an abnormal κ/λ ratio. Median values are displayed in table 1. No patients had monoclonal gammopathy, and no MALT-lymphoma patients were included in this treatment study. Rituximab reduced both FLC κ and FLC λ levels significantly over time (figure 3A). In placebo-treated patients, FLC also decreased significantly over time (figure 3B), which could be attributed to a drop only at week 5. In line with this notion, the decrease in FLC in the rituximab group over time was stronger, of longer duration, and significantly different from the placebo group ($P<0.001$ for both

Figure 3: FLC levels are lowered by immunomodulatory treatment. (A) FLC κ and FLC λ serum levels during B cell depletion (week 0-24) and B cell repopulation (week 24-48). (B) FLC κ and FLC λ serum levels in placebo-treated patients at the same time points as rituximab-treated patients. (C) FLC κ and FLC λ serum levels during abatacept treatment (week 0-24) and after cessation of treatment (week-24-48). P-values were calculated using generalized estimating equations with log-transformation of dependent variables.

Figure 4: Responsiveness of FLC κ and FLC λ in pSS patients treated with rituximab, placebo or abatacept. Standardized response means (SRM) are displayed for each treatment group at different time points during treatment (week 4/5, week 12, week 24) or after treatment (week 36 and 48). A negative SRM indicates lowering of FLC. SRM <0.5 is interpreted as small, 0.5–0.8 as moderate, and >0.8 as large.

FLC κ and FLC λ). Furthermore, during B-cell repopulation in the rituximab group, FLC κ and FLC λ levels increased to baseline values (figure 3A), whereas no changes were seen in the placebo group between weeks 24 and 48 (figure 3B). Relative changes in FLC κ and FLC λ after 24 weeks of treatment with rituximab were higher compared to IgG (median Δ -28%, -24% and -21%, respectively). SRM values for responsiveness were large (>0.8) for both FLC in the rituximab group, persisting until week 36 for FLC κ and week 24 for FLC λ (figure 4A). In the placebo group, a high SRM was found only at week 5 (figure 4B).

Abatacept At baseline, 14 (93%) patients had abnormal FLC levels, which is higher compared to the diagnostic cohort and the rituximab group. Three (15%) patients had an abnormal κ/λ ratio. Serum FLC levels were reduced by abatacept treatment (figure 3C). Levels of FLC κ decreased to a larger extent than FLC λ (figure 3C). Median relative changes between baseline and week 24 for FLC κ , FLC λ and IgG were -18%, -10% and -12%, respectively, indicating that FLC κ was most strongly reduced by abatacept treatment. SRM values were larger for FLC κ than FLC λ (figure 4C).

Associations between changes in FLC levels and systemic disease activity during treatment

Finally, we assessed if the observed changes in FLC levels correlated with clinical and biological parameters over time during treatment, namely the period of B-cell depletion by rituximab, and the period of treatment with abatacept (both week 0-24). We performed the same analyses for the period after treatment (week 24-48). The decrease in FLC κ and FLC λ in the rituximab group was significantly associated with lowering of ESSDAI and clinESSDAI scores from baseline to week 24 (table 2). Weaker correlations were observed in the placebo group (table 2). In the abatacept group, only FLC κ was

Table 2. Associations between FLC and systemic disease activity scores during and after treatment.

	ESSDAI		clinESSDAI		ESSDAI		clinESSDAI	
	During treatment (week 0-24)				After treatment (week 24-48)			
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
FLCκ rituximab	0.030	<0.001	0.024	<0.001	0.015	<0.001	0.011	<0.001
FLCκ placebo	0.015	<0.001	0.009	0.079	0.009	0.138	0.004	0.082
FLCκ abatacept	0.008	0.003	0.007	0.002	-0.004	0.425	-0.003	0.324
FLCλ rituximab	0.018	<0.001	0.015	<0.001	0.007	0.020	0.005	0.037
FLCλ placebo	0.005	0.052	0.005	0.011	0.013	0.007	0.007	0.012
FLCλ abatacept	0.002	0.188	0.002	0.235	-0.006	0.236	-0.006	0.141

Longitudinal analysis was conducted for the period during treatment (week 0-24) and after treatment (week 24-48). Logarithmic transformation of FLC values was performed, and transformed values were entered into the Generalized Estimating Equation (GEE) models. Beta represents the regression coefficient (log-transformed). ESSDAI: European League Against Rheumatism (EULAR) Sjögren's syndrome Disease Activity Index; clinESSDAI: ESSDAI without inclusion of the biological domain. Significant P-values are displayed in bold.

significantly associated with ESSDAI and clinESSDAI scores over time during treatment (week 0-24). Also after treatment, in the rituximab group, both FLCκ and FLCλ levels correlated significantly with ESSDAI and clinESSDAI scores (table 2), suggesting that the increase in both parameters after treatment occurs in a similar manner.

Discussion

Serum FLCs are biomarkers for actual B-cell activity and are frequently elevated in systemic autoimmune diseases [13,15]. This study shows that serum FLCκ and FLCλ levels are frequently elevated in pSS patients, compared to non-SS sicca patients, at the time of diagnosis. Importantly, we found that an abnormal FLC κ/λ ratio can be indicative for the presence of MALT-lymphoma. This study further shows that FLC levels rapidly decrease following treatment with rituximab or abatacept, and that these levels are associated with systemic disease activity at baseline and longitudinally in response to treatment.

In our diagnostic cohort, FLCκ and FLCλ levels were abnormal in 58% and 44% of patients, respectively. This percentage is considerably higher than the previously reported percentages of 22-24% by Gottenberg et al. [7,13]. This difference may be explained by higher B-cell activity in our cohort, reflected by higher IgG levels, and/or by the lower frequency of immunosuppressive drug use in our cohort. In line with a previous study by Sudzius et al. [23], we observed that increased FLC levels were more pronounced in anti-SSA-positive, compared with anti-SSA-negative pSS patients, suggesting that patients

with anti-SSA antibodies exhibit higher B-cell activity and hence produce more FLC. We also found a subtle, but significant increase in the κ/λ ratio in pSS patients, though only 11% of the pSS patients had an abnormal ratio according to the 95-percentile range [7]. The reason for this skewing is not clear, but one possibility is that it is due to the autoantibody status, indicating that autoreactive B-cells might express relatively more kappa than lambda chains. However, no difference in the κ/λ ratio was observed between anti-SSA-positive and -negative patients, in line with a previous report [23]. In addition to anti-SSA/-SSB antibodies, pSS patients frequently produce RF. RF-positivity in pSS is associated with a higher risk of lymphoma development [24]. Bende et al. showed that 41% of salivary gland MALT-lymphomas expressed B-cell receptors with strong RF-homology [25]. Interestingly, the vast majority of these lymphomas was typed as κ -predominant by immunohistochemistry. These data suggest that RF-producing B cells may contribute to the skewed κ/λ ratio in a subgroup of pSS patients.

Because one of the pSS patients with an abnormal κ/λ ratio in our diagnostic cohort was diagnosed with MALT-lymphoma, we evaluated FLC levels in a cohort of established pSS patients with MALT-lymphoma located in the salivary gland. A previous study by Witzig et al. revealed elevated FLC levels in 31% of MALT-lymphoma patients, but lymphoma localization was not specified [26]. Whether also salivary gland MALT-lymphomas in pSS patients present with abnormal FLC levels and/or ratios, is to the best of our knowledge not known. Our study shows that the κ/λ ratio was increased in 50% of patients with salivary gland MALT-lymphoma. In only one of the 12 (8%) pSS patients with MALT lymphoma a weak M-protein was detectable, indicating that secretion of complete immunoglobulins occurs only infrequently. A similar low frequency (9%) of M-protein in pSS-MALT patients was revealed by Wöhrer et al. [27], whereas we showed previously that M-proteins were present in 8 out 35 (23%) pSS-MALT patients [28]. Recent studies showed that the frequencies of monoclonal gammopathy in larger cohort of pSS patients were 7.4%-22% [29,30]. However, only few of the patients with M-proteins (0-6%) developed salivary gland MALT-lymphoma (follow-up time 6.3-10 years). These data strongly argue that the κ/λ ratio in serum may be more useful as indicator for the presence of MALT-lymphoma than finding a M-protein. This situation is analogous to patients with a monoclonal gammopathy of unknown significance (MGUS) in which the risk of progression to a malignant monoclonal gammopathy is higher in patients with an abnormal κ/λ ratio than in patients with a normal ratio [31]. In contrast to other pSS-lymphoma cohorts [8,32], the median ESSDAI score in our pSS-MALT cohort was relatively low. This may be explained by the fact that in our clinical work-up parotid gland biopsies are taken for diagnostic purposes. This setting results in unexpected findings of MALT-lymphoma in patients without persistent parotid gland swelling, high systemic disease activity or laboratory abnormalities. A second explanation could be that both patients with a historical and a current MALT diagnosis were included. Patients

with a historical diagnosis are closely monitored, as recurrence of MALT-lymphoma is seen rather frequently.

In addition to our findings in pSS-MALT patients, our study confirmed that abnormal FLC levels in pSS are associated with higher systemic disease activity, as measured by ESSDAI scores [7]. The biological domain of the ESSDAI score also includes elevated serum IgG levels, which obviously may bias the correlation between FLC levels and ESSDAI. For this reason we correlated FLC levels not only to ESSDAI, but also to clinESSDAI scores [20]. Interestingly, FLC κ was significantly and more strongly correlated to both ESSDAI and clinESSDAI scores than FLC λ . Thus, increased disease activity of pSS is not only associated with increased polyclonal B-cell activity, but remarkably also with preferential expansion of the kappa subtype, which is confirmed in other studies in pSS [7,8,13]. The reason for this preferential expansion remains obscure.

Besides a role as biomarker for systemic disease activity, FLC are potentially useful in monitoring the effect of immunomodulatory treatment on B-cell activity in pSS patients. Therefore, the effect of treatment with rituximab and abatacept on serum FLC levels was evaluated. Rituximab treatment significantly reduced FLC κ and FLC λ levels, reflecting the decreased number of antibody-secreting cells (i.e., B-cells, plasmablasts, plasma cells). A reduction in FLC was also seen in the placebo group at week 5, likely due to corticosteroid treatment around the rituximab infusions, but a significantly stronger decrease was observed in the rituximab group. The decrease in FLC correlated significantly with lowering of ESSDAI and clinESSDAI during B-cell depletion. These findings are consistent with studies in RA and SLE, showing a correlation between normalization of FLC levels and disease activity upon rituximab treatment [33,34]. We found that abatacept treatment also significantly reduced FLC κ and, to a smaller extent, FLC λ levels. FLC κ levels were significantly associated with ESSDAI and clinESSDAI scores over time during treatment. As B-cells are not directly targeted by abatacept, the observed decrease in FLC is likely a result of reduced T-cell help to B-cells. This is further substantiated by the previously observed decrease in serum levels of IgG, anti-SSA antibodies and RF, as well as circulating plasmablasts [19,35]. Additionally, our study reveals that FLC have a large sensitivity to change, assessed by SRM, and that relative changes in FLC κ were higher compared with IgG. An advantage of monitoring FLC is that changes in serum levels are more rapidly induced after initiation of treatment, compared with IgG. FLC have a half-life of several hours, while IgG has a half-life of several weeks [9]. Therefore, B-cell activity can be monitored by FLC levels without the delay that is seen for IgG.

In summary, this study shows for the first time that the κ/λ ratio in serum is abnormal in 50% of salivary gland MALT-lymphoma patients. Abnormal ratios should be taken

seriously and might be indicative for the presence of MALT lymphoma. Prospective analysis of the κ/λ ratio in pSS patients is necessary to confirm its potential role as predictor of MALT-lymphoma development, and to compare sensitivity with M-protein analysis. Moreover, our data underline the pathogenic role of B-cell hyperactivity, and particularly kappa-expressing B-cells, in pSS. Finally, we suggest that FLC are useful biomarkers to monitor the effect of immunomodulatory treatment on B-cell activity.

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Supplementary Table 1. The incidence of activity for each ESSDAI domain in pSS-MALT patients.

	pSS-MALT	
	No treatment* (n=12)	RTX** (n=5)
ESSDAI total score (median)	2.5	2
ClinESSDAI total score (median)	2	2
<i>Activity per domain, n (%)</i>		
Cutaneous	0 (0)	1 (20)
Respiratory	0 (0)	0 (0)
Renal	0 (0)	0 (0)
Articular	1 (8)	0 (0)
Muscular	0 (0)	0 (0)
PNS	1 (8)	1 (20)
CNS	0 (0)	0 (0)
Haematological	5 (42)	3 (60)
Glandular	2 (17)	1 (20)
Constitutional	2 (17)	0 (0)
Lymphadenopathy	1 (8)	0 (0)
Biological	8 (67)	3 (60)

*No treatment: No current B cell depletion therapy to treat MALT lymphoma. **RTX: Rituximab treatment <1 year before inclusion. ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ClinESSDAI: Clinical ESSDAI (ESSDAI without inclusion of the biological domain). PNS: Peripheral nervous system. CNS: Central nervous system.

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6

Physical fatigue characterizes patient experience of primary Sjögren's syndrome

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Abstract

Objectives: Besides ocular and oral dryness, fatigue is a major symptom in patients with primary Sjögren's syndrome (pSS). Our aim was to investigate the importance of fatigue in relation to other symptoms experienced as well as to evaluate the effect of rituximab treatment on fatigue in pSS patients with active disease.

Methods: This analysis was based on data from our open-label rituximab study in 28 pSS patients. Symptoms of dryness, physical fatigue, pain, and mental fatigue were scored on 0-10 scales (according to ESSPRI). Systemic disease activity was assessed with ESSDAI.

Results: At baseline, 24 (86%) patients rated physical fatigue as the complaint most eligible for improvement (median importance of 10), followed by pain, dryness, and mental fatigue. After rituximab treatment, physical fatigue showed maximum improvement of 2.5 points and 31% in median values at group level, and 10 (36%) patients reached physical fatigue score<5 representing patient-acceptable symptom state (PASS). In comparison, systemic disease activity improved 5.5 points and 73% at group level, and 22 (79%) patients reached ESSDAI<5 representing low disease activity. GEE analysis over time revealed that physical fatigue was significantly associated with absolute number of B cells, dryness and mental fatigue, but not with ESSDAI, IgG levels and IgM-RF.

Conclusion: Physical fatigue characterizes patient experience of pSS. Rituximab treatment resulted in significant improvement of patient-reported symptoms. However, the large majority of patients still experienced physical fatigue at an unsatisfactory level, above the cut-off value for PASS. Therefore, attention for optimal management of this prominent symptom is warranted.

Introduction

Primary Sjögren's syndrome (pSS) is one of the most common systemic auto-immune diseases. Besides ocular and oral dryness, fatigue is a major symptom in patients with pSS. The reported prevalence rates of abnormal fatigue range from 30 to 88% in pSS, depending on the study population and measurement instrument applied.[1-5]

Qualitative interviews with 9 patients demonstrated that pSS-related fatigue clearly differs from ordinary tiredness. Patients reported that their fatigue is not only characterized by a heavy and persistent lack of vitality, but also by unpredictable and uncontrollable daily fluctuations.[6] Importantly, fatigue was found to be associated with reduced health-related quality of life, impaired daily functioning, and work disability in pSS.[7-11]

Fatigue can be divided in different dimensions, e.g. physical, mental, motivational, and affective fatigue.[12] A good measurement instrument for fatigue should be reliable, sensitive to change, and easy to administer.[12] Validated questionnaires in pSS are one-dimensional such as a single item questionnaire on global fatigue,[13] and multi-dimensional such as the multi-dimensional fatigue index (MFI) and the profile of fatigue (PROF).[2,14]

The importance of fatigue in pSS is illustrated by the fact that it is frequently included in the composite primary endpoints of randomized controlled trials (RCTs) evaluating the effect of systemic treatment in pSS.[15-18] Fatigue is also part of the validated EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and the recently proposed Sjögren's Syndrome Responder Index (SSRI).[19,20] From patient perspective, it is meaningful to achieve a satisfactory state of well-being, also referred to as patient-acceptable symptom state (PASS).[21,22]

The aim of the present analysis was to investigate the importance of fatigue in relation to other symptoms experienced as well as to evaluate the effect of rituximab treatment on subjective assessment of fatigue in pSS patients with active disease.

Methods

The present analysis regarding patient experience of fatigue was based on data from our open-label rituximab study.[23] As described previously, 28 pSS patients were treated with rituximab 1000 mg intravenously at days 1 and 15. In 8 patients, this was their first course of rituximab treatment. In 20 patients, retreatment was started after recurrence

of clinical symptoms. All patients fulfilled the revised American-European Consensus Group (AECG) criteria for pSS and were over 18 years of age. The study protocol was approved by the ethics committee of the University Medical Center Groningen (UMCG; METc2008.179) and all patients provided written informed consent.

Clinical assessments

Patients were evaluated at baseline and 16, 24, 36, 48, and 60 weeks after (re)treatment with rituximab. At all visits, subjective symptoms of dryness, physical fatigue, and pain (joint or muscle pain in arms or legs) were scored on a numerical rating scale (NRS; on a scale of 0-10) according to the ESSPRI. ESSPRI total score was calculated as the mean of dryness, physical fatigue, and pain.[13] Mental fatigue (unable to think clearly, have difficulty to concentrate, forgetfulness or making mistakes) was also scored on NRS of 0-10. Patient-acceptable symptom state (PASS) refers to the highest level of symptoms beyond which patients consider themselves well. For ESSPRI, a lower score means less complaints. According to the analyses of Seror *et al.*, PASS was defined as score <5.[22]

At baseline and during follow-up, patients were asked to rank their symptoms of dryness, physical fatigue, pain, and mental fatigue in order of importance; from 1: most eligible for improvement to 4: least eligible for improvement. In addition, the importance for improvement of each symptom was scored on NRS of 0-10.

Fatigue was assessed in more detail using the Multidimensional Fatigue Inventory (MFI). The MFI consists of 5 domains (all ranging from 0-20); general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[24] MFI total score was calculated as the sum of the 5 domain scores.

Systemic disease activity was assessed using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI, range 0-123) and ESSDAI without the biological domain (ClinESSDAI; range 0-135).[25,26] Low disease activity was defined as ESSDAI <5, moderate disease activity as ESSDAI 5-13, and high disease activity as ESSDAI >13.[22] In addition, absolute number of B cells ($10^9/L$), IgG levels (g/L) and IgM-rheumatoid factor (RF; kIU/L) were measured in serum. For all these clinical assessments, higher scores represent worse outcome.

Statistical analysis

Results were expressed as number of patients (%), mean $\pm$ standard deviation (SD) or median (interquartile range; IQR) for categorical, normally distributed and non-normally distributed data, respectively. Generalized estimating equations (GEE) with

Table 1. Baseline characteristics of the pSS study population (n=28)

Female gender (n, %)	27 (96)
Age (years)	43 ± 14
Time since diagnosis (years)	5.3 (3.8-9.9)
B cells (10 ⁹ /L)	0.27 ± 0.15
IgG (g/L)	22.5 ± 7.4
IgM-RF (kIU/L)	90 (30-220)
Anti-Ro/SSA positive (n, %)	28 (100)
Anti-La/SSB positive (n, %)	20 (71)
UWS (mL/min)	0.10 (0.03-0.27)
SWS (mL/min)	0.31 (0.16-0.58)
ESSPRI total score	6.7 (5.0-8.2)
Physical fatigue	8 (6-9)
Pain	7 (4-8)
Dryness	7 (3-8)
Mental fatigue	5.5 (3-7)
MFI total score	67.2 ± 18.9
General fatigue	18 (15-19)
Physical fatigue	16 (12-19)
Reduced activity	12.5 (10-16)
Mental fatigue	11 (8-15)
Reduced motivation	12.5 (9-14)
ESSDAI total score	8.0 ± 4.5

Values are presented as mean ± SD or median (IQR), unless otherwise indicated. RF: rheumatoid factor; USW: unstimulated whole salivary flow rate; SWS: stimulated whole salivary flow rate; MFI: Multidimensional Fatigue Inventory; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

exchangeable correlation structure was used to analyze clinical assessments over time within patients. Since residuals were non-normally distributed, ESSDAI was log-transformed before entered into the equation.

Spearman correlation coefficient was used to investigate the relation of physical and mental fatigue on NRS with the MFI domains. To evaluate sensitivity to change, the standardized response mean (SRM) was calculated as the mean change score between baseline and 16 or 24 weeks divided by the SD of the change score. SRM <0.5 were interpreted as small, 0.5-0.8 as moderate, and >0.8 as large. P values <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS, Chicago, IL, USA).

Results

Of the 28 included patients with pSS, 96% were female, mean age was 43 ± 14 years, median time since diagnosis was 5.3 years (IQR 3.8-9.9), and median ESSDAI was 8.0 ± 4.5 . Baseline characteristics are presented in Table 1.

Importance of symptoms

At baseline, 24 (86%) patients reported physical fatigue as the complaint most eligible for improvement, followed by pain and dryness. Mental fatigue was ranked as the complaint least eligible for improvement by 12 (50%) patients (Figure 1). However, for all these 4 domains, patients found it very important to get rid of their symptoms, reflected by median scores of importance for improvement of 8 or higher. As shown in Figure 1, the highest scores were again given for physical fatigue (median 10, IQR 9-10). Also during follow-up, patients marked physical fatigue as most important for improvement.

Figure 1. Order of importance (A) and importance for improvement (B) of physical fatigue, pain, dryness, and mental fatigue according to the 28 pSS patients with active disease before start of rituximab treatment

Figure 2. ESSPRI total score (A), physical fatigue (B), pain (C), dryness (D), mental fatigue (E), and ESSDAI total score (F) during treatment with rituximab in 28 pSS patients.

Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers. * Statistically significant compared with baseline.

Effect of rituximab treatment

Rituximab treatment resulted in significant improvement in patient-reported symptoms of physical fatigue, pain, dryness and mental fatigue, with maximum effects of all four domains seen at 16 or 24 weeks of follow-up (Figure 2). A comparable course was found for absolute number of B cells, IgG levels, and IgM-RF (data not shown).

Figure 3. MFI total score (A) and MFI domains (B-F) during treatment with rituximab in 28 PSS patients.

Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers. * Statistically significant compared with baseline.

After rituximab treatment, the maximum absolute and relative improvement in median values at group level was 2.5 points and 31% for physical fatigue, 2.5 points and 36% for pain, 2.5 points and 36% for dryness, and 2 points and 36% for mental fatigue, respectively. The maximum improvement for the ESSPRI total score was 1.3 points and 20% at group level. In comparison, systemic disease activity assessed with ESSDAI improved 5.5 points and 73% at group level (Figure 2).

Rituximab treatment also resulted in significant improvement in all domains of the MFI. General fatigue showed 25% improvement at group level, physical fatigue 19%,

Table 2. Disease activity status before and after rituximab treatment in 28 pSS patients.

	Baseline	Week 16	Week 24
ESSPRI			
PASS total score (<5)	7 (25)	10 (36)	12 (43)
PASS physical fatigue (<5)	5 (18)	10 (36)	6 (21)
PASS pain (<5)	7 (25)	14 (50)	12 (43)
PASS dryness (<5)	9 (32)	12 (43)	14 (50)
PASS mental fatigue (<5)	13 (46)	17 (61)	13 (46)
ESSDAI			
Low activity (<5)	8 (29)	22 (79)	21 (75)
Moderate activity (5-13)	16 (57)	6 (21)	7 (25)
High activity (≥14)	4 (14)	0 (0)	0 (0)

Values are presented as number of patients (%). ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; PASS: patient-acceptable symptom state; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

Table 3. Standardized response mean (SRM) during rituximab treatment in 28 pSS patients.

	Week 16	Week 24
ESSPRI total score(22)	-0.86	-0.68
Physical fatigue	-0.95	-0.56
Pain	-0.53	-0.46
Dryness	-0.72	-0.61
Mental fatigue	-0.63	-0.20
MFI total score	-1.01	-0.84
General fatigue	-1.02	-0.81
Physical fatigue	-1.11	-0.74
Reduced activity	-0.91	-0.65
Mental fatigue	-0.38	-0.44
Reduced motivation	-0.59	-0.54
ESSDAI total score(22)	-1.19	-0.98

MFI: Multidimensional Fatigue Inventory; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

reduced activity 12%, mental fatigue 9%, and reduced motivation 16%. The maximum improvement for the MFI total score was 14% (Figure 3).

At 60 weeks of follow-up, clinical assessments had returned to baseline values (Figures 2 and 3).

GEE analysis over time revealed that physical fatigue was significantly associated with the absolute number of B cells ($B=4.309$, $p<0.001$) and the other patient-reported symptoms pain ($B=0.429$, $p<0.001$), dryness ($B=0.249$, $p=0.014$) and mental fatigue ($B=0.487$, $p<0.001$), but not with ESSDAI ($B=0.057$, $p=0.12$), ClinESSDAI ($B=0.051$, $p=0.12$), IgG levels ($B=0.046$, $p=0.17$) and IgM-RF ($B=0.001$, $p=0.43$).

Patient-acceptable symptom state

Before rituximab treatment, 18% of the patients had physical fatigue score <5 , representing a satisfactory state according to the PASS. The proportion of patients with PASS for physical fatigue increased to a maximum of 36% after treatment. For the ESSPRI total score, patients with PASS increased from 25% at baseline to 43% after treatment. In comparison, the proportion of patients with low disease activity according to ESSDAI increased from 29% at baseline to 79% after treatment (Table 2).

Physical fatigue as endpoint

Sensitivity to change of ESSPRI physical fatigue was large to moderate, with SRM of -0.95 at 16 weeks and -0.56 at 24 weeks. For MFI general and physical fatigue, SRM values were also large to moderate. In comparison, sensitivity to change of ESSDAI was large, with SRM of -1.19 at 16 weeks and -0.98 at 24 weeks (Table 3).

ESSPRI physical fatigue showed the strongest correlation with MFI general fatigue ($\rho=0.930$) and MFI physical fatigue ($\rho=0.803$) at baseline. ESSPRI mental fatigue showed the strongest correlation with MFI mental fatigue ($\rho=0.623$). Comparable results were found at 16 and 24 weeks of follow-up (data not shown).

Discussion

In this post-hoc analysis of our open-label rituximab study in 28 pSS patients, we investigated patient experience regarding the importance of fatigue compared with other symptoms as well as the effect of rituximab treatment on fatigue.

Before the start of rituximab treatment, pSS patients rated the need to reduce their fatigue symptoms as very high, reflected by median scores of importance of 10 and 8 (out of 10) for physical and mental fatigue, respectively. Interestingly, the vast majority of patients (86%) reported physical fatigue as most eligible for improvement, more than symptoms of pain and dryness. Half of the patients ranked mental fatigue as least eligible for improvement. Previous studies also showed that physical fatigue is more severe and

frequent than mental fatigue in pSS. In a cross-sectional study of 94 pSS patients, 96% reported somatic fatigue and 48% mental fatigue according to PROF scores >2 .^[1] In the development study of the ESSPRI in 230 pSS patients, dryness (39%), physical fatigue (32%), and limb pain (20%) were reported as most in need of improvement, whereas mental fatigue was least in need of improvement according to 47% of the patients.^[13]

In accordance, MFI scores were highest for general fatigue and physical fatigue in our study population. Multiple studies have shown that MFI scores are significantly worse in pSS patients compared with healthy controls.^[2,27-30] After controlling for depression, differences in general fatigue, physical fatigue, and reduced activity remained statistically significant.^[27,28] This confirms the presence of particularly physical fatigue in pSS.

The pathophysiological mechanism underlying fatigue in pSS is not yet elucidated, but is probably multi-factorial. Cytokines such as IL-6 and IFN- α , neuroendocrine disturbances, autonomic dysfunction, sleep disturbance, depression, anxiety, and tendomyogenic complaints have been suggested to be important factors in abnormal fatigue.^[5,12] Previously, we demonstrated that B cell depletion with rituximab results in a significant reduction in serum levels of several cytokines/chemokines including IL-6 and IFN- α .^[31] In line with this notion, Barr et al. provided evidence that at least part of the beneficial effects of B cell depletion therapy on autoimmune disease can be explained by deletion of IL-6 producing B cells.^[32] Thus, our finding that in patients treated with rituximab, physical fatigue over time was significantly associated with the absolute number of B cells, may suggest that B cell derived IL-6 might be directly involved in this process. Unfortunately, these cytokines were not measured in this open-label study, so the direct relation with physical fatigue could not be analyzed.

In this open-label study, rituximab treatment resulted in significant improvement in patient-reported symptoms of physical fatigue, pain, dryness, and mental fatigue. However, the improvement in subjective symptoms was much less than the improvement in objective systemic disease activity. Recently, the minimal clinically important improvement (MCII) of the ESSPRI was defined as a decrease of at least one point or 15% on NRS of 0-10.^[22] A small study of 40 pSS patients assessed the minimally important difference (MID) of patient-reported outcomes on VAS of 0-100. Interestingly, the MID scores for improvement and worsening in fatigue were found to be different. A relatively small change in VAS fatigue (mean -6.2 mm) was perceived by the patient as improvement, whereas a larger change (mean +15.2 mm) reflected worsening.^[33] At the group level, the median score of physical fatigue on NRS improved 2.5 points and 31% after rituximab in our study, which is more than the proposed MCII and MID scores. Overall, this improvement in physical fatigue seems thus to be clinically relevant.

Only a minority of our patients (36%) experienced physical fatigue below the cut-off value for the PASS after treatment. This means that although physical fatigue improved significantly after rituximab, most patients did not consider themselves in a satisfactory state. In comparison, 79% of patients reached low disease activity according to the ESSDAI, which represents an acceptable level of systemic disease activity. It should be kept in mind that the PASS was validated for the ESSPRI total score and may not be adequate for all individual symptoms.[22]

A limitation of our open-label trial is that no control group was available. However, improvement in fatigue during rituximab treatment was also found in previous RCTs. [16,34] In a pilot study, 17 pSS patients with visual analogue scale (VAS) fatigue scores >50 were randomized to receive either 2 infusions of rituximab or placebo, in combination with steroids. At 6 months, there was a significant improvement in VAS fatigue in the rituximab group, but not in the placebo group. Comparable results were found for the somatic fatigue domain of the PROF.[34] In the TEARS trial, 120 pSS patients with scores ≥ 50 mm on 2 or more of 4 VAS (global disease, dryness, fatigue, pain) were randomized to rituximab or placebo plus steroids. After adjustment for baseline characteristics, the mean decrease in VAS fatigue was larger with rituximab than placebo at 6, 16, and 24 weeks. Furthermore, fatigue responded better to rituximab treatment than the other patient-reported symptoms.[16] However, both trials did not achieve their primary study endpoint, defined as $>20\%$ decrease in VAS fatigue in the pilot study and ≥ 30 mm decrease in 2 of 4 VAS at 24 weeks in the TEARS trial.[16,34]

Recent studies showed the potential value of biologic treatment such as rituximab, abatacept or belimumab. Thus far, there is no consensus about the primary endpoint of efficacy.[35] A large cross-sectional study including 395 pSS patients demonstrated that patient-reported symptoms and systemic disease activity are complementary facets of pSS, reflected by very low correlation between ESSPRI and ESSDAI.[19,36] We found also very low correlations for ESSPRI total score as well as for the individual symptoms (data not shown). Furthermore, we showed that physical fatigue over time was significantly associated with other patient-reported symptoms, but not with ESSDAI. This again indicates that there is a discrepancy between patient experience of physical fatigue and objective systemic disease activity.

The sensitivity to change of the ESSPRI question on physical fatigue was large to moderate, but lower compared to the ESSDAI.[23] ESSPRI physical fatigue correlated strongly with MFI domains general and physical fatigue. Based on these results, a single item question on physical fatigue seems worthwhile to include in clinical trials, preferably as secondary endpoint.

In conclusion, physical fatigue characterizes patient experience of pSS. Patients rated physical fatigue as most eligible for improvement by treatment, more than symptoms of pain, dryness, and mental fatigue. Rituximab treatment resulted in a significant and clinically relevant improvement of physical fatigue. However, the large majority of patients did not achieve a satisfactory state and still experienced physical fatigue above the cut-off value for the PASS. Therefore, attention for optimal management of this prominent symptom is warranted in daily practice and future clinical trials in pSS.

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7

10-year follow-up of patients with rheumatoid arthritis and secondary Sjögren Syndrome or sicca symptoms in daily clinical practice

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Abstract

Objectives: to evaluate the presence of sicca symptoms and secondary Sjögren's syndrome (SS) and the association with clinical characteristics, functional tests and patient-reported outcomes in patients with rheumatoid arthritis (RA) at baseline and after 10 years of follow-up.

Methods: a cohort of RA patients was evaluated in 2008 and re-evaluated in 2018 with respect to sicca symptoms, presence of secondary SS according to AECG classification criteria, disease activity of RA and patient-reported outcomes. Patient characteristics were compared between the RA-non-sicca, RA-sicca and RA-SS groups.

Results: Of the original 2008 cohort of 96 RA patients, 32 (33%) had sicca symptoms and 6 (6.3%) secondary SS. Of the 36 patients who agreed to be re-evaluated in 2018, 6 (17%) had sicca symptoms and 2 (6%) developed secondary SS. In the majority of patients, sicca symptoms were reversible while the functional tests of salivary and lacrimal glands significantly decreased. 67% of RA-sicca patients had no sicca complaints at the second screening, while only two RA-sicca patients developed secondary SS. RA-SS patients and, to a slightly lesser extent, RA-sicca patients had significantly higher RA disease activity (DAS-28), lower lacrimal (Schirmer's test) and salivary gland function, more limitations in daily activities (HAQ), worse health-related quality of life (RAND-36), more fatigue (MFI) and more patient symptoms (ESSPRI) compared to RA-non-sicca patients.

Conclusions: Secondary SS was found in a minor subset of the RA patients. Sicca symptoms of the eyes or mouth were more frequent, but their presence varied over time. Higher RA disease activity was associated with SS and sicca symptoms. These patients had lower gland function and worse patient-reported outcomes.

Introduction

Sicca symptoms of eyes and mouth are rather common in patients with rheumatoid arthritis (RA). (1) (2) (3) (4) (5) (6) These sicca symptoms can be due to a variety of diseases that are associated with RA and/or the use of xerogenic medication that patients take because of these diseases. (7) More specifically, RA patients with sicca symptoms as main complaint can suffer from secondary Sjögren's syndrome (SS). (8) (9) (10) (11)

SS is a chronic autoimmune inflammatory disease characterized by progressive focal lymphocytic cell infiltration of the salivary and lacrimal glands giving rise to focal sialoadenitis with, amongst others, the sensation of a dry mouth (xerostomia) and dry eyes (keratoconjunctivitis) as a result. Moreover, extra glandular manifestations can occur in the course of SS. (12) Sicca symptoms and rheumatic nodules are the most common extra-articular manifestations in RA patients. (2) Therefore, RA patients with sicca symptoms should be evaluated for secondary SS because of the risks of excessive fatigue, early dental loss, damage of the cornea, desiccation of the oral mucosa, oral infections, increased risk of developing mucosa associated lymphoid tissue (MALT) lymphomas, and increased mortality. (13) (14) (15) (16) Additionally, treatment choice of RA should be carefully evaluated if SS is present, as some treatment modalities, like methotrexate, can predispose to lymphoma, in particular the development of MALT lymphoma. (17)

Several clinical characteristics of RA have been reported to be associated with SS: RA patients with longstanding disease, female gender, high disease activity, high titers of rheumatoid factor, erosions and extra-articular manifestations are at risk of developing sicca symptoms and SS. (11) (18) (19) (20) (21) (10) (22) Most studies evaluated either sicca complaints among the RA patients or secondary SS in RA patients. We are not aware of the studies that compared sicca complaints and secondary SS simultaneously and prospectively. Furthermore, little is known whether sicca symptoms change over time and if RA patients with sicca symptoms will develop secondary SS over time. In the present study, we assessed the prevalence and progression of sicca symptoms and secondary SS over time and the association with clinical characteristics, functional tests and patient-reported outcomes in a cohort of RA outpatients.

Methods

In 2008, established RA patients were randomly selected from eligible RA patients attending our outpatient clinic. Patients were selected by appointment time: RA patients who had an appointment at 9.00, 10.00 and 11.00 o'clock were asked to participate.

Patients were included if they were 18 years or older and have been diagnosed with RA according to American College of Rheumatology 1987 criteria. (23) All patients were on a routine six month recall schedule by their rheumatologist or had, due to their disease activity, more frequent visits. As the development of sicca complaints made RA patients suspect to have developed secondary SS, these RA patients with sicca complaints were subjected to a routine diagnostic Sjögren's work-up according to normal clinical practice. Patients with a history of HIV, hepatitis C, head and neck radiotherapy, pre-existing lymphoma, sarcoidosis, graft versus host disease and diabetes mellitus were excluded from the study. Disease activity of RA was measured by a rheumatologist using Disease Activity Score of 28 joints (DAS-28 score). (24) Age of onset of RA, duration of RA, presence of erosions and extra-articular manifestations, and current medication were recorded. Laboratory parameters, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (anti-CCP), antinuclear antibodies (ANA), anti-SSA/SSB antibodies, and immunoglobulin's (IgG, IgA, IgM) were measured.

To assess sicca symptoms, a sicca-questionnaire was applied (Table 1). Patients reporting at least one sicca symptom of the eyes or mouth were classified into the RA-sicca group. All patients from the sicca group underwent a diagnostic work-up for the presence of secondary SS according to the American-European Consensus Group (AECG) classification criteria as applied in daily clinical practice. (25) (26) In addition to whole saliva, submandibular/sublingual (SM/SL) and parotid (PAR) saliva were collected to assess salivary gland function. Glandular saliva was collected in preweighted plastic tubes from each parotid gland and simultaneously from the submandibular/sublingual (SM/SL) glands by syringe aspiration. The first five minutes unstimulated salivary secretions was collected, followed by citric acid stimulated secretions over 10 minutes. (27,28) Schirmer's test was performed to assess lacrimal function. (29) Patients were asked to complete the Health Assessment Questionnaire (HAQ) to assess functional status, RAND-36 questionnaire to assess health-related quality of life and Multidimensional Fatigue Inventory (MFI) to assess fatigue. (30) (31) (32)

In 2018, all RA patients who participated in the screening in 2008 were asked to participate again. The identical screening protocol as in 2008 was applied in 2018. In addition, patients were asked to complete the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to assess patient symptoms of dryness, fatigue and pain. (33)

The Medical Ethical Committee of the University Medical Center Groningen, Groningen, the Netherlands, assessed the study proposal and concluded that formal approval was not required as we looked to the patients from the standard of care point.

Statistical analysis

Results are presented as number of patients (%) for categorical data and mean $\pm$ SD (median) for continuous data.

Three groups were distinguished: RA-non-sicca group, RA-sicca group and RA-SS group. Because the sample size of RA-SS group was small, non-parametric statistics were used to compare clinical characteristics, functional tests and patient-reported outcomes. Continuous parameters were overall compared between these three groups with Kruskal-Wallis test. Only parameters with a P value ≤ 0.05 were further tested between each two groups with Mann-Whitney test. For categorical parameters, Chi-Square test was used, followed by Chi-Square or Fisher's exact test. Additionally, univariable and multivariable logistic regression analyses were used to assess the associations between sicca symptoms or secondary SS and disease activity parameters corrected for potential confounders (age, sex, and RA duration) at baseline.

To explore if there was potential bias in the selection of patients, Independent Samples t-test or Mann Whitney U test and Chi-Square or Fisher's Exact test were used as appropriate to compare baseline characteristics of the patients from 2008 who did and did not take part in the screening in 2018.

Clinical characteristics, functional tests and patient-reported outcome of RA patients who participated in the screening in 2018 were compared over time (2008 vs. 2018) with Paired Samples t-test or Wilcoxon Signed Rank test for continuous parameters and McNemar test for categorical parameters.

Finally, clinical characteristics, functional tests and patient-reported outcome parameters were compared between three groups based on their screening in 2018: RA-non-sicca group, RA-sicca group and RA-SS group. Continuous variables were overall compared between three groups with Kruskal-Wallis test. Only parameters with a P value ≤ 0.05 were further tested between two groups with Mann-Whitney U test. For categorical parameters, Chi-Square test was performed, followed by Fisher's exact test.

Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS). P values ≤ 0.05 were considered statistically significant.

Table 1. Patient questionnaire for the assessment of xerostomia and ocular dryness based on sicca questionnaire from the AECG 2002 classification criteria (25)

-
1. Did you have 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?
 4. Did you have daily feeling of dry mouth for more than 3 months?
 5. Did you have recurrently or persistently swollen salivary glands as an adult?
 6. Do you frequently drink liquids to aid in swallowing dry food?
-

Results

Screening 2008

From the 116 eligible RA patients invited to participate in the study in 2008, 20 (17%) patients were unwilling to participate due to lack of time (n=12) or lack of interest (n=8) in the diagnostic SS work-up. As a result, 96 RA patients accepted to join the study, of whom 75 (78%) were female with a mean age of 54 ± 10 years and a median disease duration of 10 years (IQR 5-17). 32 of the 96 (33%) included patients reported to have at least one sicca symptom of the eyes or mouth (RA-sicca group). Six (6.3%) patients were classified as suffering from secondary SS according to AECG classification criteria (RA-SS group). Most patients were using methotrexate as conventional DMARD and anti-TNF as biological DMARD. A minority of patients was using rituximab, abatacept or tocilizumab therapy.

No significant differences were found in age, gender, disease duration and the proportion of patients with RF, anti-CCP, ANA or anti-SSA/SSB antibody positivity between the three groups. RA-sicca patients used significantly more xerogenic drugs compared to RA-non-sicca and RA-SS patients. RA disease activity assessed with DAS-28 (including CRP and ESR) was significantly higher in RA-SS patients than in RA-sicca and RA-non-sicca patients. RA-sicca patients had also higher disease activity than RA-non-sicca patients (Table 2).

Functional tests of lacrimal (Schirmer's test) and salivary glands (whole and glandular saliva) were significantly impaired in RA-SS patients compared to RA-non-sicca and RA-sicca patients (Table 2). RA-sicca patients showed lower saliva production of submandibular and sublingual glands both at rest and after stimulation and also lower parotid gland secretion at rest compared to RA-non-sicca patients.

Both groups of RA patients with sicca complaints and SS had more limitations in daily activities (HAQ), experienced worse health-related quality of life (RAND-36), and reported more fatigue (MFI) than RA-non-sicca patients (Table 2).

Table 2. Clinical characteristics of RA patients with SS, with sicca symptoms but no SS, and without sicca symptoms in 2008

	RA- Non-sicca (n=58)	RA-sicca (n=32)	RA-SS (n=6)	P-value (overall)
Demographics				
Female gender	42 (72%)	28 (88%)	5 (83%)	0.241
Age (years)	54 ±12 (56)	54 ±8 (55)	58 ±7 (60)	0.655
Disease variables				
Time since RA diagnosis (years)	10 ±8 (10)	14 ±9 (11)	15 ±9 (13)	0.175
RF positive	48 (83%)	28 (88%)	6 (100%)	0.481
Anti-CCP positive	48 (83%)	27 (84%)	5 (83%)	0.584
Anti-SSA positive	4 (7%)	2 (6%)	1 (17%)	0.661
ANA positive	40 (53%)	21 (66%)	5 (83%)	0.461
IgG level	12.9 ±2.8 (12.7)	12.7 ±2.7 (12.7)	14.9 ±2.6 (15.2)	0.191
Xerogenic drug use	29 (50%)	26 (81%)*	4 (67%)	0.014
Presence of erosions	39 (67%)	27 (84%)	6 (100%)	0.068
Presence of EAMs	25 (43%)	17 (53%)	4 (67%)	0.421
DAS-28(ESR)	2.7 ±1.1 (2.6)	±1.1 (3.1)*	5.1 ±1.4 (5.9)* †	0.001
DAS-28(CRP)	2.4 ±0.8 (2.2)	2.9 ±0.9 (3.0)*	4.1 ±1.5 (4.2)*	0.001
Dryness				
Schirmer's test (mm/5min)	16.7 ±10.5 (14.0)	15.4 ±11.4 (13.8)	3.9 ±1.8 (3.0)* †	0.001
Whole rest saliva (ml/min)	0.35 ±0.27 (0.23)	0.18 ±0.12 (0.15)	0.05 ±0.04 (0.06)* †	0.001
SM/SL, at rest (ml/min)	0.27 ±0.24 (0.18)	0.15 ±0.10 (0.11)*	0.05 ±0.04 (0.05)* †	0.001
SM/SL, stimulated (ml/min)	0.55 ±0.32 (0.50)	0.38 ±0.33 (0.34)*	0.11 ±0.11 (0.07)* †	0.000
PAR, at rest (ml/min)	0.07 ±0.06 (0.07)	0.04 ±0.04 (0.03)*	0.01 ±0.02 (0.01)*	0.000
PAR, stimulated (ml/min)	0.18 ±0.12 (0.16)	0.14 ±0.11 (0.10)	0.06 ±0.04 (0.05)*	0.013
Patient-related outcomes				
HAQ	0.5 ±0.6 (0.4)	1.0 ±0.6 (1.0)*	1.4 ±1.0 (1.4)*	0.001
RAND-36				
Physical functioning	69 ±25 (75)	48 ±24 (50)*	38 ±29 (40)*	0.000
Role physical	64 ±42 (100)	35 ±41 (25)*	17 ±41 (0)*	0.002
Bodily pain	70 ±19 (67)	57 ±21 (57)*	37 ±24 (38)*	0.001
General health	54 ±22 (55)	42 ±21 (35)*	33 ±14 (35)*	0.012
Vitality	66 ±18 (70)	54 ±22 (50)*	31 ±12 (33)* †	0.000
Social Functioning	81 ±19 (88)	67 ±25 (63)*	50 ±18 (44)*	0.001
Role emotional	81 ±35 (100)	73 ±42 (100)	56 ±50 (67)	0.434
Mental health	80 ±15 (84)	76 ±20 (80)	56 ±18 (52)* †	0.020
MFI				
General fatigue	9 ±4 (10)	12 ±4 (12)*	14 ±2 (14)*	0.001
Physical fatigue	9 ±4 (10)	12 ±4 (13)*	15 ±3 (16)*	0.000
Reduced activity	9 ±4 (8)	11 ±5 (12)*	14 ±4 (16)*	0.004
Reduced motivation	9 ±4 (8)	10 ±4 (10)	15 ±4 (16)* †	0.003
Mental fatigue	7 ±3 (6)	9 ±5 (9)*	12 ±3 (12)*	0.006

Values are presented as number of patients (percentage) or mean ±SD (median) * p<0.05 compared to non-sicca group. † p<0.05 compared to only sicca group.

Figure 1. Flowchart of inclusion screening in 2008 and follow-up in 2018

Follow-up 2018

From the 96 RA patients included in the study in 2008, 36 (38%) were able and willing to participate in the follow-up screening in 2018 (Figure 1). From the 60 patients without follow-up data, 5 patients were deceased (one patient because of a pulmonary embolism after surgery, 4 other patients because of a malignancy (lung, oesophagus, breast and cholangiocarcinoma)), 38 patients were lost to follow-up and 17 patients were not willing to participate.

Table 3. Comparison of clinical characteristics of RA patients from 2008 who took part in the follow-up screening in 2018 vs. who did not take part in the follow-up in 2018

	RA-follow-up 2018+ (n=36)	RA-follow-up 2018- (n=60)	P-value
Demographics			
Female gender	27 (75%)	48 (80%)	0.615
Age (years)	54 ±10 (55)	55 ±11(56)	0.628
Disease variables			
Time since RA diagnosis (years)	13 ±9 (10)	11 ±8 (10)	0.542
RF positive	27 (75%)	54 (90%)	0.136
Anti-CCP positive	30 (83%)	50 (83%)	1
Anti-SSA positive	3 (8%)	4 (7%)	1
ANA positive	21 (58%)	39 (65%)	0.523
IgG level	13 ±3 (12.5)	13 ±3 (12.9)	0.851
Xerogenic drug use	21 (58%)	38 (63%)	0.669
Presence of erosions	24 (67%)	48 (80%)	0.154
Presence of EAMs	19 (53%)	27 (45%)	0.529
DAS-28(ESR)	3.0 ±1.2 (3.0)	2.9 ±1.1 (2.6)	0.696
DAS-28(CRP)	2.8 ±1.0 (2.6)	2.6 ±1.0 (2.4)	0.403
Dryness			
Schirmer's test (mm/5min)	16.3 ±11 (14.5)	14.5 ±10.7 (12.50)	0.552
Whole saliva (ml/min)	0.27 ±0.21 (0.20)	0.28 ±0.26 (0.20)	0.994
SM/SL, at rest (ml/min)	0.22 ±0.17 (0.16)	0.22 ±0.23 (0.14)	0.881
SM/SL, stimulated (ml/min)	0.49 ±0.36 (0.45)	0.46 ±0.31 (0.38)	0.984
PAR, at rest (ml/min)	0.05 ±0.05 (0.04)	0.06 ±0.06 (0.04)	0.584
Patient-related outcomes			
HAQ	0.8 ±0.7 (0.7)	0.7 ±0.6 (0.6)	0.287
RAND-36			
Physical functioning	57 ±28 (0.60)	61 ±26 (0.61)	0.613
Role physical	49 ±42 (0.50)	52 ±45 (0.50)	0.634
Bodily pain	61 ±21 (0.67)	64.22 (0.67)	0.338
General health	49 ±19 (0.47)	48 ±25 (0.45)	0.674
Vitality	59 ±21 (0.60)	60 ±21 (0.60)	0.994
Social Functioning	73 ±21 (0.75)	75 ±24 (0.75)	0.371
Role emotional	76 ±37 (100)	77 ±40 (100)	0.640
Mental health	80 ±14 (0.84)	76 ±19 (82)	0.560
MFI			
General fatigue	11 ±4 (12)	11 ±5 (10)	0.693
Physical fatigue	10 ±4 (11)	11 ±5 (10)	0.923
Reduced activity	10 ±4 (10)	10 ±5 (11)	0.936
Reduced motivation	9 ±4 (9)	10 ±4 (9)	0.571
Mental fatigue	8 ±4 (6)	8 ±4 (8)	0.557

Table 4. Comparison of clinical characteristics of 36 RA patients from screening in 2008 and the same 36 RA patients from follow-up in 2018

	RA- screening 2008 (n=36)	RA-follow-up 2018 (n=36)	P-value
Disease variables			
RF positive	27 (75%)	27 (79%)	1
Anti-CCP positive	30 (83%)	27 (75%)	0.375
Anti-SSA positive	3 (8%)	3 (8%)	1
ANA positive	21 (58%)	21 (46%)	0.727
IgG level	13 ±3 (12.5)	11 ±3 (11)	0.000*
Xerogenic drug use	21 (58%)	25 (69%)	0.289
Presence of erosions	24 (67%)	30 (83%)	0.109
Presence of EAMs	19 (53%)	19 (53%)	1
DAS-28(ESR)	3.0 ±1.2 (3.0)	2.8 ±1.1 (2.6)	0.251
DAS-28(CRP)	2.8 ±1.0 (2.6)	2.2 ±1.0 (2.0)	0.499
Dryness			
Schirmer's test (mm/5min)	16.3 ±11 (14.5)	10 ±9 (6.7)	0.000*
Whole rest saliva (ml/min)	0.27 ±0.21 (0.20)	0.17 ±0.21 (0.8)	0.003*
SM/SL, at rest (ml/min)	0.22 ±0.17 (0.16)	0.12 ±0.15 (0.06)	0.001*
SM/SL, stimulated (ml/min)	0.49 ±0.36 (0.45)	0.19 ±0.20 (0.09)	0.000*
PAR, at rest (ml/min)	0.05 ±0.05 (0.04)	0.05 ±0.07 (0.02)	0.742
PAR, stimulated (ml/min)	0.17 ±0.11 (0.16)	0.12 ±0.12 (0.08)	0.056
Patient-related outcomes			
HAQ	0.8 ±0.7 (0.7)	1.08 ±0.9 (1.0)	0.006*
RAND-36			
Physical functioning	57 ±28 (0.60)	56 ±29 (52)	0.828
Role physical	49 ±42 (0.50)	47 ±44 (50)	0.652
Bodily pain	61 ±21 (0.67)	63 ±24 (66)	0.858
General health	49 ±19 (0.47)	56 ±22 (55)	0.031*
Vitality	59 ±21 (0.60)	60 ±21 (60)	0.770
Social Functioning	73 ±21 (0.75)	74 ±25 (81)	0.705
Role emotional	76 ±37 (100)	79 ±38 (100)	0.752
Mental health	80 ±14 (0.84)	80 ±16 (84)	0.748
MFI			
General fatigue	11 ±4 (12)	15 ±5 (12)	0.135
Physical fatigue	10 ±4 (11)	12 ±5 (12)	0.059
Reduced activity	10 ±4 (10)	10 ±4 (9)	0.772
Reduced motivation	9 ±4 (9)	9 ±3 (9)	0.097
Mental fatigue	8 ±4 (6)	9 ±4 (8)	0.008*

To check for a potential selection bias on inclusion in 2018, we compared baseline parameters of patients who took part in the screening in 2018 (N=36) to those of patients who did not participate in 2018 (N=60, Table 3). We did not find any significant differences in clinical characteristics, functional tests and patient-reported outcome between these two groups.

In most patients, sicca symptoms were not constantly present over time. We screened 21 patients in 2018 who were originally in RA-non-sicca group in 2008. Of these 21 patients, 17 patients had still no sicca complaints and 4 patients reported to have developed at least one sicca symptom of the eyes or mouth. Furthermore, we screened 12 patients in 2018 from the RA-sicca group in 2008. Of these 12 patients, 2 patients had developed secondary SS, 2 patients still had sicca symptoms and 8 patients did not experience sicca complaints anymore after 10 years of follow-up.

Furthermore, we compared the clinical characteristics of the 36 RA-patients who participated in the screening in 2018 with their clinical characteristics from 2008. We found that except for IgG levels, all serological parameters like RF, anti-CCP, anti-SSA and ANA positivity did not change over time. RA disease activity did not change significantly over time, whereas lacrimal flow, whole rest saliva and submandibular/sublingual saliva both at rest and after stimulation were significantly lower in 2018. Furthermore, RA patients experienced more limitations in daily activities, lower general health and more mental fatigue in 2018 (Table 4).

RA-sicca and RA-SS patients showed in 2018 significant impairment in the secretion of whole rest salivary flow and submandibular/sublingual salivary flow both at rest and after stimulation. The domains Role Emotional and Mental Health of RAND-36 were impaired in both RA-sicca and RA-SS patients and these patients also reported more fatigue. In addition, patient-reported symptoms assessed with total ESSPRI score and the subscales dryness and pain were significantly higher compared to RA-non-sicca patients (Table 5).

Table 5. Clinical characteristics of RA patients with SS, with sicca symptoms but no SS, and without sicca symptoms in 2018

	RA-Non-sicca (n=25)	RA-sicca (n=6)	RA-SS (n=5)	P-value (overall)
Disease variables				
RF positive	19 (76%)	5 (83%)	3 (60%)	0.843
Anti-CCP positive	18 (72%)	5 (83%)	4 (80%)	0.482
Anti-SSA positive	2 (8%)	1 (17%)	1 (20%)	0.841
ANA positive	15 (60%)	4 (67%)	4 (80%)	0.502
IgG titer	12 ± 3 (12)	9 ± 2 (9)	8.8 ± 1.6 (9.2)	0.168
Xerogenic drug use	16 (64%)	4 (67%)	5 (100%)	0.358
Presence of erosions	21 (84%)	5 (83%)	4 (80%)	0.710
Presence of EAMs	10 (40%)	4 (67%)	5 (100%)	0.097
DAS-28(ESR)	2.8 ± 1.2 (2.6)	3.1 ± 0.8 (2.7)	2.0 ± 0.8 (1.7)	0.461
DAS-28(CRP)	2.2 ± 1.1 (2.0)	2.8 ± 0.6 (2.7)	1.8 ± 0.3 (1.7)	0.579
Dryness				
Schirmer's test (mm/5min)	10.6 ± 9.5 (7)	18 ± 11 (22)	1.4 ± 2.3 (0.5)	0.051
Whole rest saliva (ml/min)	0.21 ± 0.22 (0.10)	0.17 ± 0.15 (0.13)*	0.01 ± 0.01 (0.00) [†]	0.010
SM/SL, at rest (ml/min)	0.15 ± 0.17 (0.09)	0.10 ± 0.11 (0.04)*	0.01 ± 0.01 (0.00) [†]	0.005
SM/SL, stimulated (ml/min)	0.23 ± 0.22 (0.11)	0.25 ± 0.19 (0.24)*	0.01 ± 0.01 (0.01) [†]	0.019
PAR, at rest (ml/min)	0.05 ± 0.07 (0.04)	0.08 ± 0.05 (0.09)	0	0.092
PAR, stimulated (ml/min)	0.14 ± 0.12 (0.09)	0.14 ± 0.11 (0.16)	0.01 ± 0.01 (0.00)	0.054
Patient-related outcomes				
HAQ	0.8 ± 0.7 (0.6)	1.6 ± 0.9 (1.4)	1.9 ± 0.9 (1.9)	0.274
RAND-36				
Physical functioning	65 ± 26 (65)	43 ± 26 (45)	28 ± 29 (25)	0.136
Role physical	62 ± 43 (75)	8 ± 20 (0)	15 ± 22 (0)	0.224
Bodily pain	71 ± 23 (67)	45 ± 14 (45)	47 ± 20 (47)	0.648
General health	59 ± 23 (60)	48 ± 17 (52)	49 ± 17 (50)	0.391
Vitality	68 ± 18 (70)	45 ± 21 (52)	40 ± 13 (50)	0.084
Social Functioning	82 ± 21 (88)	65 ± 28 (69)	48 ± 42 (50)	0.125
Role emotional	88 ± 30 (100)	67 ± 52 (100)*	47 ± 45 (67) ^{†‡}	0.013
Mental health	84 ± 16 (88)	77 ± 9 (76)*	30 ± 11 (25) ^{†‡}	0.021
MFI				
General fatigue	10 ± 4 (9)	15 ± 3 (14)*	16 ± 4 (16) ^{†‡}	0.044
Physical fatigue	11 ± 5 (10)	15 ± 4 (15)	13 ± 4 (13)	0.232
Reduced activity	9 ± 4 (8)	11 ± 2 (12)*	14 ± 4 (15) ^{†‡}	0.040
Reduced motivation	9 ± 3 (9)	11 ± 1 (11)	12 ± 4 (11)	0.398
Mental fatigue	8 ± 4 (8)	9 ± 3 (9)*	13 ± 4 (16) ^{†‡}	0.033
ESSPRI				
Dryness	0.3 ± 0.7 (0)	4.0 ± 2.7 (4.5)*	8.7 ± 1.5 (9) ^{†‡}	0.037
Fatigue	3.1 ± 2.0 (3.0)	6.3 ± 1.6 (6.5)	8.0 ± 1.7 (7)	0.079
Pain	3.2 ± 2.5 (2.5)	5.7 ± 1.9 (5.5)*	7.0 ± 2.6 (6) [†]	0.024
Total ESSPRI	2.2 ± 1.3 (1.8)	5.3 ± 1.2 (5.2)*	7.8 ± 1.9 (7.3) ^{†‡}	0.021

* p<0.05 RA-Non-sicca vs RA-sicca, † p<0.05 RA-Non-sicca vs RA-SS, ‡ p<0.05 RA-sicca vs RA-SS

Discussion

To our knowledge, this is the first study evaluating as well sicca symptoms as SS in patient with RA over a period of 10 years. In this study we showed that RA patients with higher disease activity more often have sicca symptoms and more often are diagnosed with secondary SS than RA patients with lower disease activity. Furthermore, RA patients with sicca complaints and SS experienced more limitations in daily activities, had lower general health status and more fatigue. Furthermore, they had more SS-related symptoms measured by the ESSPRI total score and the subscales dryness and pain.

The prevalence of SS in RA in our study was 6.3% and the prevalence of sicca symptoms was 33%. These findings are in line with reported prevalence's in the literature. (11) (10) (34) (35) (36) (20) A Danish study reported a prevalence of 3.8% of SS in patients with RA, whereas a Brazilian study reported a prevalence of 24.3% in a similar group. These differences in the prevalence of SS in RA can be possibly explained by the definition of SS and application of different classification criteria, geographical differences and perhaps differences in the treatment modalities of RA, assuming that the disease activity may be a predicting factor for developing of SS.

The prevalence of SS in our study might be underestimated due to lack of a full diagnostic work-out in all included RA patients, i.e., salivary gland biopsy and full ophthalmologic investigation was not done in all patients. We did not add a salivary gland biopsy or a full ophthalmologic examination to the RA patients suspected for having developed secondary SS when adding these examinations would not result in a patient to be classified as secondary SS according to the AECG criteria. Furthermore, three anti-SSA positive patients from the RA-non-sicca (n=2) and RA-sicca (n=1) groups in 2008 were lost to follow-up.

The reported prevalence of sicca symptoms in RA is higher than the prevalence of SS, but is very variable as well. In a Turkish study 11.4 % of RA patients had sicca symptoms (2), whereas in a Brazilian study 57.3 % of RA patients had sicca symptoms. (36) In a population of RA patients from Egypt with high disease activity (mean DAS-28 of 5.3 ± 1.2) and duration of RA of 4.7 ± 4.2 years, 71% of the patients had sicca symptoms, but no patients were diagnosed with SS. (22) This scattered prevalence may be caused by various concomitant diseases and/or xerogenic medication use. (7) (13) Age-related alterations of salivary and lacrimal glands, irradiation and infections, such as hepatitis C and HIV, amyloidosis, diabetes mellitus (DM) IgG4 disease and sarcoidosis are all associated with sicca syndrome.

Associations between sicca symptoms and/or the presence of SS in RA patients, and poorer health status measures are frequently reported. However, there are conflicting results in the literature concerning the association between disease activity and the presence of sicca symptoms and SS.

Some studies did not report an association between disease activity, sicca and SS, while other studies found this association as well. (11) (10) (36) (20) (37) It is still not clear if secondary SS should be considered as an extra-articular manifestation of RA or as a concomitant auto-immune disease. It is known that patients with RA have more extra-articular manifestations if their disease activity is high. (18) Therefore, RA treatment should be aggressive, especially at the start of the disease, using the window of opportunity. In 2008, our RA population already had a long disease duration of at least 10 years. It will be interesting to investigate the prevalence of SS in early RA patients in the new era of biological therapies. Treatment modalities of RA can possibly be of influence on the development of SS in RA as we observed that patients with high disease activity of RA more often suffered from sicca complaints and/or SS.

We consider SS not as an extra-articular manifestation of RA, but as a distinct disease entity. SS occurs concomitantly in other diseases like SLE, scleroderma or myositis etc. Furthermore, SS can be the first auto-immune disease detected in a patients, while RA or SLE or scleroderma can be diagnosed in the same patient thereafter. Salivary gland biopsies in patients with secondary SS showed comparable abnormalities between primary SS patients, SS-RA, SS-SLE and SS-scleroderma patients, as reported by Hernández-Molina and colleagues. (26) Important shortcoming of the term 'secondary' SS is that this disease always comes to the second place and too little research is provided on this field. Moreover, probably most patients with secondary SS are not well recognized by clinicians as their attention goes to the primary disease, like RA or SLE or scleroderma. (38) (39) In our study, we found that 2 patients (6%) had developed SS during the 10 years of follow-up. Both patients had sicca complaints in 2008. This indicates that the minority of established RA-sicca patients will develop SS in the later course of RA. Both patients were anti-SSA/SSB negative, but they still met the classification criteria for secondary SS. Nowadays, 2016 ACR/EULAR classification criteria are developed for SS. (40) These criteria do not differentiate between primary or secondary SS. In these criteria, anti-SSA/SSB antibodies have a prominent weight in the diagnosis. The reported prevalence of these antibodies in secondary SS in RA is 7.3-40%. (11) (36) (41) In our study only one secondary SS patient was positive for anti-SSA/SSB antibodies. In a recent study with 300 patients with systemic lupus erythematosus, rheumatoid arthritis and scleroderma the performance of ACR/EULAR classification criteria of SS using clinical diagnosis as a gold standard was assessed. The 2016 ACR/EULAR criteria showed the best AUCs results (0.87 definitive/probable diagnosis, 0.90 definitive diagnosis) compared to AECG and

ACR criteria. It was concluded that ACR/EULAR classification criteria are applicable in the setting of secondary SS. (42) The consequence of the 2016 ACR/EULAR criteria for daily clinical practice is that patients with RA suspected to have SS should undergo salivary gland biopsy in the majority of cases. (43)

In our study over a period of 10 years we found that 2 of 6 RA-SS patients deceased and in RA-non-sicca and RA-sicca group 3 of 90 patients deceased. Although our numbers are small, previous studies also reported that SS is significantly associated with an increased morbidity and mortality. (44) (45) The prevalence of joint damage, pulmonary, neurologic, nephrologic and cutaneous organ involvement is increased in RA-SS patients compared to RA patients without SS. RA patients with SS also have an increased risk of developing non-Hodgkin lymphoma as well as other hematologic malignancies. (8) (11) (46) (47)

An important finding in our study is that sicca symptoms are not constant over time. We expected that once having sicca complaints, patients will stay in sicca group for the next years and that the number of patients in the sicca group will constantly increase. In contrary, we found that 8 out of 12 examined patients had no sicca complaints after 10 years of follow-up. These results could be a result of the use of xerogenic drugs, but we found no differences in xerogenic drug use between screening in 2008 and follow-up in 2018. In contrast, the objective measurements of functional tests decreased significantly over time, especially the submandibular and sublingual salivary flow, as well at rest as stimulated. These results indicate that there is no strong correlation between the objective and subjective sicca symptoms. The overall decrease of salivary and lacrimal flow is related to the physiological changes in the salivary and lacrimal glands with age. The size of submandibular glands and lacrimal glands decreases with age due to decline in acinar volume while the volume of adipose and fibrose tissue increases. (48) (49) (50) (51)

We did not find any association between serological parameters like RF, anti-CCP, ANA and anti-SSA/SSB and the presence of sicca symptoms and SS in RA patients. Such associations have been investigated by others too and in most studies the serological profile of RA patients with SS were not different from those without SS. (11) (37) (52) (53) In our study we did not find a relationship between the prevalence of anti-SSA/SSB antibodies and the presence of SS. IgG titer decreased after 10 years of follow-up, probably due to the B-cell depletion therapy, like rituximab. (54)

A limitations of our study is the small sample size at the 2018 follow-up, but in spite of the small sample size, we found no selection bias in our second screening group and even with this small sample size we found clear differences between the groups.

In conclusion, high disease activity of RA is associated with sicca symptoms and SS. Patients with sicca symptoms and SS had more limitations in daily activities, had lower general health status, more fatigue and patients with SS were at higher risk of mortality. Sicca complaints are not constantly present and vary over time within patients, while functional tests significantly decrease over time in all patients. During 10 years of follow-up, 2 out of 36 patients developed SS. Based on these results we suggest that RA patients with high disease activity should be monitored for development of sicca symptoms and SS.

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8

Safety of treatments for primary Sjögren's syndrome

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ABSTRACT

Introduction: Primary Sjögren's syndrome (pSS) is a disabling auto-immune disease, affecting exocrine glands and several organs.

Areas covered: In this review we analyze the safety of therapies used in pSS. Symptomatic treatment is widely applied due to the good supportive effect and good safety profile. Systemic stimulation of tears and saliva can be successful in pSS. However, cumbersome adverse events can influence the tolerability of this therapy. Evidence for the effectiveness of synthetic DMARDs therapies in pSS is limited, while there is a risk of adverse events. Several studies on biologic DMARD treatment of pSS patients have shown promising efficacy and safety results.

Expert opinion: The safety of symptomatic treatment of pSS is very good. However, systemic therapy is necessary to achieve long-term relieve and prevention of organ-damage. Synthetic DMARDs have not shown much efficacy in earlier studies, and their benefits do not weigh up to the possible harms, while biologic DMARDs show promising results regarding efficacy and cause mostly mild adverse events. Many questions remain unanswered regarding safety of DMARDs in pSS. There is a need for well-designed studies, in which safety should be evaluated in a uniform manner to be able to compare the results between studies.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands leading to, among others, sicca symptoms of the eyes and mouth. Several systemic and extraglandular manifestations can develop as well including fatigue, arthritis and involvement of organs such as the skin, lungs and kidneys. Although the pathogenesis of pSS is not fully elucidated, T-cell mediated B-cell hyperactivity is thought to play an important role, as reflected by the presence of autoantibodies, cryoglobulins and hypergammaglobulinemia¹. pSS is a disabling disease and has a large effect on health related quality of life². Besides symptomatic treatments that improve dryness, no effective treatments have yet been approved for use in pSS. However, treatment with biologic disease modifying antirheumatic drugs (DMARDs) have shown promising outcomes³.

Evaluation of treatment outcomes in pSS has been challenging in the past, due to the wide range of outcome measurements that were applied, making it difficult to compare studies. Early studies primarily focused on exocrine gland function (saliva, tears) as a primary outcome measurement, whereas later studies focused on fatigue and systemic symptoms. Furthermore, pSS has a very heterogeneous course. Most patients show a chronic progressive decrease in exocrine gland function, until a very low level or no saliva and tear production remains⁴. However, systemic symptoms can present in different patterns, as patients can show chronic involvement (e.g. polyneuropathy) and exacerbations (e.g. polyarthritis)^{5,6}. The recent development and validation of disease activity indices, the European League against Rheumatism Sjögren Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI), have enhanced clinical research as it is now possible to reliably measure changes in disease activity and patient reported complaints^{7,8}.

When assessing the efficacy of new treatments, also when applying ESSDAI and ESSPRI, it remains important to keep the balance between efficacy and adverse effects in mind. Therefore, the aim of this review is to summarize the safety of treatments currently applied in pSS and to identify in which areas knowledge is still lacking. This review will discuss symptomatic treatment, synthetic DMARDs and biologic DMARDs, with a focus on the treatments that have shown promising results.

Safety of symptomatic therapies

Symptomatic treatment of patients with pSS is widely applied due to the non-invasive nature, good supportive effect and good safety profile. Educating the patient with regard to lubricant use, preventive dental care and general personal hygiene, avoiding

windy or low-humidity environments and exposure to irritants such as dust and cigarette smoke is important. Attention should also be paid to several medical conditions and medications which can aggravate sicca symptoms.

Ocular manifestations

First line treatment of ocular sicca symptoms consists of topical treatment with artificial tears, gels and ointments⁹. If the effect of tear replacement is inadequate, topical immunomodulatory agents such as cyclosporine and corticosteroids, and systemic stimulation of tear production can be added to the treatment.

Artificial tears

Substitution therapy, like eye drops, gels and ointments are mainstay of the treatment of sicca symptoms. There are many different types of artificial tears available on the market based on hydroxypropyl methylcellulose, carboxymethylcellulose, hyaluronic acid, polyethylene glycol or propylene glycol as well as gel/lipid formulations, ointments and liposomal sprays. Ophthalmic gels and ointments may be used at night. Highly viscous drops, gels and ointments have longer effect duration, but they may cause visual blurring. In general, if used appropriately, artificial tears substitutes have good safety and tolerability characteristics. The most common adverse event is a temporary burning sensation. Other adverse events include eye redness, discharge, watery eyes, eye pain, foreign body sensation, itching, stinging and blurred vision¹⁰.

Blepharitis may worsen by the use of artificial tears, especially those with high viscosity or those containing preservatives, which also can damage the corneal epithelium and disrupt the tear film^{11,12}. The advantage of preservatives is that the drops are available in multidose administration bottles. However, patients can develop an adverse reaction to the preservative. The use of artificial tears containing preservatives should therefore be restricted to three times a day to prevent high concentrations of these substances. Preservative-free artificial teardrops should be used as single dose dispenser, to prevent infection risk, which in turn increases the costs of these substitutes. The choice of artificial tears should be based on individual patient characteristics.

Autologous serum

Autologous serum eye drops might be superior to artificial tear substitutes due to presence of a variety of biological factors, such as Epidermal Growth Factor (EGF), vitamin A, transforming growth factor beta (TGF- β), fibronectin, substance P, insulin-like growth factor 1 (IGF-1) and nerve growth factor (NGF). Moreover, autologous serum eye drops have an osmolarity comparable to natural tears¹³.

Although there is some evidence for effectiveness and safety of autologous serum eye drops in pSS patients^{14,15}, large randomized controlled trials (RCT) are warranted to provide sufficient evidence on superiority of these drops over artificial tears.

The adverse events of autologous serum eye drops are mild and include increased discomfort, slight epitheliopathy, bacterial conjunctivitis and eyelid eczema^{14,16,17}. Autologous serum eye drops should be prepared under a strict protocol and in sterile conditions.

Topical cyclosporine A

Topical cyclosporine A (tCsA) 0.05% ophthalmic emulsion is an immunomodulatory agent with the ability to down regulate T-cell proliferation, activity and receptor signal transduction. tCsA has an anti-inflammatory effect due to decreased formation of proinflammatory cytokines. The latter effects of tCsA contribute to the stability of the tear film by interruption of the inflammatory cascade, inhibition of apoptosis and stimulation of production of goblet cells in the corneal epithelium. Goblet cells produce mucin which serves as an interface between hydrophobic corneal epithelium and aqueous tear fluid^{18–21}.

tCsA is recommended for the treatment of pSS patients with moderate-to-severe inflammation of the cornea²². Long-term use of tCsA is well tolerated in pSS patients²³. A variety of adverse events is reported, including burning and stinging symptoms, foreign body sensation and blurring. These adverse effects resolve with cessation of treatment^{23,24}. No systemic side-effects were observed during tCsA treatment. Patients with ocular infections should discontinue tCsA use²³. Taken together, tCsA is an important tool in the management of ocular manifestations in SS with a good tolerability, no systemic side effects and overall good safety profile. Unfortunately, tCsA is not registered for use in pSS in several countries.

Topical glucocorticoids

Non-preserved glucocorticoid eye drops are used in pSS patients with moderate to severe disease. By reducing the levels of cytokines, such as interleukin-1 and interleukin-8, topical glucocorticoids suppress the inflammatory process. Furthermore, these eye drops reduce the activity level of matrix metalloproteinase's²⁵. Although the overall safety of topical glucocorticoids in clinical trials in pSS and keratoconjunctivitis sicca was considered satisfactory, prolonged use of topical glucocorticoids in pSS patients is restricted by their ability to induce glaucoma, cataract, decreased wound healing, increased risk of secondary infections and epithelial defects^{26–29}. Therefore, topical glucocorticoids are only recommended for short term use when treatment with artificial tears is insufficient and rapid reduction of inflammation should be achieved.

Topical NSAIDs

Use of NSAID eye drops in pSS was evaluated in a couple of studies^{30–32}. Inhibition of prostaglandins and the arachidonic acid cascade by topical NSAIDs can relieve ocular hyperalgesia. However, in patients with corneal problems, a common phenomenon in pSS patients, the use of topical NSAIDs is associated with corneal-scleral melts, perforation, and severe keratopathy^{33,34}. Therefore, there is no place for topical NSAID eye drops in the treatment of pSS patients due to potential corneal complications and inferiority to topical corticosteroids.

Oral manifestations

The treatment of a sensation of a dry mouth (xerostomia) and salivary gland hypofunction (hyposalivation) in pSS patients should be based on the following principles³⁵. Stimulate the flow of saliva by gustatory and mechanical stimulation, or systemic stimulation. If the saliva cannot be adequately stimulated, decreased sicca symptoms can be achieved by coating the surfaces of the oral mucosa with saliva replacement therapy. Preserve and protect the teeth and the oral soft tissues with topical fluorides. The mainstay of this therapy is to make it as simple and as safe as possible for the patients, e.g., limit salivary stimulation therapy to gustatory and mechanical stimulation as this is accompanied by fewer side effects than systemic stimulation therapy.

Gustatory and mechanical stimulation

The combination of chewing and taste, as provided by gums, candies and mints, can be very effective in relieving symptoms for patients who have remaining salivary function. Masticatory stimulatory techniques (non-sticky chewing gums) are the easiest to implement and have few adverse events, assuming that they are sugar-free. The same accounts to sugarfree candies, mints etc., preferably with mild acids added with a low risk to harm teeth and oral mucosa, such as malic acid.

Saliva replacement therapy

Artificial saliva (saliva substitutes) is available for the treatment of moderate to severe dry mouth in patients with pSS. A variety of saliva substitutes is available, some are water-based and often short working, others are gels which preferably used when stimulation or frequent moistening is not applicable, e.g. at night. In this respect it also has to be mentioned that many pSS patients use water to moisten their mouth, which can be used freely, but is a worse moistener of the oral mucosa.

When prescribing a saliva substitute, it is important to instruct the patient properly how to use that substitute to get the maximum effect from the therapy, as it is not an exception that use of artificial saliva is not well accepted long-term by many patients,

particularly when they have not been instructed how to use them. Moreover, it is very useful to try another type of substitute in a patient when a particular substitute does not sufficiently relieve xerostomia; which substitute is effective in a particular patient is often related to the preference of a patient and is not easy to predict. The safety of saliva substitutes is very good with a very small number of minor adverse events reported³⁶.

Topical fluorides

Topical fluorides in patients with salivary gland hypofunction are critical to control dental caries³⁷. There are different fluoride therapies available, from low-concentration, over-the-counter fluoride rinses, to more potent highly concentrated prescription fluorides (e.g., 1.0% sodium fluoride). Oral health care practitioners may also utilize fluoride varnishes. The dosage chosen and the frequency of application should be based on the severity of the salivary hypofunction and the rate of caries development^{37,38}. In addition, particularly in patients with severe oral dryness, non acidic gels and/or solutions should be used, as acidic sodium fluoride gels may induce a more rapid destruction of the teeth, and could cause sensitivity and pain in the gingival and oral mucosa. There is little information on the risk of adverse events in the available studies. Known adverse events of the use of fluorides are fluorosis, tooth staining/discoloration, oral allergic reactions, nausea or vomiting³⁹.

Systemic stimulation of tears and saliva

Pilocarpine

Pilocarpine is a cholinergic parasympathomimetic agonist with onset of action within 1 hour. It binds to muscarinic-M3 receptors of various exocrine glands to stimulate the secretion function⁴⁰. Contraindications to use pilocarpine are uncontrolled asthma, untreated cardiovascular conditions, angle-closure glaucoma and severe hepatic impairment. Precautions should be made by patients with cholelithiasis or nephrolithiasis. The effect on saliva flow is dose-dependent and time-related with duration of effect of about 3-5 hours.

Several RCTs were conducted to evaluate the efficacy and safety of pilocarpine in SS patients⁴¹⁻⁴⁴. Salivary flow rate and visual analogue scale (VAS) for dry mouth or dry eye were significantly improved in the pilocarpine groups compared to placebo. Pilocarpine showed improvement of VAS for eye dryness and Rose Bengal test compared to artificial tears alone or punctual occlusion intervention. No serious adverse events were reported. The most frequent adverse events were sweating, increased urinary frequency, headache, flu syndrome, nausea, dyspepsia, rhinitis, and dizziness. Adverse effects occurred more often at higher doses. In these studies, 0-13% of patients receiving pilocarpine discontinued treatment due to adverse events versus 0-10% of patients

receiving placebo^{41–44}. Recently, Kawakita and colleagues demonstrated that lower dose of 2.5 mg pilocarpine three times a day is effective in patients with SS and can diminish the adverse events⁴⁵. Moreover, pilocarpine seems to be safe and effective in juvenile-onset Sjögren's syndrome⁴⁶. Conclusively, pilocarpine can be successfully used in pSS patients, especially in those with sufficient remaining salivary gland function. However, common and cumbersome adverse events can influence the tolerability of this therapy.

Cevimeline

Cevimeline is a parasympathomimetic and muscarinic agonist that, just like pilocarpine, has particular effect on M3 receptors. It stimulates saliva secretion, thereby alleviating dry mouth. Cevimeline has the same contraindication profile as pilocarpine⁴⁷. Several RCTs confirm the effectiveness and favorable safety profile of cevimeline^{47–52}. Cevimeline is not yet approved for use in Europe. However, the tolerability of cevimeline seems to be better compared to pilocarpine and is associated with lower discontinuation rates during the treatment⁵³.

Safety of systemic immunosuppressive therapies

Several systemic immunosuppressive therapies have been studied in phase 2 and 3 trials with pSS patients^{3,54}. Although no systemic treatments have yet been registered for use in pSS, the number of studies with systemic therapy in pSS is increasing. In the next section, the safety of several systemic therapies that have shown some effect in pSS will be discussed.

An important safety issue during immunosuppressive therapy in rheumatic diseases is the increased risk of serious infections^{55,56}. The risk of infection in patients on systemic immunosuppressive therapy is, amongst others, influenced by comorbidity, use of other immunosuppressive medications and age. In pSS, the presence of extraglandular manifestations such as interstitial lung and renal disease may further increase the risk of infection. During treatment with any systemic DMARD, physicians should be aware of this and monitor patients for the development of infections. Careful clinical and laboratory assessments need to be carried out to minimize the potential risk of adverse effects.

Synthetic DMARD therapies

Patients treated with synthetic DMARDs have a rather high risk of developing adverse reactions. The most common adverse effects of synthetic DMARDs are infections, bone marrow toxicity, gastrointestinal symptoms and cardiovascular diseases (e.g., hypertension). Therefore, it should be assessed before onset of therapy whether the benefits of a therapy outweighs its possible adverse effects.

Most synthetic DMARDs have not been shown to be effective in patients with pSS in double blind, randomized clinical trials. Methotrexate, leflunomide and cyclosporine A have shown insufficient efficacy in clinical trials and/or their use was accompanied by unacceptable rates of adverse events^{57–61}. As a consequence, most synthetic DMARDs are not used routinely for pSS. In case of severe or life-threatening organ involvement in pSS, however, synthetic DMARDs are frequently prescribed on an empiric basis or on basis of small case series.

Hydroxychloroquine

Based on efficacy experience in systemic lupus erythematosus (SLE) patients, hydroxychloroquine (HCQ) is frequently used in pSS, to treat skin involvement, e.g. purpura associated with hypergammaglobulinemia, myalgia, arthralgia, arthritis and constitutional symptoms like fever and fatigue⁶². HCQ is also effective in prevention of cardiovascular events by reducing levels of total cholesterol, increasing high-density lipoprotein cholesterol and improving the atherogenic index⁶³. Moreover, a recent report has shown that HCQ impairs systemic IFN α production in pSS, which is hypothesized to play an important role in the pathogenesis of pSS⁶⁴. It has been shown, however, that administration of HCQ did not resolve sicca signs and symptoms or extraglandular manifestations in pSS patients^{65,66}. In both trials in pSS serious adverse events rarely occurred. Gottenberg et al. reported a similar frequency of serious adverse events in the HCQ group in the placebo group during the first 24 weeks. The most common adverse effects of HCQ are skin rash, hyperpigmentation of the skin, temporarily hair loss and blurred vision⁶². Furthermore, bilateral bull's-eye maculopathy is considered a serious adverse effect, resulting in loss of visual acuity, loss of peripheral vision and loss of night vision⁶⁷. Screening for bull's-eye maculopathy should be done at start of HCQ, after five years of treatment and yearly thereafter. The risk of eye toxicity is low, unless the patient suffers from impaired kidney function or is given HCQ in a high dose (dose of >6.5 mg/kg of ideal body weight). Furthermore, as HCQ is not retained in fatty tissues, obese patients can be seriously overdosed when HCQ is dosed on basis of the patients' actual body weight instead of the ideal body weight. Another risk group is elderly patients with retinal and macular diseases. Rare adverse effects include cardiomyopathy, hearing disorders and myopathy^{68–70}. HCQ is safe to be used during pregnancy and lactation^{71,72}. In conclusion, HCQ has a mild adverse events profile. The efficacy of HCQ in pSS patients needs further evaluation.

Glucocorticoids

Glucocorticoids are used in pSS patients with severe organ complications, like renal involvement and myelitis. The effect of glucocorticoids on sicca symptoms and signs and extraglandular manifestations has not yet been proven in RCTs. Moreover, a prospective cohort study failed to show the effect of glucocorticoids on salivary function tests⁷³.

Adverse effects of glucocorticoids are common, depending on dose and duration of the therapy. Short term adverse effects include steroid induced diabetes mellitus, hypertension, peptic ulcers of the stomach, electrolyte disturbances, heart failure and mood disorders. Long term complications are susceptibility for infections, osteoporosis, steroid induced myopathy, cataract, glaucoma, Cushing syndrome, thin skin and central adiposity. The use of glucocorticoids should always be combined with prophylaxes for osteoporosis and peptic ulcers.

Cyclophosphamide

Cyclophosphamide is used in the treatment of severe and life-threatening conditions in pSS patients, e.g., severe renal involvement, vasculitis, mononeuritis multiplex, central nervous system involvement and mucosa-associated lymphoid tissue (MALT) lymphoma⁵⁴. However, treatment efficacy regarding these extraglandular manifestations has not been assessed in RCTs and safety data is often not reported in the available pSS studies.

Hemorrhagic cystitis is more frequently seen in patients on oral cyclophosphamide than patients on IV treatment due to higher cumulative dose⁷⁴. Importantly, even in low doses (1-2 mg/kg body weight) administration of cyclophosphamide is accompanied by significant adverse effects, such as infections, pancytopenia, hair loss, sterility, hemorrhagic cystitis, urinary bladder cancer, development of lymphoma and skin malignancies. Thus, frequent clinical and biochemical evaluations of patients treated with cyclophosphamide are mandatory. Mercaptoethane sulfonate has been added to cyclophosphamide treatment in patients with rheumatic diseases to prevent adverse effects, but conclusive evidence of its protective effect is lacking⁷⁵.

Azathioprine

Potentially, azathioprine can be useful in pSS patients, analogous to SLE patients. A retrospective case series, showed that azathioprine might be effective for progressive pulmonary involvement in pSS patients⁷⁶. An RCT in pSS patients showed no significant change in clinical, serological or histological disease activity variables⁵⁹. In this study, six of 25 patients, receiving azathioprine, withdrew because of adverse events. Common adverse effects are leucopenia, abnormal liver biochemistry and gastrointestinal symptoms⁷⁴. Prolonged use of azathioprine has been associated with increased risk of skin cancer development⁷⁷. Blood cell counts are recommended for every two weeks during the first 3 months of treatment and every 2-4 months thereafter.

Mycophenolate mofetil

In pSS, mycophenolate mofetil was evaluated in an open-label pilot trial with follow up of 24 weeks. Authors reported improvement of subjective glandular and extraglandular

Table 1. Safety results of rituximab therapy in pSS

Author	Design	Follow up (weeks)	Patients		Serious AEs ^a		Infectious serious AEs ^a		Infusion reaction ^{a,d}		Serum sickness- like AE ^a		Discontinued due to AEs ^a	
			T	P	T	P	T	P	T	P	T	P	T	P
Meijer ⁸⁵	RCT	48	20	10	1 (5)	0 (0)	0 (0)	0 (0)	4 (20)	0 (0)	1 (5)	0 (0)	1 (5)	0 (0)
Devauchelle ⁹⁴	RCT	24	63	57	13 (21)	8 (14)	2 (3)	5 (9)	15 (24)	12 (21)	0 (0) ^b	0 (0)	5 (8)	1 (2)
Dass ¹⁰³	RCT pilot	52	8	9	2 (25)	0 (0)	1 (13)	0 (0)	2 (25)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)
Gottenberg ⁸⁷	Registry	152 ^c	78	0	10 (13)		3 (4)		4 (5)		1 (1)		6 (8)	
Gottenberg ¹⁰⁴	Retrospective	36 ^c	6	0	0 (0)		0 (0)		1 (17)		1 (17)		1 (17)	
Seror ⁸⁸	Retrospective	63 ^c	16	0	1 (6)		0 (0)		1 (6)		2 (13)		NR	
Carubbi ⁸⁶	Open label	120	19	22 ^e	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pijpe ⁹⁵	Open label	12	15	0	3 (20)		0 (0)		2 (13)		3 (20)		3 (20)	
Devauchelle ¹⁰²	Open label	36	16	0	2 (12)		0 (0)		2 (12)		1 (6)		0 (0)	
St Clair ⁹⁸	Open label	52	12	0	2 (17)		0 (0)		NR		0 (0)		0 (0)	

Only articles with complete safety information and populations that were not reported in other studies were included in this table. ^a Number of patients who experienced this type of event (percentage). ^b 2 patients with treatment-related purpura were reported, but human anti-chimeric-antibodies were not measured and the authors did not classify these events as serum sickness-like reactions. ^c Median follow up time. ^d Infusion reactions include non-serious as well as serious infusion reactions and exclude serum sickness-like reactions. ^e Control group received one or more synthetic DMARDs instead of placebo. AE: adverse event; P: placebo group; NR: Not reported; I: treatment group.

manifestations as well as some laboratory parameters⁶⁰. In addition, mycophenolate mofetil might be effective for progressive interstitial lung disease in pSS patients⁷⁸. No RCTs have yet been performed to confirm these findings.

Mycophenolate mofetil is associated with an increased risk of infections, gastrointestinal symptoms, bone marrow depression, metabolic changes (e.g., hyperlipidemia, hyperglycemia, hyperuricemia) and impairment of kidney and liver function⁷⁴.

Biologic DMARD therapies

Several biologic DMARDs have shown promising outcomes in pSS³. Unfortunately, for most treatments only short-term safety data from a limited number of patients is available. As some systemic treatments have been used extensively for other indications, such as rheumatoid arthritis (RA), psoriatic arthritis and SLE, long term safety data from worldwide registries are available for these indications. When applicable to pSS, these safety data will be discussed.

An important safety issue during biologic DMARD therapy are systemic infusion related reactions and injection-site reactions. The presence of anti-drug antibodies, raised against these biologics, often related to the non-human origin of the biologic DMARDs, may increase the risk of systemic reactions⁷⁹.

The risk of serious infections seems to be higher during biological DMARD therapy than during synthetic DMARD therapy for RA⁸⁰. Therefore, before biological DMARD treatment is started, patients have to be screened for latent or active infections, such as tuberculosis, HIV, and hepatitis B and C. In case of latent infections, adequate prophylactic therapy should be initiated before onset of treatment to prevent reactivation. Furthermore, influenza, pneumococcal and hepatitis B vaccination should be considered before onset of therapy, and life attenuated vaccinations should be avoided during treatment, in accordance with the European League Against Rheumatism (EULAR) guidelines for vaccination in rheumatic diseases⁸¹.

Whether patients treated with biologic DMARDs have an increased risk for development of malignancies is still under discussion. This relationship is confounded by the increased risk of hematological malignancies due to chronic inflammation in rheumatic diseases. Compared to conventional synthetic DMARDs, only patients with RA on TNF inhibitors have shown an increased risk of non-melanoma skin cancer⁵⁶. As there are no indications that rituximab is associated with the occurrence of cancers, the ACR recommends rituximab treatment for RA patients with treated melanoma and lymphoproliferative malignancies as well as treated solid and non-melanoma malignancies less than

5 years ago⁸². Insufficient long-term data is available to be able to draw conclusions about an increased risk for malignancies during and after biologic immunosuppressive treatment in pSS. When patients with prior malignancies are treated with biologicals, rheumatologists should therefore be aware of the possibility of recurrence of these malignancies.

Rituximab

Rituximab therapy (anti-CD20), counteracting the B-cell hyperactivity in pSS, is widely used in the treatment of pSS-related lymphoma, often in combination with cyclophosphamide and prednisone^{83,84}. B-cell depleting therapy is also regularly used off-label for pSS patients with severe extraglandular manifestations. In several populations with moderate to high systemic disease activity, rituximab has shown a beneficial effect on systemic disease activity and ESSDAI scores^{85–92}. Unfortunately, the effect on ESSDAI was not confirmed in two recent large RCTs^{93,94}. Regarding glandular manifestations, rituximab has been reported to improve salivary flow in patients with enough residual gland function^{85,86,95,96}. Other studies reported stabilization of exocrine gland function during rituximab treatment, whereas salivary gland function deteriorated in placebo patients^{91,93,94,97}. In most studies, patient-reported symptoms such as fatigue and dryness were improved by rituximab treatment^{86,89,91,95–99}, but in recent RCTs this effect was smaller or did not differ significantly from the placebo group^{93,94}. The differences between the results of these trials are likely explained by differences in the baseline characteristics of the study populations. Safety results of rituximab trials in pSS patients are summarized in table 1.

In a Cochrane review of the safety profile of biologics during treatment of several diseases, rituximab showed the lowest odds for serious infections compared to control treatment¹⁰⁰. The infectious side effects of rituximab also seem to be mild in pSS, as in RCTs of rituximab treatment in pSS infection rates were comparable between treatment and placebo groups^{85,94}. These results were confirmed by a prospective registry of rituximab treatment in systemic autoimmune diseases (AIR registry), in which 78 pSS patient were included with a median follow up of 34.9 months. According to the AIR registry, the rate of serious infections during rituximab treatment was lower in pSS than in SLE (1.3/100 patient years versus 6.6/100 patient years, respectively)^{87,101}.

Despite pretreatment with IV corticosteroids, antihistamines, and paracetamol, and cotreatment with oral corticosteroids in some studies, infusion reactions such as fever, rigors and urticaria occur more common during rituximab treatment than during placebo treatment, occurring in 8–25% of patients^{85,94,95,102,103}. Specifically, Devauchelle et al. reported a higher incidence of respiratory disorders within 24 hours of injection with rituximab compared to placebo⁹⁴. Gottenberg et al. reported serious infusion

reactions in 6.4% of pSS patients in the AIR registry⁸⁷. One study did not report any infusion reactions during long term treatment with rituximab in 19 patients⁸⁶. However, as no safety analysis plan was included in the methods of this study, it is unclear how infusion reactions were defined.

Patients with active pSS seem to develop serum sickness-like reactions after rituximab treatment more often than patients with other rheumatologic diseases^{88,95,103,104}. Serum sickness-like reactions were generally characterized by fever, purpura, arthralgia, myalgia, and sometimes low complement levels and proteinuria. Serum sickness-like reactions were often associated with the development of human anti-chimeric antibodies (HACA), which supports the diagnosis of true serum sickness^{88,95}. However, the presence of HACAs was not always reported and in some cases a delayed infusion reaction may have been falsely interpreted as serum sickness. The presence of hypergammaglobulinemia in pSS might explain the higher prevalence of serum sickness in pSS, as it might increase the chance of immune complex deposition. In more recent studies, the prevalence of serum sickness-like reactions was low, probably due to adequate pre-treatment with high dose corticosteroids^{85–87,94}.

Progressive multifocal leukoencephalopathy (PML) due to JC virus replication in the brain is a rare but life-threatening condition associated with rituximab treatment¹⁰⁵. Rheumatologists should be aware of the risk of developing PML during B cell depleting treatment of pSS patients, as a case of PML has been reported in a pSS patient¹⁰⁶.

In RA, vaccination response is decreased by B-cell depleting therapy, which will probably also be the case during rituximab therapy in pSS¹⁰⁷. In addition, an open label study which evaluated safety of rituximab in 12 patients with pSS reported an exaggerated adverse reaction to pneumococcal vaccination in 3 out of 8 patients who received this vaccination⁹⁸. This might be an extra argument to administer pneumococcal and influenza vaccination prior to onset of rituximab treatment in pSS, although these results have not been confirmed by larger studies of vaccination in pSS.

In conclusion, rituximab has shown promising results regarding efficacy in populations with moderate to high systemic disease activity. Rituximab is generally safe in pSS, when adequate co-treatment is given and monitoring for infusion reactions takes place. Although patients should be monitored for development of infusion reactions and serum sickness-like disease, these adverse reactions are usually fully reversible. Long term safety effects of rituximab in pSS are still unclear and should be recorded in prospective registries.

Epratuzumab

Epratuzumab (anti-CD22) targets B-cells. An advantage of epratuzumab above

rituximab is that it is fully humanized. An open label study of epratuzumab in 16 pSS patients showed a beneficial clinical response in 67% of patients, which was defined as a 20% improvement in 2 out of four domains: Schirmer score, unstimulated salivary flow, VAS fatigue and erythrocyte sedimentation rate and/or serum immunoglobulin G (IgG).¹⁰⁸ Two patients discontinued treatment due to infusion reaction and one serious infectious adverse event occurred. Three patients developed a low level of anti-epratuzumab antibodies, but these were not associated with infusion reactions.

In phase 2 trials of epratuzumab in SLE patients, rates of (serious) adverse events and infusion reactions were similar between treatment and placebo arms¹⁰⁹. In other words, epratuzumab has a good safety profile in SLE in a dose of 360 mg/m², but the tolerability of epratuzumab in pSS has to be confirmed in larger RCTs.

Belimumab

B-cell activating factor (BAFF) blockade by belimumab, a human monoclonal antibody, inhibits survival of autoreactive B-cells and could therefore be beneficial in diseases characterized by B-cell hyperactivity. In SLE, a significant greater proportion of responders according to the SLE Responder Index in belimumab plus standard therapy versus placebo plus standard therapy has been reported^{110,111}. Therefore, belimumab is already registered for use in SLE. The safety of belimumab in SLE is favorable, with low rates of infection, malignancy and infusion reactions^{110,111}. A 7 year follow up study of belimumab treatment in SLE did not report any additional safety concerns and showed a stable or decreasing rate of AEs and infections during follow up¹¹².

One open label trial has been performed in 30 pSS patients, showing a beneficial response in 60% of patients¹¹³. Although a significant improvement was shown in ESSDAI and ESSPRI scores, the minimal clinically important improvement was not reached for both indices⁸. One serious infection led to discontinuation of treatment, and in another patient breast cancer was diagnosed three months after the last infusion. No infusion reactions were reported in the pSS open label trial. The percentage of patients experiencing adverse events was lower in the open label pSS trial than in SLE trials (54% of pSS patients versus 93% of SLE patients), which might be due to the larger percentage of SLE patients receiving co-treatment with immunosuppressants^{113,114}. A 52-week extension study of belimumab treatment in 19 pSS patients did not show any additional serious adverse events or infusion reactions¹¹⁵.

In summary, belimumab is effective and well tolerated in SLE. The efficacy and safety of belimumab in pSS, although favorable in the open label trial, should be further investigated in RCTs.

Abatacept

pSS is considered to be a B-cell hyperactivity mediated disease, but co-stimulation by T-cells is needed for inducing and maintaining B-cell activation. Thus, blockade of T-cell mediated B-cell hyperactivity is an interesting approach that has to be considered in pSS treatment too. Abatacept is a fully human fusion molecule of the Fc region of IgG with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which blocks co-stimulation of B-cells by T-cells. Abatacept is currently registered for use in RA and Juvenile Idiopathic Arthritis (JIA) and has a low odds ratio for serious adverse events, serious infections and withdrawals due to adverse events compared to other biologics¹⁰⁰. Due to the molecular structure of abatacept, its immunogenicity is very low^{116,117}. Subcutaneous abatacept has a comparable safety profile as IV abatacept in RA patients¹¹⁷.

Two small open label trials of IV abatacept treatment in pSS have shown that abatacept decreases ESSDAI, ESSPRI, IgG and rheumatoid factor, improves fatigue and decreases glandular inflammation. In the study by Meiners et al¹¹⁸, mild to moderate infusion reactions occurred in 40% of patients <1 hour of infusion (mostly hypotension and dizziness) and infections occurred in 66% of patients (mostly mild upper respiratory tract infections). Adler et al did not include a safety analysis plan in their methods, but did report that 27% of the patients experienced an adverse event, of which one was infectious (diverticulitis)¹¹⁹.

In conclusion, infectious adverse events and mild infusion reactions are relatively common during abatacept treatment in pSS. However, no serious adverse events or discontinuations were reported and in general, abatacept has a good safety profile. Subcutaneous abatacept is currently studied in an RCT of 88 pSS patients (NCT02067910).

Anakinra

Anakinra is a recombinant IL-1 receptor antagonist preventing activity of IL-1 α and IL-1 β . Anakinra is used to treat RA, gout and JIA, among others. In RA, anakinra does not cause a significantly higher number of withdrawals, deaths, adverse events or infections compared to placebo groups, but it does cause a higher prevalence of injection site reactions¹²⁰. An advantage of anakinra with regard to safety is the short half-life of 6 hours, which allows for prompt discontinuation in the case of adverse events.

Because anakinra has shown a beneficial effect on fatigue in RA, the effect of anakinra in pSS on fatigue was studied in an RCT of 26 patients¹²¹. Anakinra indeed reduced fatigue, but the study was underpowered for the primary outcome measurement and treatment duration was only 4 weeks. As expected, anakinra caused injection site reactions in a large proportion of pSS patients (54%)^{121,122}. Due to the small sample size and short follow up, no definitive conclusions can be made regarding the efficacy and safety of anakinra in pSS. Further study is needed.

IVIG

Intravenous immunoglobulin G (IVIG) is applied as substitution therapy in immunodeficiency syndromes, and as immunomodulating therapy in idiopathic thrombocytopenic purpura and several neurological auto-inflammatory disorders. Furthermore, it has been shown that IVIG decreases disease activity in SLE¹²³. Possible severe side effects of IVIG treatment include renal failure, thrombo-embolic events and aseptic meningitis, which may be prevented by a slow infusion rate and pre-hydration¹²⁴. A retrospective study in 19 pSS patients with peripheral neuropathy reported a beneficial effect of monthly courses of IVIG on SS-associated sensorimotor neuropathy and non-ataxic sensory neuropathy¹²⁵. Tolerance of IVIG was good. During the median treatment duration of 7 months, only one withdrawal due to an adverse event (nausea) was reported and no serious adverse events occurred. Case reports have also suggested efficacy of IVIG in SS-associated thrombocytopenia, central nervous system involvement and congenital heart block but no safety analysis was included^{126–128}. In summary, IVIG is a promising treatment for certain systemic manifestations of pSS and seems to be well tolerated, but should be further evaluated in prospective trials.

Baminercept

Baminercept is an inhibitor of the lymphotoxin- β pathway. Although baminercept treatment did reduce the IFN signature in RA patients, baminercept treatment showed disappointing clinical results¹²⁹. As the lymphotoxin pathway might play an important role in lymphoid tissue organization and chronic inflammation in pSS, baminercept was recently retested in a RCT in 52 pSS patients¹³⁰. Unfortunately, baminercept again did not improve exocrine gland function, fatigue, pain or sicca symptoms. The ESSDAI score was slightly improved in the baminercept group, but the mean ESSDAI change from baseline of 1.6 points is below the minimally clinically important improvement of 3 points⁸. Furthermore, transaminase abnormalities occurred more often in the baminercept group, and 7 serious adverse events occurred, including two patients with grade 3 hepatic injury. Therefore, the benefits of baminercept treatment in pSS do not seem to outweigh possible safety concerns.

Anti-TNF

Two anti-TNF biologic DMARDs have been studied in pSS. In a pilot RCT by Sankar et al., 14 pSS patients were treated with etanercept and 14 patients with placebo¹³¹. The effect of infliximab on pSS was studied in an RCT of 103 patients¹³². Unfortunately, both trials did not show a significant difference between the study drug and placebo treatment. The number of treatment discontinuations due to adverse events was somewhat higher in the anti-TNF groups than in the placebo groups. Interestingly, in the study by Mariette et al., serum immunoglobulin levels were significantly increased during infliximab treatment¹³². Impaired control of the IFN α pathway and subsequent BAFF overexpression by TNF inhibition might explain the inefficacy of this group of biologic DMARDs in pSS¹³³.

Expert opinion

Symptomatic treatment, preventive measures and patient's education are of great importance in the management of pSS patients in daily practice and were for decades the only treatment modality to reduce SS-related complaints. However, although symptomatic treatment is safe and has little adverse events, commonly only short-term symptomatic relief is achieved and this treatment does not protect patients from persistent disease activity or organ damage. Therefore, there is a need for registration of systemic therapies for the treatment of pSS.

There is limited evidence in the available literature for effectiveness of systemic conventional DMARDs therapy in pSS patients. Furthermore, the knowledge about adverse events and drug toxicity of conventional DMARDs in pSS is limited and often based on expert opinion. Toxicity of conventional DMARDs in pSS patients does not appear to be different compared to patients with other auto-immune diseases for which these drugs are used. Based on the weak evidence of efficacy and high rate of adverse events of conventional DMARDs, these agents should not be used in pSS routinely. Importantly, RCT's on conventional DMARDs were performed in small groups, with heterogeneous patient populations, lack of uniform endpoints and adequate measure instruments. There is a great need for well-designed and large RCT's to assess the value of conventional DMARDs in pSS with regard to glandular and extraglandular manifestations, patient-reported and systemic disease activity and organ-specific outcomes. Safety issues should take an important place in the analysis of these RCT's.

Recent years have shown a fast development regarding biologic systemic therapies for pSS. Several studies on biologic DMARD treatment of pSS patients have shown promising efficacy and safety results, especially in populations with high baseline systemic disease activity. In summary, the most frequent adverse events during biologic therapy in pSS patients are infusion and injection reactions and infections, as in other rheumatologic diseases. The risk of infection does not seem to be high in pSS, in fact it is often comparable to the infection risk in patients on placebo, patients with pSS have an inherent increased risk for developing infections and thus appropriate preventative actions should be taken. Infusion reactions occur most often when chimeric DMARDs are used such as rituximab, necessitating pre- and co-treatment with corticosteroids and antihistamines.

As most biologic DMARDs have only been evaluated in phase 2 trials so far, only limited safety data is available specifically for pSS, making it necessary to deduce information from safety analyses of biologic therapy for other indications. However, patients with other rheumatologic diseases more often use concomitant immunosuppressive

therapy than patients with pSS, which may influence the risk of infection and other adverse events. Furthermore, patients with pSS might respond differently to certain medications than patients with other rheumatic diseases. An example of this is the increased risk of serum-sickness like reactions seen during some studies of rituximab therapy for pSS^{88,95,103}. Therefore, safety analyses should be performed specifically in pSS patients.

This review of the literature taught us that many questions regarding drug safety in pSS remain unanswered. Larger numbers of treated patients, with a longer follow-up are needed to investigate serious adverse events with a low prevalence. Further study is needed to determine the specific dosage of systemic drugs for pSS in which the benefits/harms ratio is maximal. Furthermore, for most drugs the long-term safety is still largely unknown. To answer these questions, larger RCTs are needed and off-label treatment of pSS patients should be registered in cohort studies.

New outcome parameters such as the ESSDAI and ESSPRI, with a stronger sensitivity to change, have made it easier to monitor the efficacy of DMARDs in pSS treatment. Importantly, these indices have made it possible to compare the efficacy of different therapies. Unfortunately, for safety analyses, a multitude of methods is still used in various trials, which makes it difficult to directly compare the results of different studies and drugs. For an example, authors might use different definitions of adverse events, but do not always report which definition they used. Furthermore, it should be clear if adverse events are investigated only by open-ended questioning or by specific screening for certain adverse events (e.g., by asking about it or by laboratory analysis). In addition, there are large differences in the data that authors choose to report. Some authors only report serious adverse events, or only adverse events of a certain type, while others provide a complete list of coded adverse events. Therefore, we urge authors of future therapeutic studies in pSS to follow the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement, which describes guidelines for the reporting of harms in randomized trials¹³⁴.

In conclusion, the available data suggests that the safety of symptomatic treatment is very good and symptomatic treatment should be applied in all pSS patients. However, systemic therapy is necessary to achieve long-term relieve and prevention of organ-damage and exocrine gland dysfunction. Therefore, further evaluation of the effectiveness and adverse events of systemic DMARDs in pSS is important. Conventional DMARDs have not shown much efficacy in earlier studies, and their benefits do not seem to weigh up to the risk of adverse events. However, methodological problems may have influenced these results. As biologic DMARDs cause mostly mild adverse events in pSS, and show promising results regarding efficacy, the benefits of biologic DMARD therapy seem to outweigh possible safety concerns.

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9

Discussion and future perspectives

General discussion

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease, characterized by lymphocytic infiltration of exocrine glands, in particular of the lacrimal and salivary glands. The three main features of SS are (1) presence of sicca symptoms or dry mouth and dry eyes, resulting in xerostomia and keratoconjunctivitis sicca, (2) development of extraglandular manifestations with involvement of many organs and organ systems and (3) development of chronic and profound fatigue and diffuse pain. In this chapter, these features are discussed with respect to daily clinical practice. Key findings of several clinical issues that are frequently encountered in daily practice, like age-related differences of clinical presentation, treatment modalities, disease activity scores, secondary SS and serological biomarkers, will be discussed as well as areas for future research will be indicated.

Does age matter with regard to presentation, diagnosis and treatment?

The peak incidence of SS is at age 40-55 years with an estimated female to male ratio of 9-14 to 1.¹ However, SS can also be diagnosed in children, young adults and elderly (**chapter 2**). Generally spoken, the clinical presentation of SS is somehow age dependent. Patients who are younger than 35 years, including children and adolescents,² have lower frequency of sicca complaints, have more often extraglandular manifestations and have higher frequency and titers of immunologic markers than patients aged >35 years. Children often present with persistent or intermittent parotid gland or submandibular gland enlargement. Elderly patients more often have mucosal dryness, lung involvement and anemia, but less often present with parotid gland enlargement, arthralgia, arthritis, Raynaud phenomenon and serologic abnormalities, such as anti-SSA, anti-SSB, rheumatoid factor and hyperglobulinemia.^{3,4}

Although sicca symptoms are an important symptom at presentation of SS, these symptoms are also common features in elderly without an autoimmune disease. Due to a decrease in the number of acinar cells and an increase of fatty and fibrous tissue the overall functional capacity of lacrimal and salivary glands may decrease over time. Especially submandibular salivary glands are sensitive to age-related changes compared to parotid glands and in particular the submandibular glands are responsible for secretory efficiency in resting conditions.⁵ Most healthy elderly persons who are not using xerogene medication do not experience xerostomia even if their salivary flow rate is significantly reduced and the composition of saliva is altered compared to younger persons. The capacity of the salivary glands is maintained in elderly by stronger stimuli. If this mechanism fails, the salivary secretion machinery can no longer cope and therefore up to 30% of the patients over 65 years experience xerostomia.⁵ Furthermore, besides

SS, there are multiple other factors which may reduce salivary and lacrimal flow in elderly, of which xerostomia associated with the use of medication is the most common cause.⁶ There is some disagreement whether elderly patients with sicca complaints will be diagnosed earlier or later in the course of the disease compared to younger patients. Bouma et al⁷ postulated that aging will lead to a reduced salivary gland function, what may allow earlier diagnosis upon onset of SS in elderly. Latter authors suggested that sicca symptoms may rise earlier in the disease process and will trigger consultation of a physician resulting in an earlier diagnosis of SS. However, as mentioned before, older patients with SS also have more comorbidities and use more xerogenic medication. Therefore it is less likely that a physician refers an elderly patient for a diagnostic SS-work-up. In this respect it also has to be mentioned that healthy elderly population is known to have more serologic abnormalities, like positive antinuclear antibodies, rheumatoid factor and monoclonal proteins than younger healthy controls, thus serologic abnormalities at older age should be interpreted with caution.⁸

The issues described above make it difficult for physicians to address which sicca complaints are due to SS, as differential diagnosis of SS primary includes many alternative causes of sicca symptoms, many of which are epidemiologically more common than SS. Even when a physician decides to do a full diagnostic work-up of SS in an older patient, the histopathologic diagnosis may be impaired by aging as with age lymphocytic periductal infiltrates in glandular tissue can also be due to mechanical irritation, infections, irradiation or ischemia. These phenomena might lead to inflammation and therefore a false positive focus score.^{9,10} Thus, presence of infiltrates should be interpreted with caution, and a diagnosis of SS should not only rely on focus score, but also address the shift of IgA to IgG positive plasma cells of more than 30% and the presence of lymphoepithelial lesions.¹¹

Regarding the treatment of elderly with SS there are no differences in the choice of therapy. The co-morbidities and therefore possible increased rate of adverse events and interactions should be taken into account. Furthermore, elderly patients should also be included in the clinical trials to be able to assess the adverse events in this specific population.

How to assess disease activity and effect of treatment

There are several primary end points proposed for assessing the efficacy of the treatment in SS. The variability in the applied end points makes comparison of results between studies difficult and sometimes even impossible. There is still no overall consensus whether the visual analogue scale (VAS), European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient

Reported Index (ESSPRI), physician global disease activity score or composite endpoints should be chosen as well as how to evaluate different serological parameters, fatigue, health related quality of life (HR-QoL), and cost-effectiveness and cost-utility of therapies. All these possible end points assess different disease domains and do not or only partly correlate with each other and probably should be used together in a composite endpoint.

The development of ESSDAI was a very important step forward in providing a valid and reliable measure of systemic disease activity in SS.¹² ESSDAI also provides an important tool in the daily clinical practice for systematic evaluation of the patient. In **chapter 3** we showed that ESSDAI is sensitive to measure changes overtime in disease activity in SS, so-called 'responsiveness'. ESSDAI was able to show significant changes or no changes in disease activity in patients treated with rituximab or placebo. At this moment, ESSDAI is the only available tool to assess extraglandular manifestations and since its introduction in 2011 it has been used in clinical trials. Advantages and disadvantages of ESSDAI have become more clear. As mentioned, phase II trials and registry observations have suggested that SS patients with high systemic activity well respond to rituximab and abatacept therapy, but large RCTs using rituximab and abatacept therapy unfortunately failed to prove a favorable effect of these drugs compared to placebo by using ESSDAI. There are several possible explanations to this observation. First of all, these therapies may indeed not be effective. However, based on the knowledge of the pathophysiology of SS with B-cell hyperactivity as a hallmark of the disease, there is still clinical experience that rituximab is an effective therapy in at least subgroups of patients with SS. Studies showed that rituximab lowers the levels of antibodies, like rheumatoid factor, IgG, free light chains, other B-cell associated cytokines, including IL-6, TNF-alfa and IL-10 and also partly anti-SSA/SSB.¹³ Furthermore, treatment with rituximab has shown to reduce the severity of lymphoepithelial lesions and the number of germinal centers, and led to the restoration of the epithelium of salivary glands.¹⁴ Verstappen and colleagues¹⁵ showed beneficial effect of rituximab on the proportions of circulating T follicular helper cells (cTfh). These cells are elevated in SS patients and they activate B-cells and the germinal center and plasma cell formation. The decrease of cTfh cells interrupts the positive feedback loop, leading to the down regulation of inflammatory process. Although phase III trials did not support a general favorable effect of rituximab in the treatment of patients with pSS, all the above mentioned findings support the potential beneficial role of rituximab in SS patients. For example, Delli et al. demonstrated that the baseline number of CD20 positive B cells in salivary glands may serve as a prognostic biomarker to predict response to rituximab treatment, possibly a step forward to the personalized medicine.¹⁴

So, why could the efficacy of rituximab not be proven in phase III RCTs? From pathophysiologic point of view it is known that due to B-cell depletion, the levels of BAFF cytokine increases, what possibly enhances the survival of auto-reactive B-cell clones.¹⁶ This can be a possible explanation for lesser effectiveness of rituximab in SS and may be the additional point of intervene in the future. Furthermore, after rituximab treatment, plasma cells stay in salivary glands as they do not have the expression of CD20 and can therefore continue with production of immunoglobulin's and may underlie disease relapse after treatment.¹⁷

Next to gaining more knowledge of pathophysiological mechanisms underlying the pathogenesis of and disease activity in SS, there are still a lot of questions to the design of the studies with rituximab and other biologicals. There are different study populations and inclusion criteria possible as well as that the correlation between the objective and patient-reported parameters is poor in SS.¹⁸ Furthermore, since the development of ESSDAI, this tool is broadly used in clinical trials, ESSDAI is a composite tool to measure the overall disease activity of SS. It can be very helpful to use ESSDAI in daily clinical practice, as you get one total score of the systemic activity in a patient with regard to extraglandular manifestations. But, if a patient has arthritis, physician is willing to give a therapy which will work for arthritis. Possibly, rituximab is a good therapy for this manifestation of disease. However, ESSDAI measures not only arthritis component, but also all other extraglandular manifestations. In other words, if analyzing individual domains, there is still improvement possible in a single domain which is not detected by the total ESSDAI score as it has a composite nature. In addition, ESSDAI not only measures disease activity but also disease damage as it is sometimes difficult to distinguish these two features. If damage is also measured by ESSDAI, no chance for improvement exists because damage is irreversible. It has already been demonstrated that not all ESSDAI domains can show the sensitivity to change.¹⁹ For example, if patients with peripheral or central neuropathy are included in the study, no improvement may occur on week 24, as the recovery of the nerves, when it occurs, usually takes much more time. Furthermore, the stabilization of neurological decline can be clinically sufficient, but will not be detected by ESSDAI in the study as a successful therapy. Therefore, focusing on one or two domains in detail might be a solution for several particular aspects of the disease.

In **chapter 4** a study is described in which we evaluated the articular domain in pSS patients after treatment with rituximab, abatacept or placebo. Articular involvement was assessed with the DAS28 score, which is extensively used in rheumatoid arthritis (RA).²⁰ We showed that DAS-28BSE and DAS28CRP were sensitive enough to detect the effect of biological therapies in SS patients with arthritis and arthralgia. The improvement was detected for all four components of DAS28 (ESR/CRP, visual analogue scale (VAS), swollen joint count (SJC) and tender joint count (TJC)). The advantage of this instrument

is that DAS28 tool is reliable, well-known and very frequently used by rheumatologist in the daily clinical practice as well as in research settings. Therefore, we suggest that DAS28 can be used in clinical practice and in trials with SS patients. Analogue to DAS28, other organ specific disease activity tools should be considered to use in evaluation of therapy effects in SS.

Furthermore, except clinical parameters to assess the disease activity of SS and monitoring of the treatment, we showed in **chapter 5** that free light chains (FLCs) can be used as a biomarker of the disease. FLCs are sensitive to change and have more favorable kinetics than IgG, as the relative changes of FLCs induced by treatment were higher compared to IgG. FLCs can also be used as a biomarker of salivary gland MALT lymphoma, as 50% of the MALT lymphoma patients had a deviated ratio of FLCs.

How to treat SS

The three features of SS (sicca symptoms, extraglandular manifestations, fatigue and pain) have to be taken into account and be discussed with a patient when treating patients with SS in the daily clinical practice.

Symptomatic treatment

There are several therapeutic options for the somewhat effective topical symptomatic treatments of sicca in SS (**chapter 8**), however these treatments do not halt progression of the disease and not always protect against the occurrence of new damage. These symptomatic treatments may only temporarily relieve sicca symptoms, but have no influence on extraglandular manifestations, which are the main cause of morbidity and mortality. Therefore, the research on development of more effective targeted treatments, reducing disease activity and slowing disease progression is highly needed.²¹

Systemic treatment

Yet, no systemic treatment has been proven effective and registered for SS, but there are several conventional and biologic DMARDs used in SS, often based on small cohort or case-report studies and expert opinion.

Rituximab, a chimeric anti-CD20 monoclonal antibody, was shown to be a potent drug in encouraging small phase II trials and is still used for several extraglandular manifestations, like vasculitis, interstitial lung disease, lymphoma. Phase II studies also indicated that sicca complaints and fatigue improved over time after rituximab treatment.^{22,23,24} Two large randomized controlled trials showed no difference between rituximab and placebo treated patients on primary end points.^{25,26} A possible explanation for the phase III studies being negative is the primary endpoints chosen as

well the heterogeneity of the SS patients included in these larger studies. SS has not yet a fully unraveled pathogenesis and the inclusion of patients in the smaller single center trials was more strict than in the larger multicenter trials. This is also supported by the observation of Delli et al. that distinct patients groups are still responsive to rituximab treatment.²⁷

Abatacept was a next promising biological based on the pathophysiologic knowledge of SS. Abatacept is a human fusion protein produced with recombinant DNA technology, which blocks the co-stimulation of CD80 and CD86 molecules on the surface of antigen presenting cell, namely of CD28-receptor of T-lymphocytes. As T-cell dependent B-cell hyperactivity plays an important role in the pathogenesis of SS, prevention of T-cell activation is a promising approach to the therapy. In an open-label study with abatacept in 15 pSS patients abatacept showed improvement in ESSDAI, ESSPRI, laboratory parameters, fatigue and HR-QoL after 24 weeks.²⁸ Because of these favorable results, a randomized double-blind, placebo controlled trial (ASAP-III trial) was conducted to assess the efficacy and safety of abatacept compared to placebo to decrease systemic disease activity (ESSDAI) at 24 weeks.²⁹ Despite of clear biological effects of abatacept, no significant difference was found between abatacept and placebo groups on the primary endpoint. The same consideration as in rituximab trials can be made about this abatacept trial. SS is a highly heterogeneous disease and probably for the particular extraglandular manifestation a particular DMARD should be evaluated. The choice of primary endpoint of a trial influences the outcome of a trial.

Therefore, a scientific discussion is ongoing concerning the characteristics of patients (SSA positivity, biopsy proven, short disease duration etc.), patient stratification and the most suitable primary endpoint for clinical trials.

SS is a heterogeneous disease with a variable course, therefore inclusion criteria for the trials should not only be based on the classification criteria in general, but patients should also be selected on manifestations that are specifically targeted by the drug studied. For example, when focusing on the treatment effect on extraglandular manifestations, the disease activity at inclusion should be high enough to be able to show the effect of the therapy. The minimal clinically important difference of the disease activity has already been determined for ESSDAI and ESSPRI.³⁰ A power analysis should have been performed to make the trial to a valid trial. At inclusion, not only activity of the disease should be evaluated, but also the existing damage which will not improve over time anymore, like chronic kidney insufficiency or polyneuropathy. On the other hand, since patients are selected for trial when they have (very) active disease, it is important to perform placebo-controlled trials to ensure that the improvement is not biased by regression to the mean.

Belimumab, a human monoclonal antibody against B-cell activating factor (BAFF), also known as B lymphocyte stimulator, and registered for use in systemic lupus erythematosus (SLE), was studied in 30 patients with pSS in an open-label study.³¹ ESSDAI scores, VAS on dryness and serological markers as hypergammaglobulinemia and RFs decreased after 28 weeks, although no change was found in the stimulated salivary flow rate or Schirmer's tests. Salivary gland biopsies after treatment showed no changes in lymphocytic infiltrations.

Ianalumab, another BAFF antibody preventing BAFF signaling via its receptor, was investigated in a pilot study with 18 pSS and in a phase II clinical trial with 190 patients.^{32,33} Although no differences in the reduction of ESSDAI scores, fatigue, or salivary flow rates were found in a pilot study, ianalumab led to a significant decrease in ESSDAI scores compared to placebo-treated patients in a phase II trial.

Next to BAFF/IL-6 and IL-21 pathways, which complicit in B-cell hyperactivity, patients with SS have an interferon signature. The interferon signature means that there is enhancement of expression of interferon genes and their downstream targets. Although targeting IFN α or its receptor itself have not been studied yet in pSS, depletion of plasmacytoid dendritic cells, the producers of type I IFN, targeting upon downstream intracellular pathways of type I IFN, like Jak1 inhibitors are currently under evaluation. Also, small molecular inhibitors (SMIs) targeting toll like receptor and NF κ B are currently under investigation.³⁴

Patients with SS have different genetic backgrounds and variety of clinical manifestations due to several pathophysiological pathways. Therefore, personalized treatment providing 'the right patient with the right drug at the right dose at the right time, is warranted for the treatment of SS.¹⁴

Fatigue and pain, how the clinician can deal with these complaints

Chronic fatigue and diffuse pain are common and very cumbersome disease manifestations of SS. Depression is associated with these symptoms as well.³⁵ Fatigue, pain and depression have large impact on daily life of the patients and impede the participation in family life, work and in social contacts.^{36,37} In daily clinical practice, these aspects of the disease are often not discussed during the consultation by the rheumatologist, while the importance of fatigue was rated as extremely high by SS patients. To underline the importance of fatigue and pain as the third important feature of SS, we assessed the effect of rituximab therapy on fatigue in SS patients treated with rituximab in our open-label trial (**chapter 6**). 86% of pSS patients rated physical fatigue as most eligible symptom for improvement. After rituximab treatment 36% of patients

with physical fatigue reached patient-acceptable symptom state (PASS). However, the large majority of patients did not achieve a satisfactory state and still experienced physical fatigue above the cut-off value for the PASS. Therefore, attention for optimal management of this prominent symptom is warranted in daily practice.

The pathophysiological mechanisms of chronic fatigue and pain in SS are largely unknown. Several factors play a role in the development of fatigue. These include continuous inflammation state and cellular stress responses, leading to cytokines production and signaling in the brain. These responses may lead to pain and fatigue. Therefore, careful interpretation of these symptoms by the physician is needed, as these are not just a result of being unlucky due to having a chronic disease. Omdal and colleagues³⁸ hypothesized that in pSS, due to chronic inflammatory origin of the disease, fatigue becomes chronic possibly as a result of increased IL-1 signaling in the brain, as IL-1 signaling was demonstrated to have fundamental role in pathways involved sickness behavior in several animal studies.³⁹ This pathway is activated leading to behavior changes that were meant to increase survival during stress moments. IL-1 pathway has also been associated with depression and depression is in its turn associated with fatigue.

Fatigue is not a well-defined condition and is often confused with other psychosocial states. Therefore, symptoms of fatigue and pain in SS are often classified by rheumatologists as fibromyalgia, even when physical fatigue was more prominent than mental fatigue in our study. When treating SS patients, most doctors focus mainly on sicca symptoms and extraglandular manifestations, while in our rituximab trial we showed that the large majority (86%) of the patients found physical fatigue as most eligible for improvement, more than symptoms of pain and dryness.

Several years ago it was almost impossible to measure dryness, fatigue and pain during an outpatient consultation as the available questionnaires were too long and too complex. In 2011 the ESSPRI was developed.⁴⁰ This is a simple and easy to apply instrument to rate the above mentioned symptoms in daily clinical practice as well as for symptom assessment in clinical trials. ESSPRI is certainly a step forward to a better assessment of fatigue and pain in SS patients. However, the management of these symptoms is still difficult as there is still no registered treatment available to reduce fatigue and pain in SS.

Physical exercise on regular basis starting with low intensity and increasing intensity over time with enough time to recover can lead to physiological stress training and therefore possibly decreasing of fatigue and pain in SS. In a study with SS patients, exercising at least 30 minutes three times a week exhibited higher resilience than patients who

did not exercise.⁴¹ From a personal point of view, I like to pose that the first step in dealing with fatigue in daily clinical practice will be to acknowledge this problem to the patient. Thereafter, to speak to the patient about the impact of fatigue and pain on daily functioning and to discuss how to handle these problems within the limited options available. The empathy and recognition of these symptoms from the perspective of the patient is the first step to the approach of this problem. Advice to exercise at least 30 minutes three times a week should be given to all SS patients. Furthermore, we hope for better treatments to come available soon.

Secondary SS and sicca complaints in patients with rheumatoid arthritis

While primary SS is an important subject of scientific research, there are far less studies concerning secondary SS. The recognition and acknowledgement of secondary SS in daily clinical practice can also be challenging as physicians may concentrate on the treatment of the accompanying diagnosis, such as SLE or RA, and patients may not report sicca complaints spontaneously. In the study described in **chapter 7**, we evaluated SS and the course of sicca complaints in patients with RA. The main conclusion of our study is that although a small proportion of RA patients met classification criteria for SS (6%), one third of RA patients had sicca symptoms, which should be a concern in the management of RA. Furthermore, the development of sicca symptoms and SS is associated with high disease activity of RA as well as that sicca symptoms and SS impair daily activities and quality of life, as SS patients experience more fatigue and pain. These conclusions underline the impact of SS and sicca complaints in RA patients and call for more research in this area. For future research, there are unfortunately still several challenges to overcome.

The first challenge is the diagnosis of secondary SS (in fact whether SS and other autoimmune diseases are associated). The American European Consensus Group (AECG) criteria include distinct sets of criteria with which secondary SS classification can be made. The recent ACR/EULAR criteria do not make the difference between secondary or primary SS, they are in fact just developed to classify primary SS patients. The ACR/EULAR criteria which are proposed to be used nowadays instead of AECG criteria, are not tested yet in a cohort of secondary SS patients. ACR/EULAR criteria lend a high weight of 3 points (from 4 needed for classification) to the presence of anti-SSA antibodies. From the studies on secondary SS in RA it is known that anti-SSA antibodies are less frequently present than in primary SS.^{42,43,44} Therefore, these criteria presume that the majority of secondary SS patients with RA should undergo a biopsy to be classified as SS and the question is whether this is desirable and achievable in the daily clinical practice.

The second challenge is the question whether SS is a distinct and associated rheumatologic disorder or whether secondary SS should be seen as an extra-articular manifestation of RA or another auto-immune/connective tissue disease. SS represents a unique feature, namely the development of auto-immune epitheliitis due to the activation of innate as well as acquired immune systems. The nature of this intrinsic epithelial activation is still unknown, but suggests a different pathophysiologic mechanism than inflammatory processes in RA.

Furthermore, besides the unique epithelial dysfunction in SS, exogenous agents and epigenetic influences are proposed to activate the epithelia, like epitheliotropic microorganisms, aberrant expression of various immune-modulatory proteins, such as MHC proteins, co-stimulatory proteins, adhesion molecules, TLRs, cytokines and chemokines.⁴⁵

RA is a chronic inflammatory disease where the development of extra-articular manifestations represents the disease activity even in the absence of joint inflammation. The question is whether the inflammation in salivary and lacrimal glands is etiologically related to systemic manifestations of RA or has a different origin.

The third dilemma is how to treat RA patients with secondary SS. Is standard treatment of RA with methotrexate and/or anti-TNF suitable for patients who also have secondary SS? It is known that patients with SS have increased risk of hematologic malignancies, especially Non-Hodgkin's MALT lymphoma, but also nodal marginal zone lymphoma and diffuse large B-cell lymphoma, which are the most threatening risk of morbidity and mortality.^{46,47} Increased risk of lymphoma has also been associated with use of methotrexate in patients with RA.^{48,49} In addition, discontinuation of MTX can lead to spontaneous disappearance of lymphoma in some patients.⁵⁰ Anti-TNF use has also been associated with lymphoma development.⁵¹ Although the risk of lymphoma in SS is higher than in RA and treatment with methotrexate possibly increases risk of lymphoma, the nationwide population-based cohort study found that of the 16,396 SS patients, 128 patients were treated with DMARD therapies, including methotrexate. None of these patients developed NHL over a period of 10 years.⁵² Among the issues that still remain unsolved is whether the development of lymphoma in RA patient with secondary SS treated with MTX and/or anti-TNF is increased due to the medication or due to the natural origin of the disease and higher disease activity and other unfavorable prognostic factors which are more associated with the development of lymphoma than the medication itself.

A clinical implication of these findings is that patients with RA and secondary SS should be evaluated for the risk of lymphoma and if increased, careful evaluation of the therapy

should be made. Patients with features of salivary gland enlargement, splenomegaly, lymphadenopathy, purpura, abnormal FLC κ/λ ratio, low complement level, especially of C4, monoclonal gammopathy, cryoglobulinemia, neutropenia and lymphopenia are at increased risk of development of lymphoma.

In **chapter 7** we described a study showing that the κ/λ ratio of free light chains (FLCs) in serum is abnormal in 50% of patients with MALT-lymphoma. This can also be an important possible biomarker of lymphoma in secondary SS patients, but further studies are warranted to investigate this question.

The last issue addressed to secondary SS to be discussed is which RA patients should be evaluated for secondary SS? As discussed in **chapter 7**, patients with RA have increased incidence of sicca symptoms. The majority of these sicca patients do not have secondary SS. In our study, we found that patients with high disease activity of RA are at increased risk of associated SS. These patients should be evaluated more extensive in the daily clinical practice. Both anamnesis of sicca symptoms and parotid gland enlargement and additional laboratory tests (ANA, ENA, IgG, complement C3, C4, FLCs) should be performed looking for the secondary SS. Nowadays, the treatment of RA is conducted according to the window opportunity and treat to target principles. This implicates that rapid decline of disease activity of RA may protect patients from further development of SS. This statement should be the matter of further research. Anyway, early treatment of disease activity of RA should be the primary point of interest of rheumatologist in order to avoid further disease progression and organ damage. Furthermore, patients with RA, sicca and hematologic abnormalities, like anemia, trombopenia or leucopenia or interstitial lung disease or auto-immune liver disease or kidney disease should also be evaluated for concomitant SS.⁴⁴

As our study was performed only in RA patients, the discussion in this thesis focuses only on RA subjects. However, secondary SS can also be present in other auto-immune diseases. Therefore, additional research is needed for patients with SLE, mixed connective tissue disease (MCTD), myositis, dermatomyositis and systemic sclerosis. This lack of studies on the secondary SS with other auto-immune disorders demonstrates the complexity of secondary SS research, as SS is known to be a very heterogeneous disease itself and if associated with other also heterogeneous auto-immune diseases, it is difficult to perform neat and conclusive studies.

Future perspectives

SS is a heterogeneous disease with glandular involvement (sicca), extraglandular organ manifestations and fatigue and pain as three main features and therefore there are many challenges dealing with SS patients in daily clinical practice. Age-related differences of clinical presentations, making the diagnosis, treatment options and estimation of the prognosis for SS patients are still to be further investigated. Awareness of the heterogeneity of the disease and individual patient approach can help the physician to make a good clinical decision. An important recommendation for the future studies will be stratification of patients on age, systemic manifestations and biological markers, hopefully leading to effective therapies and personalized medicine. European collaboration is needed to solve these challenges and is already undertaken within two consortia (HarmonicSS and Necessity) under the EULAR umbrella of ESSENTIALS. Resolving methodological questions when conducting clinical trials in SS patients can help to demonstrate the treatment efficacy. One of these methodological challenges will be determinations of usefulness of ESSDAI in clinical trials. Furthermore, to make the evaluation of systemic manifestation easier, organ-specific disease evaluation tools can be chosen or developed if needed. Last but not least, the development of a composite endpoint, existing of patient related outcome measures and systemic disease manifestations is promising.

At this moment, there are only classification criteria in SS and no diagnostic criteria. New ACR/EULAR criteria should be evaluated and accepted not only for primary SS, but also for secondary SS in a defined cohort of RA, SLE, dermatomyositis, myositis, systemic sclerosis and MCTD patients. Awareness and importance of research on secondary SS should be acknowledged.

Furthermore, the value of these criteria in elderly should be evaluated as well, as the unstimulated whole saliva (UWS) secretory capacity of salivary glands decreases with age physiologically and the threshold for the UWS in elderly should be assessed. Furthermore, in elderly, the incidence of anti-SSA antibodies is less frequent than in younger patients, thus leading to the need of more frequently taking a biopsy according to the ACR/EULAR criteria. Several studies on ultrasound evaluation of the salivary glands showed to be of high value in classifying patients as SS.

Progress in understanding of SS pathology allowed development of new targeted therapies. Although rituximab and abatacept showed promising results in small trials, the role of rituximab and abatacept in the treatment of SS should still be pointed. Furthermore, combination of rituximab and belimumab could possibly be more successful than rituximab monotherapy. There are several potential therapies to

evaluate, such as tocilizumab (humanized monoclonal antibody against IL-6 receptor), anti-CD40 monoclonal antibody, Bruton tyrosine kinase inhibitors, tyck2 inhibitors, phosphoinositide 3-kinase (PI3K) delta inhibitor. Hopefully, future studies will result in registration of systemic therapies for SS.

And last but not least, we still need to unravel the pathogenic mechanisms of fatigue and pain in SS. The importance to find a treatment against fatigue and pain should be of high priority for researches as fatigue and pain have great impact on the wellbeing of the patients and their participation in society.

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10

Summary

Summary

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and in particular the lacrimal and salivary glands. SS has three main disease manifestations. The most common disease manifestation is the presence of sicca symptoms of the mouth and eyes resulting in xerostomia and keratoconjunctivitis sicca. A second major disease manifestation is the development of extraglandular manifestations with involvement of many organs and organ systems, among others, arthritis, skin disease, lung disease, renal disease, neurological disease and lymphomas. A third major manifestation that is present in most patients is chronic and profound fatigue and diffuse pain.

SS can be primary or secondary, the latter being associated with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, dermatomyositis and mixed connective tissue disease. The peak incidence of SS is at age 40-55. The estimated prevalence of primary SS is 0.04–1%. The estimated prevalences of secondary SS associated with RA and SLE are 19.5% and 14.0%, respectively. There is a clear predominance of women with SS over men with an estimated female to male ratio of 9:1 (up to 14:1).

The pathogenesis of SS is still largely unknown, however genetic, epigenetic, gender-related, environmental factors and involvement of both innate and adaptive immune systems have been suggested to play a role in the development of the disease. The hallmark of SS appears to be B-cell hyperactivity, as there are multiple serological manifestations of the B-cells. These are high serum IgG levels, the presence of autoantibodies (rheumatoid factor, anti-SSA/SSB and ANA), elevated levels of polyclonal or monoclonal free light chains, β 2-microglobulin, cryoglobulins and increased risk of the development of non-Hodgkin lymphoma.

The overall aim of the research reported in this thesis was to assess major clinical manifestations and potential biomarkers of primary and secondary SS. These are clinical aspects which the rheumatologist can come across in daily clinical practice.

In **chapter 2** the diagnosis and treatment of elderly patients with SS is discussed. Diagnosis of SS in the elderly population can be challenging because xerostomia, xerophthalmia, fatigue, weight loss and muscle pain are also common features of old age. Delay between clinical onset and diagnosis of SS in the elderly may be due to the shared features of SS and old age. Treatment of SS in the elderly does not differ from that in younger patients. The aims of the treatment of SS are to control glandular and extraglandular manifestations, to prevent damage to organ systems and loss of function

and to decrease morbidity and mortality. Treatment of the elderly can be complicated by co-morbidities, an increased rate of adverse events related to therapeutic agents and polypharmacy. Therefore, careful follow-up of the treatment is required.

In **chapter 3** a study is described in which the sensitivity to change of the European League against Rheumatism (EULAR) Disease Activity Index (ESSDAI) was assessed in a phase II randomized controlled trial. We showed that the ESSDAI score can reveal significant changes in disease activity in patients with pSS treated with rituximab compared to placebo. Based on the outcome of this phase II trial it was concluded that ESSDAI might be a good tool to detect changes in disease activity over time in clinical trials.

In **chapter 4** it was discussed whether the 28-joint Disease Activity Score (DAS28) can be used as a good tool to assess the effect of a treatment with biologicals on the joint complaints of patients with primary SS in addition to ESSDAI. Therefore, DAS28 and the ESSDAI articular domain was assessed to evaluate the effect of rituximab and abatacept on articular involvement in primary SS. Patients with primary SS treated with rituximab (n=18) or abatacept (n=13) and having a DAS28 erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) level ≥ 3.2 at baseline were selected. Generalized estimating equations were used to analyze the DAS28 and ESSDAI articular domain over time. We showed that in the rituximab group, DAS28-ESR/CRP decreased significantly up to 48 weeks. In the abatacept group, DAS28-ESR/CRP decreased significantly up to 24 weeks. Furthermore, DAS28 correlated significantly with ESSDAI articular domain. DAS28 is useful to evaluate the effect of biologicals on articular involvement in patients with pSS. On basis of these results it was concluded that DAS28 is useful to evaluate the effect of biologicals on articular involvement in patients with pSS in addition to the articular domain of ESSDAI.

Besides the clinical aspects of evaluation of SS the clinician has also laboratory evaluation possibilities. For example, serum immunoglobulin free light chains (FLCs) are frequently elevated in B-cell-mediated autoimmune diseases, including primary SS. Therefore, in **chapter 5** a study is described in which it was assessed whether serum FLCs can be used as a biomarker for systemic disease activity and mucosa-associated lymphoid tissue (MALT) lymphoma. Serum samples of 100 consecutive patients suspected of primary SS were included. Forty-five patients fulfilled ACR-EULAR criteria for primary SS. Additionally, samples of 17 primary SS patients with MALT lymphoma and longitudinal samples of primary SS patients treated with rituximab (n=20), placebo (n=10) or abatacept (n=15) were included. Serum FLC κ /FLC λ was measured by nephelometry or turbidimetry. At diagnosis, FLC κ and FLC λ serum levels were significantly higher in primary SS compared to non-SS sicca patients. The FLC κ /FLC λ ratio was abnormal in

11% of primary SS patients. In established MALT-primary SS patients, without recent rituximab treatment ($n = 12$), 50% had abnormal FLC κ /FLC λ ratios. FLCs measurement had no additional value for pSS classification, compared to IgG and anti-SSA levels. FLCs levels correlated significantly with systemic disease activity, assessed by EULAR SS Disease Activity Index (ESSDAI) and clinical ESSDAI, both cross-sectionally and longitudinally following treatment. Treatment with rituximab or abatacept significantly lowered FLCs levels. FLCs show a large sensitivity to change and relative changes induced by treatment were higher compared with IgG levels. We concluded that serum FLCs are elevated in primary SS, and abnormal FLC κ /FLC λ ratios may be indicative for the presence of MALT lymphoma. FLCs levels can be used as a biomarker for systemic disease activity and monitoring.

In **chapter 6** the data from our open-label rituximab study with 28 pSS patients was analyzed regarding fatigue as well as the effect of rituximab treatment on fatigue. Symptoms of dryness, physical fatigue, pain and mental fatigue were scored on 0-10 scales according to EULAR Sjögren's syndrome patient reported index (ESSPRI). Systemic disease activity was assessed with ESSDAI. At baseline 24 (86%) patients rated physical fatigue as the complaint most eligible for improvement (median importance of 10), followed by pain, dryness and mental fatigue. After rituximab treatment physical fatigue showed maximum improvement of 2.5 points and 31% in median values at group level, and 10 (36%) patients reached physical fatigue score <5 representing patient-acceptable symptom state (PASS). In comparison systemic disease activity improved 5.5 points and 73% at group level, and 22 (79%) patients reached ESSDAI <5 representing low disease activity. Generalized estimating equations analysis over time revealed that physical fatigue was significantly associated with absolute number of B cells, dryness and mental fatigue, but not with ESSDAI, IgG levels and IgM-RF. It was concluded that physical fatigue characterizes patient's experience of primary SS. Rituximab treatment resulted in significant improvement of patient-reported symptoms. However, the large majority of patients still experienced physical fatigue at an unsatisfactory level, above the cut-off value for PASS. Therefore, attention for optimal management of this prominent symptom is warranted.

Nowadays, there is still little research conducted with regard to secondary SS (SS associated with another auto-immune disease). In **chapter 7** we evaluated sicca symptoms and secondary SS in patients with rheumatoid arthritis over a period of 10 years. We found that patients with higher disease activity of RA experienced more sicca symptoms and had more often secondary SS. Furthermore, RA patients with sicca symptoms and secondary SS have more limitations in daily activities, worse health-related quality of life and more fatigue and pain. Initially our theory was that sicca symptoms will be constant over time in the same patient and will get worse over time

due to physiological decrease of salivary secretion rate. On the contrary, after 10 years of follow up we found that sicca symptoms varied over time and were not constantly present in the same patient, while the functional capacity of salivary and lacrimal glands significantly decreased as expected in all patients.

Finally, in **chapter 8** the safety of treatments for pSS are reviewed. According to the literature, symptomatic treatment is widely applied due to the good supportive effect. Systemic stimulation of tears and saliva can be successful in primary SS, however cumbersome adverse events can influence the tolerability of this therapy. Evidence for the effectiveness of synthetic disease modifying antirheumatic drugs (DMARD) therapies in pSS is limited, while there is a risk of adverse events. Although the safety of symptomatic treatment of pSS was shown to be very good, systemic therapy is necessary to achieve long-term relieve and prevention of organ-damage. Synthetic DMARDs have not shown much efficacy in earlier studies, and their benefits do not weigh up to the possible harms, while biologic DMARDs show promising results regarding efficacy and cause mostly mild adverse events. Many questions remain unanswered regarding safety of DMARDs in pSS. There is a need for well-designed studies, in which safety should be evaluated in a uniform manner to be able to compare the study results.

11

Samenvatting
Dankwoord
Curriculum Vitae

Samenvatting

Het syndroom van Sjögren (SS) is een chronische, systemische auto-immuunziekte die wordt gekenmerkt door destructie van de speeksel- en traanklieren. Meest voorkomende uitingen van de ziekte zijn droogheid van mond en ogen, de zogenaamde sicca symptomen. Daarnaast kunnen meerdere organen betrokken zijn, zoals bijvoorbeeld de gewrichten, huid, longen, nieren en het zenuwstelsel. Verder ontwikkelen 5-10% van de patiënten kwaadaardige aandoeningen van lymfklieren (lymfomen). Deze lymfomen betreffen vaak een zogenaamd mucosa associated lymphoid tissue lymfoom (MALT lymfoom) en ontwikkelen zich vooral in de oorspeekselklier (de glandula parotidea). Andere manifestaties die bij de meeste patiënten aanwezig zijn, zijn vermoeidheid en pijn.

SS kent twee vormen, primair en secundair. Er wordt van primair SS gesproken wanneer SS de enige auto-immuunziekte is die bij een patiënt aanwezig is. Van secundair SS wordt gesproken wanneer tegelijkertijd een andere auto-immuunziekte aanwezig is, bijvoorbeeld reumatoïde arthritis (RA), systemische lupus erythematosus (SLE), systemische sclerose, dermatomyositis of mixed connective tissue disease (MCTD). SS kan zich op elke leeftijd ontwikkelen, maar wordt het vaakst gediagnosticeerd bij mensen tussen 40 en 55 jaar. SS komt vaker voor bij vrouwen dan bij mannen, de geschatte verhouding varieert van 9:1 tot 14:1. De prevalentie van de primaire vorm van SS ligt in de orde van 0,04-1%. Geschat wordt dat circa 19,5% van de patiënten met RA en 14% van de patiënten met SLE tevens lijden aan de secundaire vorm van SS.

Het overkoepelende doel van het in dit proefschrift beschreven onderzoek was het in kaart brengen van belangrijke klinische manifestaties, potentiële biomarkers en het effect van behandeling bij patiënten met primaire en/of secundaire SS.

In **hoofdstuk 2** worden de diagnostiek en behandeling van oudere patiënten met SS besproken. Op oudere leeftijd komen sicca symptomen, vermoeidheid, gewichtsverlies, spierpijn op voorhand al vaker voor, wat het moeilijk maakt om deze symptomen te onderscheiden van symptomen die het gevolg zijn van de auto-immuunziekte. Deze maskering van symptomen zou kunnen leiden tot vertraging bij het stellen van de diagnose SS. Verder verschilt de behandeling van ouderen met SS niet van die van jongere patiënten. De behandeling is gericht op het onder controle houden van droogheidsklachten en het monitoren van de schade in de organen, met als doel het verlichten van klachten en het voorkomen van functievermindering en vroegtijdig overlijden. De behandeling van oudere patiënten wordt gecompliceerd door het vaker gelijktijdig aanwezig zijn van andere ziekten, polyfarmacie en daardoor verhoogde kans op bijwerkingen. Deze aspecten vergen extra aandacht tijdens het behandeltraject.

In **hoofdstuk 3** wordt een studie beschreven, waarbij wordt gekeken naar de bruikbaarheid van de ziekteactiviteit score, de EULAR disease activity index (ESSDAI), bij patiënten met primaire SS. Voor deze analyse is gebruik gemaakt van gegevens uit een eerdere fase 2 studie, waarbij patiënten met primair SS zijn behandeld met het medicament rituximab of met een placebo. Uit de analyses kwam naar voren dat de ESSDAI potentieel geschikt is voor het meten van veranderingen in de ziekteactiviteit en kan worden gebruikt als uitkomstmaat in geneesmiddelen studies.

In de studie die is beschreven in **hoofdstuk 4** wordt de bruikbaarheid van een andere ziekteactiviteit score geanalyseerd, namelijk de disease activity score (DAS-28). Dit instrument wordt wereldwijd gebruikt voor het beoordelen van gewrichtsontstekingen in patiënten met RA. De bruikbaarheid van de DAS-28 bij SS werd onderzocht in patiënten met primair SS die waren behandeld met biologische therapieën, namelijk met rituximab en abatacept. In deze patiënten werd de DAS-28 score vergeleken met de score op het gewrichtsdomein van de ESSDAI. Uit de analyse kwam naar voor dat patiënten uit beide behandelgroepen een significante verbetering van hun gewrichtsontstekingen ervoeren, ongeacht of deze was gemeten met de DAS-28 en ESSDAI. Met andere woorden, de DAS-28 kan goed worden gebruikt bij patiënten met primair SS voor het beoordelen van gewrichtsbetrokkenheid.

Naast de klinische problematiek van patiënten met SS, zijn ook afwijkingen in het bloed aanwezig die aandacht behoeven bij de evaluatie van SS patiënten. Het is bekend dat serum IgG en vrije lichte ketens verhoogd zijn in de auto-immuunziekten met B-cel hyperactiviteit, zoals in SS. In **hoofdstuk 5** wordt een studie beschreven waarin is onderzocht of vrije lichte ketens als biomarker kunnen dienen voor het beoordelen van de systemische activiteit van SS en het hebben van een lymfoom. Van 100 personen met sicca klachten werd bij 45 patiënten SS vastgesteld. Daarnaast werden 17 SS patiënten met MALT lymfoom meegenomen in de studie. Een aantal patiënten met SS was behandeld met rituximab of abatacept. Van alle patiënten was bloedmateriaal aanwezig, waarin vrije lichte ketens konden worden bepaald. Uit de resultaten kwam naar voren dat de titer van vrije lichte ketens niet bijdragend was voor het stellen van de diagnose SS, hoewel patiënten met SS wel een significant hogere titer aan vrije lichte ketens hadden dan patiënten zonder SS. 50% van de patiënten met MALT lymfoom had een abnormale ratio van vrije lichte ketens. De titer van vrije lichte ketens correleerde goed met de ziekteactiviteit van SS, gemeten met de ESSDAI. Concluderend, het bepalen van de vrije lichte ketens is een bruikbare biomarker voor het beoordelen en monitoren van de systemische ziekteactiviteit van SS.

In **hoofdstuk 6** wordt een studie beschreven waarin is gekeken naar de aanwezigheid van vermoeidheidsklachten en het effect van rituximab op deze klachten bij patiënten met primair SS. De systemische ziekteactiviteit werd wederom gemeten met de ESSDAI. Symptomen van droogheid, vermoeidheid en pijn werden gemeten met de ESSPRI vragenlijst. De ESSDAI en ESSPRI zijn ontwikkeld door de EULAR, de Europese organisatie van reumatologen. Het bleek dat 86% van patiënten met primair SS fysieke vermoeidheid als het meest hinderlijke en voor verbetering vatbare symptoom ervaren, meer dan pijn, droogheid en mentale vermoeidheid. Na de behandeling met rituximab bleek dat systemische activiteit van SS was gedaald naar het niveau van lage ziekteactiviteit bij 79% van SS patiënten, terwijl slechts 36% van de patiënten een acceptabele status van vermoeidheidsklachten rapporteerde. De mate van fysieke vermoeidheid was geassocieerd met de absolute aantallen van B-cellen, droogheidsklachten en mentale vermoeidheid, maar hing niet samen met de systemische ziekteactiviteit score ESSDAI, de IgG waarden en de reumafactor waarden. Op grond van deze bevindingen werd geconcludeerd dat fysieke vermoeidheid een belangrijke kenmerk is van vermoeidheid bij patiënten met primair SS. Behandeling met rituximab gaf een significante verbetering van vermoeidheid, maar desondanks bleef een groot aantal van de patiënten klachten van fysieke vermoeidheid houden. De vermoeidheidsproblematiek is een belangrijk aandachtspunt bij de begeleiding van SS patiënten in de dagelijkse praktijk.

Er was nog relatief weinig onderzoek verricht naar secundair SS. In **hoofdstuk 7** zijn resultaten weergegeven van een studie waar het voorkomen van sicca klachten gedurende 10 jaar follow-up werd onderzocht bij patiënten met RA. Patiënten met hogere ziekteactiviteit van RA bleken op termijn vaker sicca symptomen en secundair SS te ontwikkelen. Bovendien ervoeren RA patiënten met sicca klachten en secundair SS meer beperkingen in hun dagelijks leven, ondervonden zij meer hinder van vermoeidheid en pijn, en was hun kwaliteit van leven slechter. Hoewel bij het initiëren van de studie werd gedacht dat sicca klachten bij patiënten met RA onveranderd aanwezig zouden blijven of zouden verslechteren in de loop der tijd, kwam uit het onderzoek naar voren dat de oorspronkelijke sicca klachten bij veel van deze patiënten na tien jaar waren afgenomen, ondanks de bevinding dat de functionele capaciteit van speekselklieren in de tijd bij vrijwel alle patiënten verder achteruit was gegaan.

In **hoofdstuk 8** wordt een overzicht gegeven van de veiligheid en bijwerkingen van verschillende medicamenteuze behandelingen voor patiënten met primair SS. Symptomatische behandelingen zijn veilig en goed toepasbaar voor het verlichten van droogheidsklachten van mond en ogen. Er zijn wel een aantal hinderlijke bijwerkingen beschreven van de medicamenten die productie van speeksel en tranen systemisch stimuleren, waardoor een systemische therapie niet routinematig wordt toegepast bij de SS patiënten. Hoewel symptomatische therapieën verlichting van de klachten

geven, beschermt een symptomatische therapie patiënten met SS niet tegen het ontwikkelen van orgaanschade. Helaas zijn tot nu toe nog geen bewezen effectieve en geregistreerde therapieën beschikbaar voor de behandeling van patiënten met primaire SS. Wel zijn er beperkt mogelijkheden voor de behandeling van specifieke orgaanmanifestaties, waarbij de voordelen van de ingestelde therapie moeten worden afgewogen tegen de nadelen van deze therapie. De veiligheid van deze therapieën is vaak nog onvoldoende onderzocht.

In **hoofdstuk 9** worden de bevindingen uit de verschillende in dit proefschrift beschreven studies in een breder perspectief geplaatst en besproken.

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Ongelooflijk maar waar, mijn boekje is af! Tussen eerste onderzoeksdag van mijn wetenschappelijke stage bij de afdeling Reumatologie en Klinische Immunologie in het UMCG en nu zitten 14 jaar! In al deze jaren heb ik zo veel bijzondere, mooie, leuke, lieve, talentvolle, zorgzame, grappige, hardwerkende mensen ontmoet, dat ik zelfs bang ben om iemand te vergeten, maar ik ga de poging wagen.

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Mijn liefste Marco, it's your turn.

Curriculum Vitae

Personalia

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Opleidingen

2014 - 2017 Opleiding tot reumatoloog in het Universitair Medisch Centrum te Groningen (UMCG).
 2014 Medisch Centrum Leeuwarden (MCL) perifere stage reumatologie.
 2010 - 2014 Martini Ziekenhuis (MZH) vooropleiding interne geneeskunde.
 2007 - 2010 Master Geneeskunde/coassistentenschappen (curriculum G2010), Rijksuniversiteit Groningen (RuG).
 2004 - 2007 WO: Bachelor diploma Geneeskunde (curriculum G2010), RuG.
 2003 - 2004 HBO-Verpleegkunde (HBO-V), Hogeschool Windesheim te Zwolle. Propedeuse.
 2001 - 2002 Staatsexamen Nederlands als Tweede Taal.
 1997 - 1999 Moscow Medical Academy Setsenov te Moskou, Rusland. Propedeuse.
 1989 - 1995 Middelbare School te Moskou, Rusland.

Werkervaring

2017 – heden Reumatoloog Martini Ziekenhuis te Groningen.
 2014 - 2017 Arts in opleiding tot reumatoloog, UMCG.
 2014 Arts in opleiding tot reumatoloog, MCL (perifere stage reumatologie).
 2010 - 2014 Arts in opleiding tot reumatoloog, MZH (vooropleiding interne geneeskunde).
 2004 - 2007 Medewerkster studenten prikdienst, UMCG.
 2004 Stagiaire op de verpleegafdeling van ziekenhuis Aleida Kramer te Coevorden.
 2003 - 2004 Helpende bij Woon- en Zorgcentrum De Schutse te Coevorden.
 1995 - 1997 Secretaresse bij een handelsbedrijf in medische apparatuur te Moskou, Rusland.

Publicaties

Sjögren's syndrome in older patients: aetiology, diagnosis and management. **Moerman RV**, Bootsma H, Kroese FG, Vissink A. *Drugs Aging*. 2013 Mar;30(3):137-53. Review.

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Serum immunoglobulin free light chains are sensitive biomarkers for monitoring disease activity and treatment response in primary Sjögren's syndrome. Verstappen GM, **Moerman RV**, van Nimwegen JF, van Ginkel MS, Bijzet J, Mossel E, Vissink A, Hazenberg BPC, Arends S, Kroese FGM, Bootsma H. *Rheumatology (Oxford)*. 2018;57(10):1812-21.

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Talenkennis

	Geschreven	Gesproken	Gelezen
Nederlands	goed	goed	goed
Engels	goed	goed	goed
Russisch	moedertaal	moedertaal	moedertaal

Aanvullende vaardigheden

Goede beheersing van de meest gebruikte computersoftware:

Microsoft® Windows® en Microsoft® Office (Excel, Word en PowerPoint), SPSS, Mendeley, Refworks.

Hobby's en persoonlijke interesses:

Russische literatuur, bergwandelen, muziek