Proposed Core Set of Outcome Measures in Patients with Primary Sjögren's Syndrome: 5 Year Followup

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ABSTRACT. ***Objective.*** To clarify the spontaneous course of important disease manifestations (a core set of outcome measures) over a period of 5 years in patients with primary Sjögren's syndrome (SS), and to analyze predictors of unfavorable outcome. To test the usefulness of the recently proposed core set of outcome measures.

Methods. A cohort of patients with primary SS according to the American-European consensus criteria (AECC) (n = 58) was followed over a period of 5 years. Measures for subjective and objective disease characteristics, IgG concentrations and health related quality of life were analyzed on 2 occasions and compared.

Results. During followup, symptoms of dry eyes, dry mouth, fatigue, and health related quality of life were stable. Regarding objective signs, there was a modest but statistically significant worsening of the van Bijsterveld score. Seropositivity for anti-SSA and low complement levels predicted further decline in the van Bijsterveld score. Floor/ceiling effects in the outcome measures in the core set complicate documentation of further decline, but may allow monitoring of improvement in established primary SS.

Conclusion. Primary SS, if classified according to the strict AECC criteria, is a bothersome and slowly progressive disease, with fatigue and discomfort developing early. The proposed outcome measures may be suitable for assessing improvement in randomized controlled trials. (J Rheumatol 2005;32:1495–502)

Key Indexing Terms:
SJÖGREN'S SYNDROME
LONGITUDINAL FOLLOWUP
OUTCOME MEASURES
QUALITY OF LIFE

Primary Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease. Its main manifestation is an autoimmune epithelitis[1], most often in the exocrine glands of the eye and mouth, quite often in other glandular tissues, and more rarely expanding into a disease with non-exocrine manifestations of various degree of severity. Stomatitis sicca and keratoconjunctivitis sicca (KCS) are the classical disease manifestations. If fatigue is accepted as a non-exocrine manifestation, then the majority of patients will have extraglandular disease at some time during the course of the disease, and in most cases during long periods of time.

The course of primary SS is generally assumed to be characterized by mild variations in disease symptoms with no or very slow deterioration. It has been shown in recent years that longterm outcome with respect to survival is not different from the general population[2,3]. Lymphoma development is the most serious complication, and its incidence is increased in patients with primary SS, as described in several studies since the original observation by Kassan, *et al*[4]. Some predictive factors for this unfavorable outcome have been identified[2,3,5]. The course of the most common symptoms and signs of the disease have not been so thoroughly investigated in longterm followup studies. Only a few such studies have been performed in primary SS. Kruize, *et al* studied patients with isolated KCS (n = 56) and primary (n = 31) or secondary (n = 19) SS over 10–12 years, and concluded that glandular and extraglandular manifestations are relatively stable[6,7]. Similar results were found in a Japanese cohort including 31 patients with primary SS[8]. Gannot, *et al*[9] studied salivary, oral, and serologic aspects in a longterm followup study, but excluded signs and symptoms from the eye. They concluded that primary SS is a very slowly progressive disease with respect to the variables studied[9]. In their 10 year followup of 100 patients with primary SS, Davidson, *et al* focused on serological subgroups and found that antibody status and the expression of systemic or organ-specific disease characteristics did not change[10]. They did not evaluate the longterm course of signs or symptoms of eye and mouth dryness. The same investigators report on a 10 year followup of pulmonary function in 30 patients with SS. Most patients did not develop progressive lung disease[11]. The longterm followup study by Pertovaara, *et al* (n = 110) also focuses more on immunological and serological disease characteristics than on signs and symptoms of stomatitis sicca and KCS[12]. Botsios, *et al*[13] studied longterm outcome in 68 patients with primary SS according to the Fox criteria[14]; serological findings remained constant.

In 2002 new classification criteria for primary SS were

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published as a result of the efforts of an American-European consensus group, the American-European consensus criteria (AECC)[15]. This criteria set differs from the 1993 European Union criteria[16] by requiring signs of apparent autoimmune disease, either histologically or serologically. Patients not fulfilling the AECC, but who did fulfill the former 1993 EU criteria, are referred to as non-SS sicca or non-AECC sicca syndrome here.

Until recently, there was no agreement about outcome measures or the definition of disease activity in primary SS, in contrast to diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus, where efforts were made years ago to define outcome measures to facilitate longterm followup studies or intervention trials according to standardized requirements. In April 2003, a workshop on outcome measures in primary SS was held in Bethesda, Maryland, USA, resulting in a consensus on a core set of outcome measures to be included in longterm or intervention studies in SS[17]. According to the workshop consensus, the following signs and symptoms should be evaluated and assessed in longterm studies of primary SS: (1) oral symptoms, (2) ocular symptoms, (3) oral signs, (4) ocular signs, (5) fatigue, (6) health related quality of life, and (7) IgG (Table 1). Secondary measures were recommended to be included as far as possible: for example, additional signs and symptoms, including laboratory results, such as autoantibodies and complement factors.

During 1996 and 1997 we started a randomized controlled trial with oral gammalinolenic acid (GLA) versus placebo[18], where all the above assessments were performed on all patients, with the exception of measurement of health related quality of life [by Medical Outcome Study Short Form-36 (SF-36)], which was assessed in a subgroup of 68 patients as part of a psychometric study addressing coping strategies[19]. The patient selection process was described in detail[18]. The treatment effect of GLA did not differ from that of placebo.

We decided to perform a 5 year followup assessment of the core set of outcome measures using identical methodology, instruments, equipment, and personnel to achieve optimal standardization. Our aim was to analyze spontaneous longitudinal change of these outcome measures, and define predictors for this change. This study focuses on those patients who fulfilled the AECC criteria at baseline according to a retrospective evaluation.

Table 1. Core set of outcome measures in primary Sjögren's syndrome, as proposed by the workshop at the NIH in April 2003[17].

	Tests applied in present study
1. Oral symptoms	VAS scale
2. Ocular symptoms	VAS scale
3. Oral signs	UWS
4. Ocular signs	Schirmer-1, van Bijsterveld
5. Fatigue	VAS, vitality in SF-36
6. Health related quality of life	SF 36
7. IgG	g/l

VAS: visual analog scale, UWS: unstimulated whole sialometry.

MATERIALS AND METHODS

One-hundred twenty patients with primary SS were included in 2 studies investigating the effect of GLA on fatigue. The first was a pilot study comprising 30 patients, followed by the main study comprising 90 patients. The conclusion of these double-blind randomized placebo controlled trials was that GLA is ineffective, for both the primary outcome measures, fatigue (assessed by visual analog scale, VAS) and sleeping time (hours resting/24 hours), and also for all the secondary outcome indicators, such as subjective and objective measures of eye dryness, mouth dryness, muscle and joint pain, and others[18].

The diagnosis of primary SS was confirmed using the Copenhagen[20] or 1993 EU criteria[16], the criteria sets predominantly used in Sweden during 1996-97. Exclusion criteria as proposed in the European criteria were respected. According to a retrospective evaluation, 58 (48%) patients would have fulfilled the AECC[15] at entry; 11 of these did not participate in the followup study. Four formerly AECC-negative patients evolved into positives during followup. Disease duration from the time of diagnosis was a median 5.8 years (range 0.1–11.5) at the baseline visit and median 11.1 years (range 5.4–18.2) at the followup visit. Table 2 gives patient and disease characteristics at baseline and followup.

Assessments. The following investigations were performed in all patients at both visits: VAS for eye dryness and mouth dryness for assessment of ocular and oral symptoms, with responses from 0 mm = extremely dry, to 100 mm = not dry at all; and Schirmer-1 test, breakup time, and van Bijsterveld score using Lissamine green for assessment of ocular signs[21]. Identical standardized Schirmer test papers were used on both occasions. For evaluation of oral signs, unstimulated whole sialometry (UWS) was performed for a 15 min period according to a standardized protocol, where patients were instructed not to eat, drink, smoke, chew gum, or perform oral hygiene for at least 60 min prior to saliva collection[22]. Serum immunoglobulins were analyzed by immunonephelometry on both occasions. Complement factors C3 and C4 were measured by nephelometry at baseline. Health related quality of life was assessed by using the Swedish version of the SF-36[23,24]. Fatigue was measured on a VAS at baseline and followup (0 mm = extreme fatigue and 100 mm = no fatigue at all). In addition, the vitality item of the SF-36 was used for the evaluation of fatigue[24]. All study procedures were performed by one physician (ET) and 2 specially trained study nurses.

Identical questionnaires and equipment were used. Autoantibody status was examined in all patients. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using HEp-2 cells. Anti-SSA (Ro) and anti-SSB (La) and the other autoantibodies to extractable nuclear antigens were analyzed by immunodiffusion and results were registered either positive or negative. IgM rheumatoid factor (RF) measurement was performed by ELISA, with positive results of > 20 IU/ml, based on standardization with a World Health Organization RF reference preparation.

Lower lip salivary gland biopsy was usually performed at the time of

Table 2. Patient and disease characteristics at baseline and followup.

Characteristic	Baseline	Followup
No.	58	47
Age, yrs, median (range)	64 (16–85)	69 (30–84)
Disease duration*, yrs, median (range)	5.8 (0.1–11.5)	11.1 (5.4–18.2)
Anti-SSA/SSB, n (%)	32 (56)	29 (62)
Biopsy positive, n (%)	54 (93)	43 (94)
ANA, n (%)	46 (81)	33 (70)
RF, n (%)	26 (46)	21 (45)
Deceased, n (%)		4 (7)
Unable to participate due to severe somatic disease or social reason (%)		7 (12)

Positive biopsy means a salivary gland biopsy (performed when diagnosing SS) with a focus score > 1. ANA: antinuclear antibody, RF: rheumatoid factor. * Since diagnosis.

diagnosis and was not repeated. Detailed recording of present and previous medication was performed on both occasions, mainly to be able to attribute any changes in outcome variables to specific medication, such as pilocarpine, cytotoxic drugs, tumor necrosis factor blockers, or steroids. Comorbidities such as additional autoimmune diseases, lymphoma development, and signs of severe non-exocrine disease or death were recorded.

Patients were invited to a single followup visit, lasting 1 to 1.5 hours, at which a standardized interview was performed regarding medication, comorbidity, and non-exocrine disease manifestations and all procedures. The study was approved by the Ethics Committee of Lund University.

Statistical methods. Paired samples t test and McNemar test were used to compare the results of subjective and objective variables from both study visits. We also defined significant improvement or deterioration as being at least a 30% modification from the baseline result for VAS scores and measurements of oral and ocular signs, in order to calculate the number of patients with spontaneous changes or stable disease. Comparisons between fatigue VAS and SF-36 at followup were performed by calculating Spearman's rank correlation coefficient. The SF-36 questionnaire and its use in SS and other rheumatic diseases and the statistical evaluation process have been described[23,24]. In short, the patients' results were compared to age and sex adjusted expected scores for each individual patient using the paired-samples t test. Relationships between the variables within the core set and between baseline values and the outcome after 5 years were analyzed using bivariate correlations and linear regression analysis.

RESULTS

Participation at followup. Four (7%) of the 58 original AECC patients with SS had died. The causes of death were lung and colon malignancy, gastrointestinal bleeding due to primary biliary cirrhosis (PBC), and pulmonary fibrosis. Seven patients were unable to participate, in 2 cases due to dementia and in 5 because of severe somatic disease (advanced lung cancer and breast cancer) or psychosocial problems. One patient lived too far from Malmö to allow a visit in person, which resulted in an incomplete followup with only laboratory measurements and questionnaires, excluding objective ocular or oral tests.

Core set of outcome measures

Longterm development in oral symptoms, ocular symptoms, and fatigue. No statistically significant changes were seen between evaluations at baseline and followup (Table 3). Baseline and followup results correlated well in all 3 variables. Analyzing changes in individual patients, rather large fluctuations were observed. Thirty-two percent of AECC patients improved in at least 2 out of the 3 VAS scales by ≥ 30%, and 17% deteriorated in at least 2 VAS scales.

Using the vitality item of the SF-36 as a measure of fatigue, SS patients differed significantly from expected scores at both visits ($p < 0.001$; Figure 1). The SF-36 vitality score and the VAS fatigue score correlated well at both visits ($r_s = 0.48$ and 0.62, $p < 0.01$ and $p < 0.001$).

Longterm outcome in ocular signs. Table 3 shows the followup results of the ocular signs. Baseline and followup values were highly correlated (r_S = 0.36–0.80). The van Bijsterveld score deteriorated significantly ($p = 0.04$), while the Schirmer test deteriorated, without reaching statistical significance. Thirty-three percent of the AECC patients had a Schirmer-1 value of 0 or 1 (mm/5 min, sum of both eyes) and 26% had a van Bijsterveld score ≥ 14 (sum of both eyes) at baseline, making significant further deterioration difficult due to a floor/ceiling effect of the outcome measure. No patient with a van Bijsterveld score ≥ 14 was improved. Good correlation was seen between the Schirmer-1 test and the van Bijsterveld score at both baseline and followup (r_S = –0.45, –0.46; Table 4).

Longterm development in oral signs. AECC patients showed only a slight nonsignificant deterioration in UWS (Table 3). Forty percent of the AECC patients had results of 0.0 or 0.1 ml/15 min in unstimulated sialometry at baseline, giving a floor effect in this measure as well, not allowing significant further decline. No patient improving in UWS ≥ 30% was taking a secretagogue at the followup visit. Significant correlations between the Schirmer-1 test and UWS, and the van Bijsterveld score and UWS, could be detected (Table 4).

Seven percent of the AECC patients spontaneously improved in at least 2 out of the 3 objective dryness measurements (Schirmer-1 test, van Bijsterveld score, and UWS); 33% worsened in at least 2 out of the 3.

Age and disease duration were not correlated with any of the objective ocular or oral measures at baseline or followup, or with changes in them (statistical data not shown).

Table 3. Core set of outcome measures: mouth dryness, eye dryness, fatigue, ocular and oral signs, and IgG. All patients fulfilled the AECC criteria.

Variable	n	Baseline	Followup	Mean Difference	95% CI	p
VAS mouth dryness*	47	27.8 (17.8)	33.3 (27.3)	5.5 (26.7)	–2.3/+13.4	0.16
VAS eye dryness*	47	38.6 (24.5)	42.4 (28.2)	3.8 (30.8)	–5.2/+12.9	0.39
VAS fatigue*	47	33.0 (25.2)	37.3 (26.2)	4.3 (26.4)	–3.5/+12.0	0.28
Schirmer-1 test**	45	9.8 (12.9)	7.3 (8.5)	–2.5 (11.2)	–5.8/+0.9	0.15
Van Bijsterveld score***	45	10.8 (4.1)	11.6 (4.3)	0.9 (3.1)	0.03/1.7	0.04
UWS†	43	0.8 (1.2)	0.7 (1.9)	–0.1 (2.0)	–0.7/+0.5	0.75
IgG††	47	14.8 (6.5)	15.0 (6.2)	0.2 (3.1)	–0.8/+1.1	0.73

All values represent mean (SD). Only patients with measurements from both study visits are included. * VAS: visual analog scale 0–100 mm. 0 = worst possible. 100 = best possible. ** Values represent the sum of both eyes in mm/5 min. *** Values represent the sum of van Bijsterveld scores for both eyes using Lissamine green dye. † Values represent unstimulated whole sialometry (UWS) measurements in ml, measured during 15 min. †† IgG, measured in g/l by immunonephelometry, normal range 6.19–14.9. AECC: American-European consensus criteria.

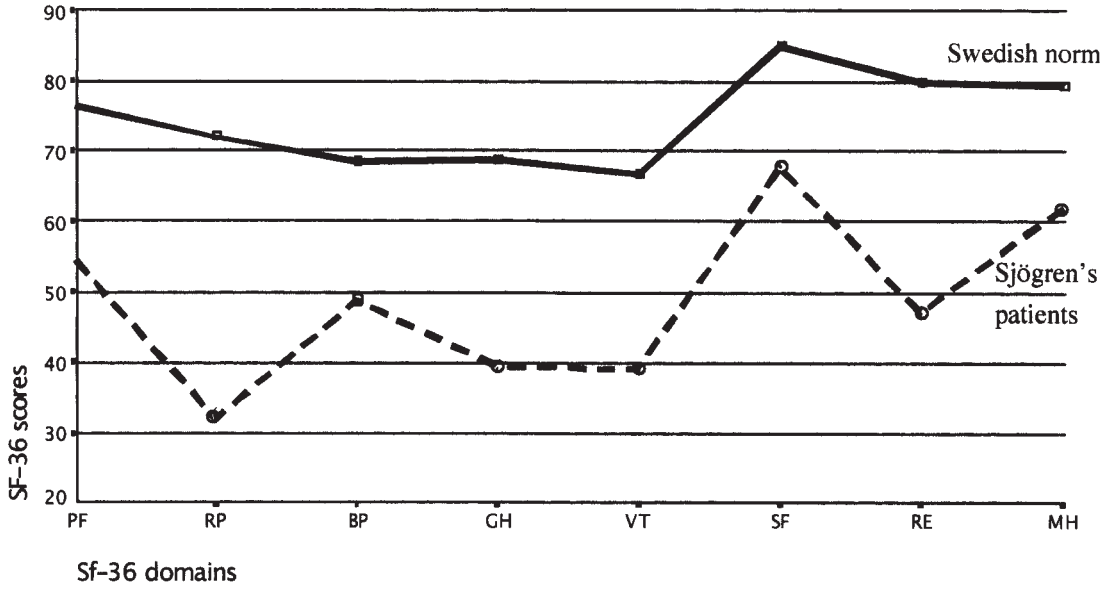

Figure 1. SF-36 scores at baseline in SS patients fulfilling the American-European consensus criteria (n = 35) compared with expected scores from the Swedish reference population. SF-36 health domains: PF: physical functioning, RP: role function–physical, BP: bodily pain, GH: general health perception, VT: vitality, SF: social functioning, RE: role functioning–emotional, MH: mental health. Higher scores mean better health.

Table 4. Spearman correlations between variables included in the core set of outcome measures in patients fulfilling the AECC criteria.

Variables	Correlation Coefficient Baseline	Followup
Objective-objective		
Schirmer-Bijsterveld	–0.48***	–0.46**
Schirmer-UWS	0.30*	0.26
Bijsterveld-UWS	–0.44***	–0.20
Objective-IgG		
Schirmer-IgG	–0.21	–0.33*
Bijsterveld-IgG	0.32*	0.49***
UWS-IgG	0.04	0.07
Subjective-subjective		
Eye dryness-mouth dryness	0.36**	0.64***
Eye dryness- fatigue	0.24	0.45**
Mouth dryness-fatigue	0.25	0.52***
Objective-subjective		
Schirmer-eye dryness	0.22	0.13
Schirmer-mouth dryness	0.02	0.29
Schirmer-fatigue	–0.30*	0.28
Bijsterveld-eye dryness	–0.14	0.02
Bijsterveld-mouth dryness	0.07	–0.13
Bijsterveld-fatigue	0.26*	0.13
UWS-eye dryness	0.15	0.43**
UWS-mouth dryness	0.23	0.57***
UWS-fatigue	0.25	0.16

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$.

Longterm followup of health related quality of life. At baseline, 68 patients completed the SF-36 questionnaire; 35 of these fulfilled the AECC criteria. Scores for the 8 domains of the SF-36 are shown in Figure 1, compared with the age and sex matched Swedish reference population. Patients with SS had considerably and significantly lower health related quality of life in all dimensions ($p < 0.001$), on both study occasions. Over a 5 year period there is an expected age related decline in most SF-36 scores in the healthy population. We compared this expected decline for every domain with the observed decline in the patient group (Figure 2). The patients differed only in the expected loss of vitality: surprisingly, the patient group improved in contrast to the reference population ($p = 0.026$).

Serum IgG. Serum IgG levels were unchanged in the AECC patients (Table 3). IgG levels correlated significantly with the van Bijsterveld score at baseline and followup, and with the Schirmer-1 test at followup (Table 4).

Autoantibodies. At baseline, 32 patients had anti-SSA and/or anti-SSB autoantibodies. Five of these did not participate at the followup visit. At followup, 2 formerly negative patients had become positive. SSA positivity was associated with a higher van Bijsterveld score at both baseline and followup ($p = 0.01$ and $p < 0.001$, respectively). Other autoantibodies: 9 (20%) AECC patients had anticardiolipin antibodies, but mostly in low titers, and no patient had any signs of clinical antiphospholipid syndrome. Seven patients had anti-smooth-muscle or antimitochondrial antibodies (mostly low titers). Two patients had biopsy verified PBC. One patient had anti-centromere antibodies. No patient had anti-dsDNA, anti-Smith, anti-Scl-70, or anti-Jo1 antibodies at followup.

Comorbidity. One patient fulfilling the AECC criteria had developed a follicular non-Hodgkin lymphoma in the salivary glands shortly after the initial study. None of the 7 patients

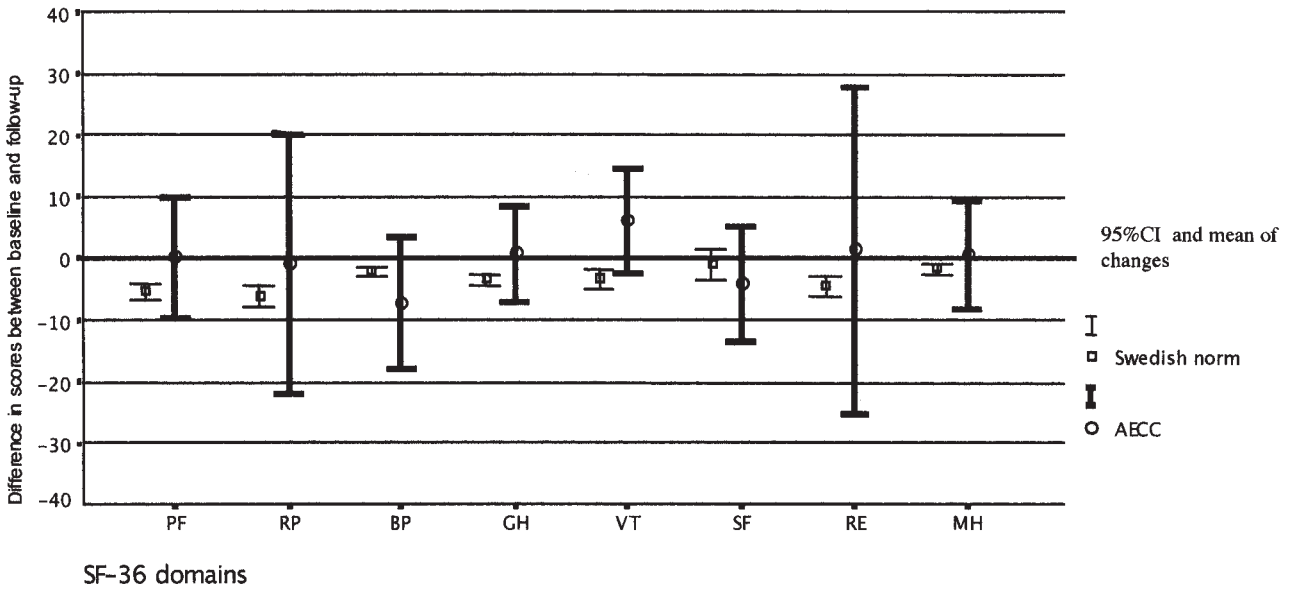

Figure 2. Changes in SF-36 scores between baseline and 5 year followup in patients fulfilling the American-European consensus criteria (AECC; n = 35) compared with expected changes in the Swedish reference population. SF-36 health domains: PF: physical functioning, RP: role function–physical, BP: bodily pain, GH: general health perception, VT: vitality, SF: social functioning, RE: role functioning–emotional, MH: mental health. Lines represent 95% confidence intervals for the mean change. Positive values indicate improvement.

still living but not participating had developed a lymphoma. At the baseline visit one patient had chronic lymphatic leukemia, one a pseudolymphoma, and 2 had benign paraproteinemias. None of these had progressed into frank or more aggressive lymphomas. One patient had developed RA and was treated with etanercept, with good effect on her arthritis, but no effect on sicca signs or symptoms. Twelve (26%) patients had a history of salivary gland swelling; Raynaud's phenomena were objectively diagnosed in 14 (30%). Waldenström purpura was present or documented earlier in 9 (20%) patients.

Medication. At baseline, 5 patients were treated with antidepressant drugs, 3 with beta-receptor blockers, and 2 with diuretics. At the 5 year followup visit, 6 were taking antidepressants, 3 beta-receptor blockers, and 9 diuretics. None of these differences were statistically significant. At the baseline visit, pilocarpine was not available in Sweden as a drug for treatment of sicca syndrome. At followup only 2 patients (4.4%) were taking pilocarpine, while 10 more had tested but stopped the drug due to side effects or lack of efficacy. One of the 2 currently treated patients had a better Schirmer result, the other better Schirmer and van Bijsterveld scores; but neither had consistently improved in subjective sicca symptoms.

Predictors of unfavorable development. Generally, both subjective and objective outcome measures showed strong correlation between baseline and followup values: i.e., fatigue: baseline to followup, $r_S = 0.49$, $p = 0.001$; van Bijsterveld score, baseline–followup, $r_S = 0.71$, $p < 0.001$. Similar strong correlations between baseline and followup were found for mouth dryness, eye dryness, Schirmer-1 test, and UWS, with correlation coefficients ranging between 0.35 and 0.64, generally being higher in the objective tests than in the symptom VAS. The baseline values predicted changes during followup. For example, the Schirmer-1 test at baseline showed significant negative correlation with the difference in Schirmer-1 test measured at followup, which means that higher Schirmer score (i.e., closer to normal) is associated with a greater (possibility of) decline than lower baseline Schirmer score ($r_S = –0.61$, $p < 0.001$). UWS at baseline correlated negatively with the change in UWS at followup ($r_S = –0.71$, $p < 0.001$), which means higher (more normal) UWS predicted (or allowed) greater reduction during followup. Less strong correlation was found for the van Bijsterveld score at baseline compared with changes at followup ($r_s = 0.26$, $p = 0.09$).

Positivity for SSA predicted further decline in the van Bijsterveld score ($p = 0.02$), but not in the Schirmer-1 test and UWS. An inverse correlation was also revealed between complement C3 and C4 levels at baseline and deterioration in the van Bijsterveld score ($r_s = –0.39$, $p = 0.009$ and $r_s = –0.41$, $p = 0.006$, respectively). Lower levels of C3 and C4 predicted deterioration of the van Bijsterveld score: C3, regression coefficient –4.7 (95% CI –8.2 to –1.3); and C4, regression coefficient –13.8 (95% CI –23.5 to –4.2). After adjustment for baseline values of the van Bijsterveld score, the slopes increased to –5.5 and –16.9, respectively. IgG levels at baseline did not influence outcome of the objective disease variables.

DISCUSSION

We describe the 5 year followup of a subgroup of a cohort of patients with primary Sjögren's syndrome who in 1996-97 all

fulfilled the recently published AECC[15]. We performed a systematic followup of the complete proposed core set of outcome measures[17] in primary SS 5 years after an initial evaluation, at a mean disease duration of 11 years from the time of diagnosis. The core set of outcome measures for primary SS was proposed by an international workshop held in April 2003[17]. The proposed measures were evaluated by widely accepted tests. According to the workshop proposal, assessment of ocular and oral symptoms, ocular and oral objective signs, fatigue, health related quality of life, and IgG were the primary study measures.

Important findings of our study are the following:

1. Primary SS, when characterized according to the strict AECC criteria, is a relatively stable condition, with only modest progressive worsening of the main disease characteristics including fatigue and health related quality of life. However, considerable loss of function and quality of life was noted at a median disease duration of 6 years, although they did not decline much thereafter. In the vitality item of the SF-36, patients even avoided the further expected age-dependent decline. The explanation for this is unclear, but may be due to patients acquiring effective coping strategies.
2. The observed ceiling and floor effects in the outcome measures deserve attention. The lack of additional decline in the objective measurements may be related to the floor or ceiling properties of the tests, while further deterioration might have been observable with more sensitive instruments.
3. Within the proposed core set of outcome measures, objective disease measures correlated with each other, as did the subjective VAS results for fatigue, eye dryness, and mouth dryness at both test occasions. VAS fatigue and vitality on the SF-36 were also correlated. The correlations were not very strong, arguing against omitting part of the core set by substituting tests for each other (as proposed by Kalk, *et al* in 2002[26]). Subjective and objective measures did not correlate well. The presence of correlation between eye and mouth test results may be evidence for a shared pathophysiology for the glandular disturbance.
4. Immunological variables such as positive SSA, high IgG, and low level of complement factors were correlated with more severe objective glandular dysfunction in primary SS. In established AECC defined disease, low complement levels also predicted further impairment of the van Bijsterveld score, as did seropositivity for anti-SSA. These correlations may indicate that systemic inflammation or immune dysregulation is involved in the progressive glandular dysfunction that occurs in some patients. That is also supported by several recent studies[26,27]. The effect of low complement levels has not been studied before in relation to deterioration of glandular function.
5. Considering the course of the disease in individual patients, our study revealed considerable variations with both improvement and impairment. For instance, 32% of the AECC patients improved in at least 2 out of the 3 subjective VAS evaluations of mouth dryness, eye dryness, and fatigue. This is in agreement with findings in the placebo controlled infliximab study by Mariette, *et al*[28], where 26% of the placebo treated patients improved in at least 2 out of 3 VAS scales including fatigue and dryness. Based on only 2 measurements it is not possible to conclude if these findings indicate a steady improvement or deterioration or spontaneous flares and remissions in some patients. Repeated longitudinal assessments would be necessary.

The etiology of primary SS is poorly understood, and so is the exact mechanism for the functional impairment in the glands. Function, inflammatory infiltrates, and symptoms are not very well correlated[29,30]. We tried to determine predictors of favorable or unfavorable outcomes. There are many possible candidates for explaining changes in exocrine function in SS (and non-SS) populations: age[27,31], disease duration[27,32], genetic background[33,34], systemic or local inflammation[29], drugs[35], concomitant metabolic disorders[36,37], viral or other infections[38,39], neurohumoral or autonomic nervous system disturbances[40,41], or other concomitant diseases with possible influence on glandular function or fatigue, such as fibromyalgia[42] or chronic fatigue syndrome[43]. Most of these factors were not studied in our investigation, since we focused on assessment of the components of the core set of outcome measures. The only strong predictors of unfavorable development were the baseline levels of the corresponding variables: a more normal baseline level indicates higher risk for impairment at followup. This was true for most of the objective and subjective outcome variables (except IgG and health related quality of life), consistent with a ceiling/floor effect for most of the tests. Most of the decline in function seems to occur relatively early in the course of the disease.

Comparison with results from earlier studies. The complete core set has not been investigated in one single patient cohort before, and serial assessments of health related quality of life have not been performed, to our knowledge.

Results supporting ours for the relative stability of the objective disease measures in primary SS were found by Kruize, *et al*[7]. After 10–12 years of followup in 21 patients with primary SS, the Schirmer-1 test was slightly but significantly improved, while the Rose-Bengal score was slightly but significantly worse. Our findings are also in accord with a Japanese 10–20 year followup of 31 primary SS patients, where signs and symptoms did not differ between the time of diagnosis and followup visit[8], and with the study by Gannot, *et al* with respect to the oral component and serological markers[9]. Our findings of correlations of disease measures from eye and mouth testing and the correlation of serological and immunological markers with objective disease manifestations are supported by others[26,27]. However, the importance of factors of the complement system, which recently have been found to predict lymphoproliferative disease and death in SS[2,3], has not previously been analyzed in relation to glandular function.

Age and disease duration did not influence changes at fol-

lowup in our study. This is in contrast to findings from The Netherlands[26,44], where ocular and oral glandular function and structural changes were found to correlate with disease duration. Cross-sectional groups of patients were studied as early as within one year from symptom onset and subsequently compared with patients with one to 4 or more years of symptom duration. Those with disease duration less than one year had significantly better function. The Dutch study included patients with early disease, who usually are not included at most centers. We did not investigate an early disease population, even though time from diagnosis at the baseline study visit was short in a few patients. The influence of disease duration on disease manifestations in primary SS was also studied by Haga and others, with no significant correlations reported[27,45]. These findings together underline the importance of longitudinal studies in patients with earlier diagnosis, to enable better understanding of pathogenetic events and provide interventions before irreversible damage has occurred.

Followup of serological markers was not a primary objective of our study, since autoantibodies are not included in the core set of outcome measures. However, we analyzed autoantibodies as secondary indicators, and the results were comparable with some previous studies[5,9,10,13], with only a few patients acquiring new autoantibodies or changing diagnosis during followup.

In contrast to some longterm followup studies[6-8,10,12], the starting point in our investigation was not the time of diagnosis, but between one month and 12.5 years after diagnosis. This gives a more heterogeneous study population, but one that is more similar to potential study populations for intervention trials. The high degree of spontaneous changes is in line with the high rate of placebo responses in some recent intervention trials in primary SS[28,46], and poses a potential problem when designing treatment trials.

The strengths of our study are the prospective one-center design, the standardization of measurements and tests, and the low number of subjects lost to followup, allowing assessment of the spontaneous course of components of the core set of outcome measures, before they are used in future intervention trials. A drawback is the assessment on only 2 occasions with a relatively long period between, making it difficult to interpret whether the observed spontaneous variations were part of a steady development or expression of flares and remissions. Several measurements would also have allowed other statistical approaches such as area under the curve (AUC) analysis for predictors of outcome.

Our study confirms the rather stable course of the main disease manifestations in primary SS, with only a modest tendency for deterioration on average, while individual patients may show flares and remissions as in other rheumatic diseases. The measures in the proposed core set of outcome variables are stable if primary SS is analyzed as a group. Although a ceiling/floor effect in several important measures precludes assessment of further functional decline in patients with established disease, the core set may be a suitable instrument for intervention trials aiming at improving the most common disturbances in primary SS. Signs of systemic immune activation expressed by disturbances in complement levels and anti-SSA antibodies may predict not only lymphoma and death, but also further decline in glandular function, and may have the potential to serve as substitute outcomes for these longterm consequences of the disease in clinical studies.

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