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Natural history and Predictors of Progression to Sjögren's Syndrome Among Participants of the SICCA registry

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Abstract

Background/Purpose—To explore changes in the phenotypic features of Sjögren's syndrome (SS), and in SS status among participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry over a 2 to 3-year interval.

Methods—All participants in the SICCA registry who were found to have any objective measures of salivary hypofunction, dry eye, focal lymphocytic sialadenitis in minor salivary gland

biopsy, or anti-SSA/B antibodies, were recalled over a window of 2 to 3 years after their baseline examinations to repeat all clinical examinations and specimen collections to determine whether there was any change in phenotypic features and in SS status.

Results—As of September 15, 2013, 3,514 participants had enrolled in SICCA, and among 3,310 eligible, 771 presented for a follow-up visit. Among participants found to have SS using the 2012 ACR classification criteria, 93% again met the criteria after 2 to 3 years, and this proportion was 89% when using the 2016 ACR-EULAR criteria. Among those who did not meet ACR or ACR-EULAR criteria at baseline, 9% and 8%, respectively, had progressed and met them at follow-up. Those with hypergammaglobulinemia and hypocomplementemia at study entry were respectively 4 and 6 times more likely to progress to SS by ACR criteria than those without these characteristics (95% Confidence Interval: 1.5 – 10.1 and 1.8 – 20.4, respectively).

Conclusion—While there was stability over a 2–3-year period of both individual phenotypic features of SS and of SS status, hypergammaglobulinemia and hypocomplementemia at study entry were predictive of progression to SS.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic multi-organ autoimmune disease characterized by secretory dysfunction (1) and slow progression. Few studies have followed patients over time while taking into account all the components (serologic/rheumatologic, oral, and ocular) of the disease. Instead, most longitudinal studies of SS have focused on only one or sometimes two components,(2–8) while others have explored morbidity and mortality, particularly with respect to lymphoproliferative diseases.(9–14)

The Sjögren's International Collaborative Clinical Alliance (SICCA) is an NIH-funded international registry (15, 16) that enrolled participants with suspected or established SS from 2003 to 2012 to: 1) develop standardized SS classification criteria; and 2) establish a longitudinal data and biospecimen repository for use by the scientific community for future SS-related epidemiologic, pathogenesis, and genetic studies. A standardized set of clinical and biological measures and information from standardized questionnaires were collected from participants at study entry and at about 2 to 3-year follow-up. SICCA investigators developed SS classification criteria that were approved as provisional by the American College of Rheumatology (ACR), and published in 2012.(17) The complexity of the disease and the requirement for interdisciplinary collaboration in diagnosis and management likely explain why multiple sets of diagnostic and classification criteria had been proposed and utilized in the past 40 years, yet none had been endorsed until recently by the ACR and the European League Against Rheumatism (EULAR).(18–28)

The objectives of this study are to use SICCA data to 1) explore changes in the phenotypic features (serologic, oral, and ocular) of SS, and in SS status among participants over a 2 to 3-year time interval; and 2) explore specific serologic markers of autoimmunity as potential predictors of progression to SS.

METHODS

Study Population

The SICCA project began in 2003, with five academically-based research groups, located in Argentina, China, Denmark, Japan, and the United States, and directed from the University of California San Francisco.(15) One research group in the United Kingdom joined the effort in 2007, and three additional groups, from the United States (Johns Hopkins University and University of Pennsylvania) and India, joined in 2009. Each of the nine groups included one or more rheumatologists, ophthalmologists, and oral medicine/pathology specialists with extensive experience in the diagnosis and management of SS. All groups enrolled participants until September 30, 2012 using broad criteria to include individuals who either had SS or had symptoms or signs indicating they may develop SS. Eligibility criteria to enroll in SICCA have been published.(15, 17) We did not exclude participants who were taking prescription drugs that may affect salivary or lacrimal secretion, but recorded their use and all other medications taken at the time of study entry, and at follow-up.

All participants found to have any objective measures of salivary hypofunction, dry eye, any amount of focal lymphocytic sialadenitis (FLS) in their labial salivary gland (LSG) biopsy specimen, or positive anti-SSA/-SSB, were recalled 2 years after their baseline examinations to repeat all procedures, including specimen collections. The planned 2-year recall interval was prescribed by the funding period of the NIH contract, Although the majority of recalls occurred close to this timeline, we extended the interval for an additional year to accommodate participants' schedules and to maximize the number of return visits.

Variables and Measures

The multidisciplinary SICCA panel of experts developed a list of variables that were deemed reliable, precise, and feasible to measure within each of the clinical specialties. The list included both objective diagnostic tests and clinical signs and symptoms (17):

- Serologic measures of auto-immunity: serum anti-SSA/-SSB, ANA titer, RF, IgG, C3, and C4.(29) All serologic tests were performed by the same commercial laboratory (Quest Diagnostics, Madison, NJ).
- Measures of the ocular component of SS: dry eye symptoms; Schirmer's test without anesthesia, tear film break up time; ocular surface staining score (OSS) using lissamine green staining of bulbar conjunctiva and fluorescein staining of the cornea to diagnose dry-eye disease, as previously described.(16)
- Measures of the oral component of SS: presence of FLS in a LSG biopsy with a focus score (FS) (measured as number of foci/4 mm²), with all slides read by the same pathologists (30); unstimulated whole salivary (UWS) flow rate; stimulated parotid saliva flow rate (mean flow rate between right and left parotid glands was used in our analyses); dry mouth symptoms.

Examiners were trained by site and specialty in the use of the various diagnostic tests as described in previous publications.(15–17) Periodic retraining was performed within 2 years after the baseline training. SICCA clinical examination forms, questionnaires and specimen

collection and examination protocols are available for review at <http://siccaonline.ucsf.edu>). One questionnaire administered by a clinical coordinator at baseline and follow-up visits collected information about all current medications. Immuno-modulating/suppressive medications including corticosteroids, alkylating agents, antimetabolites, TNF-alpha inhibitors, other disease-modifying anti-rheumatic drugs, antimalarials, and anti-CD-20 were recorded.

The 2012 ACR Classification Criteria for SS were developed as part of the SICCA contract being one of its main goals (requiring for an individual to be classified as having SS to have at least 2 out of the following 3: 1) Positive serum anti-SSA/SSB or [positive RF and ANA 1:320]; 2) OSS ≥ 3 ; 3) Presence of FLS with FS ≥ 1 focus/4 mm² in LSG biopsies.(17). Subsequently, the 2016 ACR-EULAR Classification Criteria for SS were developed and validated, and are now considered the definitive set of SS criteria having been endorsed by both ACR and EULAR.(31, 32) This provides the unique opportunity to compare the two criteria sets with respect to change in SS status over time. The 2016 criteria are based on the weighted sum of 5 items: anti-SSA(Ro) antibody positivity and FLS with FS ≥ 1 foci/mm², each scoring 3; OSS ≥ 5 , Schirmer test ≥ 5 mm/5 min, and UWS flow rate ≥ 0.1 mL/min, each scoring 1. Individuals (with signs/symptoms suggestive of SS) who have a total score ≥ 4 for the items above, meet the criteria for SS.

Statistical Analysis

We used frequency table methods to compare phenotypic baseline variables between SICCA participants who returned for a follow-up visit, and those who were eligible but did not. We used descriptive statistics to summarize socio-demographic and phenotypic sample characteristics of the SICCA cohort by SS status, using both the 2012 ACR and the 2016 ACR-EULAR criteria. Among participants who presented for a follow-up visit, we assessed concordance of phenotypic features at baseline and follow-up. For features represented as binary indicators, the “percent unchanged” was defined as the sum of participants with concordant test results at baseline and follow-up divided by the total number of participants in whom the test result was available at both time-points, multiplied by 100. Estimated percentages were summarized with exact binomial 95% confidence intervals (CI). For features represented as continuous variables, we computed median and range at baseline and follow-up, and the median difference between follow-up and baseline values. Signed-rank tests were used to evaluate statistical significance of within-participant changes in these features. We also examined the change in SS status, using both the ACR and the ACR-EULAR criteria, between baseline and follow-up, using a Kappa statistic (with 95% CI) to assess level of concordance, overall, and in subgroups differentiated by use of any immuno-modulating/suppressive medications.

Because hypergammaglobulinemia and hypocomplementemia have been shown to predict unfavorable outcomes among patients with SS (9, 10, 12–14), we examined the potential effect of baseline levels of IgG, C3, and C4 on progression to SS among all SS-negative participants who had a follow-up visit using logistic regression. These measures were represented as binary indicators in models, using established cut-off values (hypergammaglobulinemia defined as IgG >1445 mg/dL and hypo-complementemia defined

as C3 <90 and/or C4 <16 mg/dL). Models included age, race, and gender as potential confounders. Separate models were fitted with progression to SS alternatively defined using the ACR and the ACR-EULAR criteria.

RESULTS

Sample characteristics

As of September 15, 2013, 3,514 participants had enrolled into SICCA, 3,409 had received the standardized set of evaluations described above, and 3,310 were eligible for a follow-up visit. Among these, 771 presented for a follow-up visit where all tests and questionnaires were repeated (although only 498 agreed to a second LSG biopsy). Among those eligible for a follow-up visit, when comparing those who returned with those who did not, we found no statistically significant difference with respect to baseline anti-SSA/B antibody status, IgG, C4, and OSS. However, the participants who returned for follow-up differed from those who did not in that a higher proportion had ANA titers $\geq 1:320$ (44% versus 29%), were RF-positive (42% versus 34%), and had FLS with FS ≥ 1 (45% versus 39%). The median time between baseline and follow-up visits was 2.3 years [1st quartile (Q1):2; 3rd quartile (Q3):3]. The overall cohort consisted predominantly of women (91%) over the age of 50 years (59%), and with a high level of education (Table 1). The largest proportion of participants was recruited from the US (38% from the three centers combined), Denmark (18%), Argentina (13%), and Japan (11%), but among participants with SS 16% were from China. The majority of participants across sites were Caucasian (55%), followed by Asian (27%). Ten percent were current smokers, with a predominance of smokers among participants not found to have SS.

A large majority of participants in both SS status sub-groups (85% or more) reported dry mouth or dry eyes (Table 2). Among participants with SS (based on the 2012 ACR criteria), three quarters had positive anti-SSA, and more than half had positive RF, ANA titer $\geq 1:320$, and hypergammaglobulinemia (IgG >1445 mg/dL). Similarly, nearly 80% of the participants with SS had FLS with FS ≥ 1 focus/4 mm². These phenotypic features were rare in the non-SS group. A large proportion in both groups (SS and non-SS) had moderate punctate erosions of the cornea and lissamine green staining of the bulbar conjunctiva, and 80% of the individuals with SS had OSS ≥ 5 versus only 33% in the non-SS group. All sample characteristics were also summarized by SS status using the 2016 ACR-EULAR criteria, and frequencies were all within 1 to 2 percentage points of the results displayed in Tables 1 and 2.

Change in SS phenotypic features over time

Overall there was stability over the short follow-up time interval in the three categories of SS phenotypic features (serology, oral, ocular), with the percent unchanged ranging from 78% (for Schirmer's test) to 97% (for anti-SSA/-SSB; Table 3). Although, for most phenotypic features the percent unchanged exceeded 80%, we found a significant difference between baseline and follow-up OSS values. The median score was 5 at baseline versus 6 at follow-up. Stimulated parotid flow rate also decreased significantly over time.

Among participants with FLS and FS = 1 focus/4 mm², 75% still had this histopathologic diagnosis after 2 to 3-year follow-up, while 17% were not found to have FLS at follow-up (Table 4). Among the 37 participants whose LSG biopsy diagnosis changed from FLS with FS = 1 at baseline to no FLS at follow-up, 24% were taking an immuno-modulating/suppressive medication at the time of their baseline exam, and 30% at the time of the follow-up visit.

Change in SS status over time

A total of 677 (88%) participants with baseline and follow-up evaluations had the required test results so that their SS status could be assessed using the 2012 ACR criteria at both time points. When using the 2016 ACR-EULAR criteria, 652 (85%) had the required test results at both time points. Among participants classified as having SS at baseline by ACR criteria, 334 (93%) also met the criteria at follow-up, and this proportion was 89% when using the ACR-EULAR criteria (Table 5). Among those who did not meet the ACR criteria at baseline, 28 (9%) had progressed and met them, while 290 (91%) remained negative for SS at follow-up, and 22 (8%), had progressed when using the ACR-EULAR criteria. The level of concordance with respect to SS status at baseline and follow-up was high when the ACR criteria were used (Kappa = 84%; 95%CI: 80% – 88%), and slightly lower when the ACR-EULAR criteria were used with a Kappa of 81% (95%CI: 76% – 85%). An additional 15 participants who met SS criteria at baseline, did not meet them at follow-up when using the ACR-EULAR criteria versus the ACR criteria. The receipt of immuno-modulating/suppressive medications at either baseline or follow-up or both did not seem to affect the change in SS status over time; we found similar results in various sub-groups defined according to the use of these medications using either criteria. However, the highest percentage of progression from not meeting the SS criteria at baseline to meeting them at the 2 to 3-year follow-up was among those who reported receiving immuno-modulating/suppressive medications at both time points, both when using the ACR criteria (18% progressors), and the ACR-EULAR criteria (12% progressors). Although, when comparing SS status at baseline and follow-up in any of the sub-groups defined by use of immuno-modulating/suppressive medications, the Kappa statistic remained near or above 80%, suggesting high concordance in results between the two time points also in these subgroups using either criteria set.

Among 25 and 40 participants who reverted from being classified as having SS at baseline by ACR and ACR-EULAR criteria, respectively, to not having it at follow-up, 14 (60%) and 30 (75%) did so because their LSG biopsy results changed over time. Among 14 and 30 participants with SS by ACR and ACR-EULAR criteria, respectively, who had a diagnosis of FLS at baseline, 3 (21%) and 8 (27%) went from a FS = 1 at baseline to a FS <1 at follow-up. The second most common reason to revert to a non-SS status by ACR criteria was a change in the OSS that occurred in 9 participants (36%), although 2 of these also had another objective test that became negative at follow-up. Among those who reverted from meeting the ACR-EULAR criteria at baseline to not meeting them at follow-up, 6 (14%) reverted because either their Schirmer test (7%) or their UWS rate (7%) became negative.

Among 28 and 22 participants who did not have SS at baseline and progressed to SS at follow-up by ACR and ACR-EULAR criteria, respectively, 12 (43%) and 16 (73%) did so because of the change in their LSG biopsy results. Ten (36%) participants did so because their OSS progressed from <3 to 3 when using ACR criteria, while only 1 (4%) progressed to meeting ACR-EULAR criteria because the OSS changed from <5 to 5.

Predictors of progression to SS

A logistic regression model exploring progression to SS using the ACR criteria among participants who did not meet the SS classification criteria at baseline revealed that those with hypergammaglobulinemia defined as IgG >1445 mg/dL at study entry were 4 times more likely to progress to SS than those with IgG ≤1445 mg/dL (95%CI: 1.5 – 10.1; $p = 0.006$; Table 6, Model 1). Similarly, participants with hypocomplementemia, defined as C4 <16 mg/dL, at study entry were 6 times more likely to progress to SS than those without this phenotypic feature (95%CI: 1.8 – 20.4; $p = 0.004$). The model controlled for age and gender as potential confounders. Race, C3 level, and other serologic markers of autoimmunity were also included in an earlier model, but not retained in the final one as they were not associated with progression to SS. When using the ACR-EULAR model to define progression to SS, the strong predicting effect of IgG >1445 mg/dL remained, but the effect of C4 was not statistically significant even though the point estimate for the adjusted OR was 2.6.

Occurrence of lymphoma

One case of mucosa-associated lymphoid tissue (MALT) lymphoma was detected in a follow-up LSG biopsy.(33) Three other cases of non-Hodgkin's lymphoma (NHL) were diagnosed by a physician outside of SICCA, but reported to SICCA through our systemic-diagnosis confirmation protocol. Thus the overall incidence of lymphoma among participants for whom follow-up data was available was very low (0.5%).

DISCUSSION

The SICCA Registry represents a unique opportunity to study the phenotypic features of SS over time in an international and geographically diverse cohort. Although we found stability over time for both individual phenotypic features of SS and SS status, the conversion towards SS among SS-negative participants over a median 2.3 years of 9% and 8% participants when using the 2012 ACR and 2016 ACR-EULAR criteria, respectively, is somewhat impressive. However, while the subgroup who returned for follow-up was representative of the broader cohort (eligible for follow-up) with respect to anti-SSA, IgG, C4, and OSS, it included a slightly higher proportion of participants with high-titer ANA, RF positivity, and FLS. Thus this subgroup may have been more susceptible to progression than the broader cohort. This, however, would not bias the finding that hypergammaglobulinemia and hypocomplementemia at baseline were both statistically significant predictors of progression to SS, using the ACR criteria, among participants who did not meet these criteria at baseline. When using the ACR-EULAR criteria to assess SS status, only hypergammaglobulinemia was statistically significant as a predictor of progression. Hypocomplementemia not being found to be a significant predictor when using

the latter criteria may be explained by the lower number of observations available for the model.

Overall, a slightly lower number of participants had data available to assess their SS status both at baseline and follow-up using the ACR-EULAR (n = 652) than the ACR criteria (n= 677). However, while the proportion of those who progressed from not meeting criteria at baseline to meeting them at follow-up was similar with either criteria set (8% and 9%, respectively) slightly higher proportion of participants regressed when using the ACR-EULAR than when using the ACR criteria (11% versus 7%, respectively). This is due for the most part to the higher OSS required for the latter criteria (OSS = 5) than for the ACR criteria (OSS = 3). If we restricted the analysis to participants who were taking immunomodulating medication at both time points, the proportion of conversion to SS was 12% with ACR-EULAR and 18% with ACR criteria, which are higher proportions than in any other sub-groups. This may be interpreted in several ways: this subset of participants may have been placed on immunosuppressive medications by their individual rheumatologist because they had more severe clinical disease, even though they did not meet the classification criteria at baseline. Alternatively, it could suggest that currently available immunomodulating medications are not very effective at altering the progression to full-blown SS disease that meets classification criteria. The lower percentage of progression in this sub-group when using the ACR-EULAR criteria, may again be explained by the higher OSS requirement for the latter criteria set.

Several studies have revealed a significant increase in FS among patients with SS followed over time.(4–6) Jonsson et al reported a mean change in FS from 3.4 to 4.4 among 21 patients with primary SS, and a mean change from 2.0 to 3.7 among 18 patients with secondary SS, followed for a mean duration of 3.2 years.(5) Others reported an even higher increase from a mean FS of 4.2 to 6.1 among 14 SS patients.(4) These findings are in contrast to those of the SICCA registrants, where salivary gland histopathology did not change appreciably. These differences may be explained by the shorter follow-up among SICCA participants.

Anti-SSA/-SSB antibodies and RF precede the diagnosis of SS for up to 20 years,(34, 35) and persist with largely stable levels during the disease course.(36–39) However, serum IgG levels may decline during the course of follow-up.(3, 11) The findings in the SICCA cohort were comparable, even with an interval of only 2–3 years. Anti-SSA/-SSB serology and RF did not change, while there was a significant decrease in serum IgG levels. SS patients are prone to the development of extraglandular manifestations or a second autoimmune disease during the course of their disease.(40–42) Examples of the latter include autoimmune thyroid disease, primary biliary cirrhosis, autoimmune hepatitis, celiac disease, and cutaneous lupus. The development of extraglandular manifestations occurs more frequently in SS patients with anti-SSA/-SSB antibodies or cryoglobulinemia.(42) The incidence of other systemic disorders was relatively uncommon in the SICCA cohort as described by Malladi et al.(29)

The low incidence of lymphoma in our cohort (<1%) may reflect not only the short period of follow-up, but also the recruitment of participants from a broader population, many of whom

may have had lower disease activity than is typically observed in medical center patient cohorts. For example Johnsen & Brun observed lower standardized incidence ratios of lymphoma in their population-based study (43) than others in clinic-based cohorts.(44, 45) Overall, studies with longer follow-up duration than that of the SICCA registry detected a higher proportion of lymphoma: Gannot et al reported a cumulative 12% prevalence of B-cell lymphoma among 49 patients with SS followed over a mean period of 7 years.(8) Skopouli et al reported the development of lymphoproliferative disorder in 4% of 261 patients with SS followed for a median duration of 3.5 years.(10) Similarly, Pertovaara et al. reported that 4% of 81 patients with SS developed NHL over a median 9 years duration of follow-up.(11) Finally, Ioannidis et al reported lymphoproliferative disorder among 5% of 723 patients with primary SS followed for a median 5.1 years.(9)

Others have found that both hypergammaglobulinemia and hypocomplementemia detected at SS diagnosis are predictors of unfavorable outcomes over time.(12–14) We found that hypergammaglobulinemia and hypocomplementemia at baseline were both statistically significant predictors of progression to SS among participants who did not meet the ACR criteria at baseline. The early identification of patients with rheumatic diseases, such as SS, rheumatoid arthritis and systemic lupus erythematosus, may allow early treatment that could potentially prevent progression to frank disease and the development of clinically-apparent organ damage.(46–48) This is fostered by the detection of autoantibodies that characterize these rheumatic diseases and are known to precede their clinical onset by up to 20 years.(35, 49, 50) However, not all patients with these autoantibodies develop clinical disease and research studies are underway to define other host and environmental factors which influence this progression.(46)

In summary, our study is the largest to date to examine longitudinal changes in the key ocular, oral and serologic phenotypic features of SS. The study included 771 individuals with at least one objective feature of SS at baseline in the follow-up cohort, spanning the spectrum of possible to established SS. Our study was limited by the relatively short duration of follow-up and the possibility of a self-selection bias as to which participants agreed to participate in the follow-up examination. However, we found a statistically significant worsening of ocular surface staining scores and stimulated parotid saliva secretion rates during this 2 to 3-year time period. Furthermore, we found that hypergammaglobulinemia and hypocomplementemia at baseline were predictive of progression to SS. Otherwise, we observed remarkable stability over 2–3 years for both individual phenotypic features of SS and SS status, a finding consistent with smaller prospective studies with longer durations of follow-up. Future research should focus on recalling SICCA participants after 5–10 years.

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Significance and Innovation

- Identification of serological variables that predict the development of Sjögren's syndrome (SS) may contribute to earlier diagnosis and treatment of the disease, and ultimately better long-term outcome.
- The large Sjögren's International Collaborative Clinical Alliance (SICCA) registry provides a unique opportunity to study changes in SS status and in the phenotypic features (serologic, oral, and ocular) of SS over time.
- While the phenotypic features of SS were overall stable over a 2 to 3-year period, non-SS individuals with hypergammaglobulinemia and hypocomplementemia at study entry were significantly more likely to progress to SS than those without these characteristics.

Table 1

Socio-demographic characteristics by Sjögren's syndrome (SS) status according to the 2012 ACR Classification Criteria for SS¹ among 3409 participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) as of September 15, 2013

Characteristics	SS (N = 1578) n (%) ²	non-SS (N = 1831) n (%) ²	Total (N=3409) n (%) ²
Sources of baseline enrollment			
United States (US): UCSF	306 (19)	395 (22)	701 (21)
Denmark	168 (11)	430 (23)	598 (18)
Argentina	172 (11)	265 (14)	437 (13)
Japan	202 (13)	163 (9)	365 (11)
China	250 (16)	60 (3)	310 (9)
United Kingdom (since 5/2007)	147 (9)	157 (9)	304 (9)
US: Johns Hopkins University (since 12/2009)	129 (8)	176 (10)	305 (9)
US: University of Pennsylvania (since 12/2009)	118 (7)	137 (7)	255 (8)
India (since 12/2009)	86 (5)	48 (3)	134 (4)
Gender			
Women	1468 (93)	1635 (90)	3103 (91)
Men	107 (7)	190 (10)	297 (9)
Age (years)			
40	340 (22)	307 (17)	647 (19)
41–50	352 (22)	395 (22)	747 (22)
51–60	421 (27)	546 (30)	967 (28)
> 60	462 (29)	575 (32)	1037 (31)
Race			
Caucasian	689 (44)	1175 (64)	1864 (55)
Asian	609 (39)	318 (17)	927 (27)
Other	247 (15)	293 (17)	540 (16)
Unknown	33 (2)	45 (2)	78 (2)
Education			
Graduated from college/university	618 (39)	717 (39)	1335 (39)
Some college/university education	288 (18)	398 (22)	686 (20)
Graduated from high school	299 (19)	306 (17)	605 (18)
Did not graduate from high school	360 (23)	404 (22)	764 (23)
Current cigarette smoking	76 (5)	250 (14)	326 (10)

¹All sample characteristics were also summarized by SS status using the 2016 ACR-EULAR criteria, and frequencies were all within 1 to 2 percentage points of the results above

²Denominators may vary due to missing observations for some variables

Table 2

Serologic, ocular, and oral/salivary characteristics by Sjögren's syndrome (SS) status according to the 2012 ACR Classification Criteria for SS¹ among 3409 participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) as of September 15, 2013

Characteristics	SS (N = 1578)	non-SS (N = 1831)
<u>Categorical Variables</u>	n (%) ¹	n (%) ²
Serology³		
Anti-SSA/Ro positivity	1146 (74)	76 (4)
Anti-SSB/La positivity	757 (49)	38 (2)
Anti-SSA/Ro or anti-SSB/La positivity	1198 (77)	98 (5)
IgG > 1445 mg/dL	848 (55)	202 (11)
C4 < 16 mg/dL	282 (18)	169 (9)
ANA titer 1:320	914 (59)	163 (9)
RF positivity	950 (61)	227 (12)
Ocular⁴		
Schirmer < 5mm/5min	669 (43)	357 (20)
Tear break-up time	1459 (93)	1409 (77)
Ocular Staining score 3	1503 (96)	1018 (56)
Ocular Staining score 4	1382 (88)	819 (45)
Ocular Staining score 5	1261 (80)	609 (33)
Dry eye symptoms	1338 (85)	1578 (86)
Oral/Salivary⁵		
LSG biopsy with FLS & FS 1	1206 (79)	99 (5)
LSG biopsy with germinal centers	286 (21)	17 (3)
UWS flow rate < 0.1/min	971 (62)	797 (44)
Unilateral parotid enlargement	74 (5)	90 (5)
Bilateral parotid enlargement	212 (13)	169 (9)
Dry mouth symptoms	1415 (90)	1647 (90)
Mouth feels dry when eating	940 (60)	921 (51)
Reports difficult swallowing	885 (56)	895 (49)
Need to sip liquid to swallow food	1068 (68)	1048 (57)
Cannot swallow cracker w/o fluid	942 (60)	889 (49)
<u>Continuous variables:</u>		
Unstimulated whole salivary flow rate in ml/min: median [25 th ; 75 th percentile]	0.07 [0.02; 0.16]	0.12 [0.05; 0.22]
Stimulated parotid flow in ml/min: median [25 th – 75 th percentile]	0.02 [0.001; 0.05]	0.02 [0.006; 0.05]

¹ All sample characteristics were also summarized by SS status using the 2016 ACR-EULAR criteria, and frequencies were all within 1 to 2 percentage points of the results above

² Denominators may vary due to missing observations for some variables

³ C4: complement 4; ANA: antinuclear antibody; RF: rheumatoid factor

⁴Ocular staining score is assessed by fluorescein staining of the cornea and lissamine green staining of the interpalpebral conjunctivae. We used the maximum OSS between the right and left eye because 80% of participants had a minimal difference of 0 or 1 between the 2 eyes. However, the Schirmer test had skewed distribution and higher variability between right and left eyes; therefore, we used the mean Schirmer test values between the 2 eyes for each participant.

⁵LSG: labial salivary gland; FLS: focal lymphocytic sialadenitis; FS: focus score; UWS: unstimulated whole saliva

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Table 3
 Change in Sjögren’s syndrome phenotypic features among 771 participants in the Sjögren’s International Collaborative Clinical Alliance (SICCA) seen at 2–3-year follow-up as of September 15, 2013

	Baseline / Follow-up ¹				% unchanged [95%CI]	P-value ⁴
	+ / + n (%)	- / - n (%)	+ / - n (%)	- / + n (%)		
SS Phenotypic Features²						
Binary Variables						
<i>Serology</i>						
Anti-SSA/B	301 (39)	440 (57)	17 (2)	9 (1)	97 [95; 98]	
Rheumatoid factor	272 (36)	440 (57)	10 (1)	44 (6)	93 [91; 95]	
ANA titer (1:320 / <1:320)	253 (33)	372 (49)	60 (8)	82 (11)	81 [79; 84]	
Oral variables						
FLS with FS 1 / no FLS or FS<1	162 (33)	246 (49)	36 (7)	54 (11)	82 [78; 85]	
UWS(< 0.1/min / 0.1/min)	396 (52)	210 (27)	85 (11)	78 (10)	79 [76; 82]	
Parotid enlargement	49 (6)	601 (78)	56 (7)	64 (8)	84 [82; 87]	
Dry mouth symptoms	663 (86)	30 (4)	23 (3)	55 (7)	90 [88; 92]	
Eye-related variables						
OSS (3 / <3)	527 (69)	114 (15)	67 (9)	57 (7)	84 [81; 86]	
OSS (4 / <4)	449 (59)	169 (22)	78 (10)	69 (9)	81 [78; 84]	
OSS (5 / <5)	382 (50)	246 (32)	86 (11)	51 (7)	82 [79; 85]	
TBUT (<10 / 10)	591 (77)	65 (9)	57 (7)	49 (6)	86 [83; 88]	
Schirmer (5 / >5)	190 (25)	404 (53)	91 (12)	80 (11)	78 [75; 81]	
Dry-eye symptoms	632 (82)	54 (7)	34 (4)	51 (7)	89 [87; 91]	
Continuous Variables	Median [Q1; Q3]³	Median [Q1; Q3]³	Median [Q1; Q3]³	Median [Q1; Q3]³	Median [Q1; Q3]³	
	Baseline (B)	Follow-up (FU)	Baseline (B)	Follow-up (FU)	(FU minus B)	
<i>Serology</i>						
IgG	1215 [991; 1660]	1140 [871; 1530]			-79 [-302; 26]	<0.0001
C3	116 [100; 135]	115[94; 134]			0 [-21; 16]	0.74
C4	24 [19; 30]	23 [18; 30]			0 [-5; 3]	0.28
Oral variables						
UWS flow (ml/min)	0.07 [0.02; 0.15]	0.06 [0.01; 0.15]			0 [-0.03; 0.03]	0.88

SS Phenotypic Features ²	Baseline / Follow-up ¹					% unchanged [95% CI]	P
	+/+	-/-	-/+	+/-	n (%)		
Binary Variables	n (%)	n (%)	n (%)	n (%)	n (%)		
Stimulated parotid flow ⁵ (ml/min)	0.11 [0.02; 0.24]	0.08 [0.002; 0.21]	-0.009 [-0.09; 0.031]	-0.009 [-0.09; 0.031]	-0.009 [-0.09; 0.031]	<0.0001	
<i>Eye-related⁶</i>							
OSS	5 [3; 9]	6 [3; 10]	0 [-1; 2]	0 [-1; 2]	0 [-1; 2]	<0.0001	
Schirmer test	8 [4.5; 15]	6.5 [3.5; 13.5]	0 [-3; 2.5]	0 [-3; 2.5]	0 [-3; 2.5]	0.13	

¹ +/+; positive at baseline and follow-up; -/-; negative at baseline and follow-up; +/-; negative at baseline and positive at follow-up (i.e., progressors); +/-; positive at baseline and negative at follow-up (i.e., regressors).

² ANA: antinuclear antibody; FLS: focal lymphocytic sialadenitis; FS: focus score; UWS: unstimulated whole salivary; OSS: ocular staining score; TBUT: tear break-up time.

³ Q1: 25th quantile; Q3: 75th quantile

⁴ P-value for signed-rank test for differences (follow-up-baseline)

⁵ The stimulated parotid flow rate is defined as the mean flow rate between right and left gland. If the flow rate for one gland was missing due to a technical problem, the flow rate for that individual is that of the other gland

⁶ We used the maximum OSS between the right and left eye because 80% of participants had a minimal difference of 0 or 1 between the 2 eyes. However, the Schirmer test had skewed distribution and higher variability between right and left eyes; therefore, we used the mean Schirmer test values between the 2 eyes for each participant.

Table 4

Change in labial salivary gland (LSG) diagnosis of focal lymphocytic sialadenitis (FLS) and focus score (FS) over 2 years among 498 participants with biopsy results as of September 15, 2013

Baseline LSG FLS and FS	Follow-up LSG FLS and FS		
	FLS FS = 1 n (%) ¹	FLS FS < 1 n (%) ¹	no FLS n (%) ¹
FLS with FS = 1	162 (75)	17 (8)	37 ² (17)
FLS with FS < 1	21 (20)	27 (25)	58 (55)
No FLS	15 (9)	44 (25)	117 (66)

¹Row percentage

²Among the 37 participants who regressed from FLS with FS = 1 to no FLS, 24% were taking an immunomodulating or immunosuppressive medication at the time of the baseline visit, and 30% at the time of the follow-up visit

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Change in Sjögren's Syndrome (SS) status', stratified by use of immuno-modulating/suppressive drugs,² among participants with available test results allowing assessment of their SS status at baseline and 2-year follow-up (as of September 15, 2013)

Table 5

SS status at Baseline visit	SS status at follow-up visit				Kappa [95%CI]
	2012 ACR	No SS n (%)	SS n (%)	2016 ACR-EULAR	
All participants					
2012 ACR; N=677					
SS	334 (93)	25 (7)			
No SS	28 (9)	290 (91)			0.84 [0.80; 0.88]
2016 ACR-EULAR; N=652					
SS			324 (89)	40 (11)	
No SS			22 (8)	266 (92)	0.81 [0.76; 0.85]
Participants not taking immuno-modulating/suppressive² drug(s) at the follow-up visit					
2012 ACR; N=468					
SS	215 (92)	18 (8)			
No SS	16 (7)	219 (93)			0.85 [0.81; 0.90]
2016 ACR-EULAR; N=450					
SS			210 (88)	30 (12)	
No SS			14 (7)	196 (93)	0.80 [0.75; 0.86]
Participants not taking immuno-modulating/suppressive² drug(s) at either visits					
2012 ACR; N=420					
SS	196 (93)	15 (7)			
No SS	12 (6)	197 (94)			0.87 [0.82; 0.92]
2016 ACR-EULAR; N=401					
SS			192 (88)	25 (12)	
No SS			12 (7)	172 (93)	0.82 [0.76; 0.87]
Participants taking immuno-modulating/suppressive² drug(s) at both visits					
2012 ACR; N=132					
SS	72 (95)	4 (5)			

SS status at follow-up visit					
SS status at Baseline visit	2012 ACR		2016 ACR-EULAR		Kappa [95%CI]
	SS n (%)	No SS n (%)	SS n (%)	No SS n (%)	
No SS	10 (18)	46 (82)			0.78 [0.67; 0.89]
2016 ACR-EULAR; N=129					
SS			66 (92)	6 (8)	
No SS			7 (12)	50 (88)	0.80 [0.69; 0.90]

¹ SS status assessed using both 2012 ACR and 2016 ACR-EULAR Classification criteria for SS

² Immuno-modulating/suppressive drugs included corticosteroids, alkylating agents, antimetabolites, TNF alpha inhibitors, other DMARDs, antimalarials, and anti-CD-20.

Table 6

Effect of baseline IgG and C4 on progression to SS among SICCA participants who were SS-negative at study entry

Model 1:			
Progression to SS outcome based on 2012 ACR classification criteria for SS (N = 317)¹			
Predictors	Adjusted OR	95% CI	P-value
IgG > 1445 mg/dL	3.9	1.5; 10.1	0.006
C4 < 16 mg/dL	5.9	1.8; 20.4	0.004
Age (years)	0.99	0.9; 1.02	0.60
Gender (F vs M)	0.19	0.02; 1.8	0.15
Model 2:			
Progression to SS outcome based on 2016 ACR-EULAR classification criteria for SS (N = 287)¹			
Predictors	Adjusted OR	95% CI	P-value
IgG > 1445 mg/dL	3.2	1.1; 9.3	0.03
C4 < 16 mg/dL	2.6	0.6; 10.9	0.19
Age (years)	1.0	0.9; 1.1	0.31
Gender (F vs M)	0.8	0.2; 4.3	0.83

¹Participants SS-negative at baseline, and who had a follow-up visit, and tests required for the 2012 ACR criteria (Model 1) and for the 2016 ACR-EULAR criteria (Model 2)