Original Article

Longitudinal Changes in the European League Against Rheumatism Sjögren's Syndrome Patient Reported Index in Real-Life Practice

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Objective. To investigate longitudinal changes in the European League Against Rheumatism (EULAR) Sjögren's syndrome patient reported index (ESSPRI) and to study the clinical features associated with favorable ESSPRI changes in primary Sjögren's syndrome (pSS). **Methods.** At baseline and after a median period of 6.6 years, 41 pSS patients were evaluated using the ESSPRI, EULAR Sjögren's syndrome disease activity index (ESSDAI), short-form 36, xerostomia inventory (XI), and visual analog scale (VAS) scores for symptoms. The favorable subgroup included patients who were stable or showed improved to satisfactory symptom status (ESSPRI < 5) and the unfavorable subgroup included those with stable or worsening to an unsatisfactory symptom status (ESSPRI ≥ 5). **Results.** Median ESSPRI increased from 4.11 to 5.33 (p < 0.05), although XI scores (p = 0.01) and oral dryness (p < 0.05) were significantly decreased. Serum immunoglobulin G level was significantly reduced (p < 0.001) but ESSDAI scores were unchanged. Six (14.6%) patients showed clinical improvement in ESSDAI, and 11 (26.8%) showed improvement in ESSPRI. On comparing the favorable (n = 17) and unfavorable (n = 24) subgroups, the former exhibited significantly lower VAS scores for sicca and depression and XI and ESSPRI scores at baseline (all p < 0.05) and more lacrimal flow (p < 0.05). The favorable subgroup received a significantly lower cumulative dose of pilocarpine and glucocorticoids (both p < 0.05). **Conclusion.** About 25% of pSS patients showed clinically significant ESSPRI improvement and about 40% showed a favorable ESSPRI course. Because the favorable subgroup had more lacrimal flow and less sicca symptoms at baseline, long-term patient-derived outcomes could depend on residual exocrine function at pSS diagnosis. **(J Rheum Dis 2019;26:191-199)**

Key Words. Sjögren's syndrome, Patient outcome assessment, Quality of life, Xerostomia, Xerophthalmia

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease characterized by lymphocytic cell infiltration of salivary and lacrimal exocrine glands, resulting in functional impairment. However, the inflammatory process can extend beyond the exocrine glands and affect various non-exocrine organs such as the joints, skin, lungs, kidneys, nerves, and small vessels [1,2]. Although the prevalence or incidence of pSS is debated, it has been considered a rare disease and a recent meta-analysis reported a global worldwide prevalence of 0.06% [3,4].

A variety of extraglandular manifestations have been reported in pSS patients and a large Spanish registry revealed that 13% had a potentially life-threatening systemic manifestation [5]. However, most pSS patients have benign subjective conditions such as sicca symptoms, arthralgias, and fatigue. In line with these findings, pSS has not been associated with increased mortality [6,7], even though it negatively affects health-related quality of life [8-10].

To assess disease activity and outcome measures, the European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient reported index (ESSPRI) have been developed [11,12]. The ESSDAI and ESSPRI have now been validated as outcome measures for pSS in many studies. These indices reflect 2 facets of pSS: 1) benign but disabling subjective symptoms and 2) systemic and potentially severe manifestations. The two indices reportedly had good sensitivity to change in clinical trials, although the change in the ESSPRI was smaller than that in the ESSDAI [12]. The ESSPRI levels are reportedly well-correlated with quality of life and functional status [8,13]. Since the two indices are poorly correlated with each other, each should be evaluated separately and independently.

However, to our knowledge, no report has investigated longitudinal ESSPRI changes in routine clinical practice for pSS. Additionally, we do not know how many patients obtain clinically meaningful ESSPRI improvement with routine therapies. We evaluated temporal changes in the ESSPRI and ESSDAI and clinical features associated with favorable ESSPRI changes in Korean patients with pSS.

MATERIALS AND METHODS

Patients

Among 104 pSS patients enrolled in a previous study [8], 63 had been followed by our rheumatology clinic and 41 were reevaluated between January 2015 and April 2016. The median follow-up period was 6.6 (4.9~8.3) years (range 3.5~9.8 years). All patients met the 2002 American-European Consensus Group classification criteria for SS [14], and all but 1 were females. Median age was 49.0 (39.0~57.0) years and the median duration of sicca symptoms was 8.0 (3.0~10.8) years at enrollment. Eight (19.5%) had moderate-to-high disease activity status and the most common extraglandular manifestation was arthralgia/arthritis (31.7%). Baseline characteristics are summarized in Table 1. This study was approved by our institutional review board (IRB No. B-0506/021-004) and written informed consent was obtained from all participants.

Methods

At enrollment and follow-up, the ESSDAI, ESSPRI, and EULAR sicca score (ESS) were calculated using a previous definition [11,15]. Patients also completed ques-

tionnaires and provided a visual analog scale (VAS) score; the short-form 36 (SF-36) and Xerostomia Inventory (XI) scores were determined, and patients were assessed for dry eye, dry mouth, joint pain, myalgia, anxiety, depression, fatigue, and global status. Demographic, clinical, and laboratory variables were collected using medical records review. Cumulative dose and prescription duration of pilocarpine, glucocorticoids, and hydroxychloroquine were calculated during the follow-up period. Satisfactory refill adherence of pilocarpine was defined as dispensed refills covering >75% of the follow up period.

Table 1. Baseline clinical characteristics of study participants with primary Sjögren's syndrome

Demographics and clinical characteristics	Total patients (n = 41)
Age (yr)	49.0 (39.0~57.0)
Female	40 (97.6)
Menopause	29/40 (72.5)
Duration of sicca symptoms (yr)	8.0 (3.0~10.8)
Dry mouth/eye	40 (97.6)/34 (82.9)
Salivary gland*/Lacrimal gland[†] dysfunction	41 (100)/28 (68.3)
Anti-Ro/La positivity	38 (92.7)/20 (48.8)
Focal sialadenitis (focus score ≥1)	18/20 (90.0)
Extraglandular manifestations	23 (56.1)
Arthritis/arthralgia	13 (31.7)
Raynaud's phenomenon	12 (29.3)
Cutaneous involvement	6 (14.6)
Peripheral neuropathy	2 (4.9)
Renal tubular acidosis	1 (2.4)
Interstitial lung involvement	1 (2.4)
Disease activity status assessed by ESSDAI	
Low (ESSDAI <5)	33 (80.5)
Moderate (5≤ESSDAI≤13)	7 (17.1)
High (ESSDAI >13)	1 (2.4)
Unsatisfactory symptom state (ESSPRI ≥5)	16 (39.0)
Comorbidities	
Hypertension	5 (12.2)
Diabetes mellitus	2 (4.9)
Hyperthyroidism	2 (4.9)
Hypothyroidism	8 (19.5)
Depression	2 (4.9)

Values are presented as median (interquartile range) or number (%). ESSDAI: European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity, ESSPRI: EULAR Sjögren's syndrome patient-reported index. *Defined using unstimulated whole salivary flow or salivary scintigraphy; [†] defined using Schirmer's test or Rose Bengal score.

Based on the definition proposed by the EULAR Sjögren's Task Force [16], pSS was classified according to low (ESSDAI <5), moderate ($5 \leq$ ESSDAI ≤ 13), and high disease activity (ESSDAI ≥ 14). Additionally, unsatisfactory symptom status was defined as ESSPRI ≥ 5, and minimal clinically important improvement was defined as an increase in ESSPRI of ≥ 1 point or by 15%, or an increase in ESSDAI of ≥ 3 points, as previously proposed [16]. Based on temporal ESSPRI changes, pSS patients were classified into favorable (F) or unfavorable (UF) outcome subgroups. The F subgroup was defined as showing an improvement in ESSPRI (from baseline ESSPRI ≥ 5 to follow-up ESSPRI <5) or maintenance of satisfactory symptom status (ESSPRI <5). The UF subgroup showed worsening of ESSPRI (from baseline ESSPRI <5 to follow-up ESSPRI ≥ 5) or maintenance of unsatisfactory symptom status (ESSPRI ≥ 5).

Statistical analysis

Continuous variables are expressed as median with interquartile range (25th to 75th percentile). Statistical analysis was performed using the Mann–Whitney test for continuous variables and Wilcoxon signed-rank test for paired values. The chi-square test or Fisher's exact test was used for categorical variables. To identify clinical factors associated with favorable outcome, multivariate

Table 2. Patient-oriented measurements and laboratory variables at baseline and follow-up

Variable	Baseline (n=41)	Follow up (n=41)	p-value*
VAS for oral dryness	70 (40~85)	50 (24~80)	0.035
VAS for eye dryness	60 (40~70)	49 (20~72)	0.248
XI score	42 (35~47)	39 (29~47)	0.010
VAS for joint pain	10 (0~49)	20 (5~50)	0.316
VAS for myalgia	20 (0~49)	20 (0.5~40)	0.604
VAS for anxiety	20 (0~30)	10 (0~40)	0.641
VAS for depression	20 (0~40)	20 (0~40)	0.933
VAS for fatigue	50 (20~60)	40 (20~60)	0.237
Patient global assessment	45 (20~80)	30 (10~59)	0.009
ESS	6.33 (4.67~7.67)	5.00 (4.67~7.33)	0.182
ESSPRI	4.11 (3.22~5.56)	5.33 (3.50~6.67)	0.047
ESSDAI	2 (1~4)	2 (1~4)	0.936
SF-36 domains			
Physical functioning	53.91 (45.84~53.91)	51.61 (45.85~56.22)	0.679
Role limitation owing to physical health	49.1 (32.22~55.36)	49.19 (33.76~55.36)	0.523
Bodily pain	44.53 (35.13~39.9)	44.53 (35.13~49.9)	0.993
General health perceptions	40.33 (31.84~48.83)	41.83 (34.34~50.32)	0.319
Vitality	41.3 (31.98~49.06)	41.3 (35.09~47.51)	0.694
Social functioning	56.14 (42.18~56.14)	49.16 (35.2~56.14)	0.159
Role limitations due to emotional health	46.72 (33.74~55.37)	51.05 (35.91~55.37)	0.479
Physical component summary	46.66 (39.1~52.36)	46.2 (37.6~54.4)	0.959
Mental component summary	44.64 (37.75~50.65)	45.1 (36.01~54.13)	0.821
White blood cells (/mm^3)	4,880 (4,020~6,030)	4,930 (3,920~5,790)	0.620
Hemoglobin (g/dL)	12.6 (11.9~13.3)	13.2 (12.3~13.6)	0.046
Platelet (/mm^3)	203 (186~244)	221 (183~257)	0.914
ESR (mm/h)	19 (9~43)	16 (10~30)	0.295
CRP (mg/dL)	0.01 (0.01~0.11)	0.04 (0.03~0.10)	0.075
Total immunoglobulin G (mg/dL)	1,980 (1,710~2,460)	1,710 (1,530~1,950)	$<1.0 \times 10^{-5}$
Complement C3 (mg/dL)	105.0 (92.5~114.5)	100.5 (85.7~111.8)	0.007
Complement C4 (mg/dL)	19.0 (15.7~23.0)	22.40 (18.4~24.8)	0.041
β 2-microglobulin	2.16 (1.81~2.68)	2.25 (1.73~2.67)	0.975

Values are presented as median (interquartile range). VAS: visual analog scale, XI: xerostomia inventory, ESS: European League Against Rheumatism (EULAR) sicca score, ESSPRI: EULAR Sjögren's syndrome patient-reported index, ESSDAI: EULAR Sjögren's syndrome disease activity, SF-36: short-form 36, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. *Calculated using Wilcoxon signed-rank test.

models were created using the variables with a statistical significance of p<0.1 from the univariate analyses. Statistical analysis was performed using IBM SPSS version 21 (IBM Co., Armonk, NY, USA); p<0.05 was considered significant.

RESULTS

Longitudinal changes in patient-oriented and laboratory measurements

The median daily dose of pilocarpine was estimated as 8.4 (2.8~10.1) mg/day in the study subjects. During the follow-up period, 17 patients (41.5%) showed satisfactory refill adherence and 6 had never received pilocarpine. Patients with satisfactory refill adherence of pilocarpine showed a significantly higher age (55.0 [48.0~59.0] vs. 43.5 [36.0~53.3] years, p=0.011) and baseline ESS (6.33 [5.33~8.50] vs. 5.67 [3.00~7.33], p=0.033) and ESSPRI (4.11 [3.17~5.95] vs. 3.78 [2.85~5.19], p=0.014) levels (Table 2) than the those without satisfactory refill adherence.

After a median 6.6 years of follow-up, ESSDAI scores were not significantly changed but ESSPRI scores were statistically marginally increased (p=0.047). The median change was 0 (−1.0~2.0) in ESSDAI and 0.6 (−0.8~2.0) in ESSPRI. Six (14.6%) patients showed clinically important improvement based on ESSDAI, as did 11 (26.8%) based on ESSPRI, over a median of 6.6 years.

Follow-up VAS scores for dry eye or extraglandular manifestations and physical or mental component summary scores on the SF-36 were not significantly improved. However, VAS scores for dry mouth (p=0.035) and XI scores (p=0.010) were significantly decreased from baseline. Moreover, VAS scores for patient global assessment improved from 45 (20~80) to 30 (10~59) (p=0.009).

The temporal changes in ESS (from 6.33 [5.33~8.50] to 6.00 [5.00~7.17]) and ESSPRI (from 4.11 [3.17~5.95] to 5.33 [3.84~6.84]) were not significant in patients with satisfactory refill adherence of pilocarpine, although VAS for sicca symptoms tended to decrease (from 80 [55.0~95.0] to 47.0 [33.5~80.0] of oral dryness VAS, p=0.062; from 70 [45~70] to 50 [40~80] of eye dryness VAS, p=0.426).

Among laboratory variables, the levels of total immunoglobulin G (IgG) were significantly decreased from 1,980 (1,710~2,460) to 1,710 (1,530~1,950) mg/dL (p<1.0×10^{-5}). However, the magnitude of decrease in serum

IgG levels was not significantly correlated with patient-oriented measures for sicca symptoms. Hemoglobin, C-reactive protein, and complement levels showed a statistically significant change, but these were not clinically significant.

Comparison between favorable and unfavorable outcome groups

When pSS patients were stratified into F or UF subgroups, 17 patients (41.5%) showed a favorable outcome over a median of 6.6 years and 4 of these had unsatisfactory symptom status at baseline. In other words, 4/16 pSS patients (25.0%) with baseline unsatisfactory symptom status achieved better symptom status during the follow-up period (Figure 1). In patients with baseline unsatisfactory symptom status, 5/16 (31.3%) exhibited clinically meaningful improvement. However, in those with baseline satisfactory symptom status, about half (n=12/25, 48.0%) reported worsening of symptoms at follow-up.

When F and UF outcome subgroups were compared, the F subgroup had a significantly increased prevalence of premenopausal status (p=0.025) or Raynaud's phenomenon (p=0.045), and greater tear production (the sum of Schirmer's test results in both eyes, p=0.049; Table 3). Additionally, the F subgroup had significantly less severe symptoms of dry mouth, dry eye, and depression at baseline than the UF subgroup. Accordingly, the F subgroup showed better baseline assessment using the ESS, ESSPRI, and some domains of SF-36, including bodily pain, general health, and vitality (all p<0.05). At follow-up, the F outcome subgroup had a significantly lower ESSPRI (2.67 [2.00~4.00] vs. 6.50 [5.42~7.00], p<1.0×10^{-7}) than the UF outcome subgroup. During the
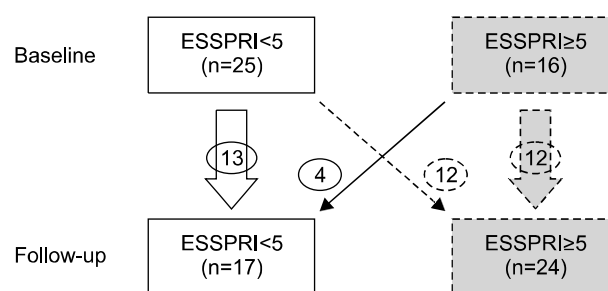

Figure 1. Flow of primary Sjögren's syndrome patients during the follow-up period based on European League Against Rheumatism Sjögren's syndrome patient reported index (ESSPRI) status.

Table 3. Comparison between favorable (F) and unfavorable (UF) outcome subgroups*

Variable	F (n = 17)	UF (n = 24)	p-value*
Age (yr)	44 (40~58)	51 (38~58)	0.156
Duration of symptoms (yr)	7.0 (3.0~10.0)	9.5 (2.3~13.3)	0.702
Menopause	5 (29.4)	15/23 (65.2)	0.025
Sum of Schirmer's test results (mm)	20 (10~26)	11 (4~18)	0.049
Raynaud's phenomenon	8 (47.1)	4 (16.7)	0.045
VAS for oral dryness	60 (35~70)	80 (45~90)	0.047
VAS for eye dryness	40 (20~60)	70 (40~70)	0.013
XI score	37 (35~44)	45 (36~55)	0.025
VAS for depression	15 (0~20)	20 (10~40)	0.043
VAS for fatigue	40 (20~50)	50 (30~60)	0.084
ESS	5.33 (3.34~6.50)	7.17 (5.33~8.00)	0.014
ESSDAI	2 (1~5)	2 (1~3)	0.182
ESSPRI	3.25 (2.73~5.06)	4.67 (3.56~5.67)	0.026
ESSPRI at follow-up	2.67 (2.00~4.00)	6.50 (5.42~7.00)	$< 1.0 \times 10^{-7}$
SF-36			
Physical functioning	53.9 (49.3~53.91)	51.6 (44.7~56.2)	0.808
Role limitations due to physical health problems	52.3 (41.5~55.4)	46.1 (28.4~55.4)	0.335
Bodily pain	45.4 (42.3~53.5)	40.1 (32.1~45.4)	0.028
General health perceptions	47.8 (39.8~50.3)	36.1 (30.0~42.6)	0.005
Vitality	47.5 (41.3~50.6)	35.1 (28.9~43.6)	0.002
Social functioning	56.1 (42.2~56.1)	45.7 (30.0~56.1)	0.085
Role limitations due to emotional health problems	46.7 (40.2~55.4)	44.6 (29.4~55.4)	0.395
Physical component summary	50.0 (44.6~53.7)	42.4 (37.8~51.4)	0.101
Mental component summary	47.8 (40.8~53.7)	42.5 (34.3~49.0)	0.106

Values are presented as median (interquartile range) or number (%); all variables not shown in the table were not significant. VAS: visual analog scale, XI: xerostomia inventory, ESS: European League Against Rheumatism (EULAR) sicca score, ESSDAI: EULAR Sjögren's syndrome disease activity, ESSPRI: EULAR Sjögren's syndrome patient-reported index, SF-36: short-form 36. *Calculated using Mann–Whitney, chi-square or Fisher's exact test when appropriate.

follow-up period, the F subgroup received a significantly lower cumulative dose of pilocarpine (p=0.022) and glucocorticoids (p=0.039), while more patients in the UF subgroup took mucolytics (p=0.004) and nonsteroidal anti-inflammatory drugs (p=0.012; Table 4). Additionally, UF subgroup tended to have a higher refill adherence for pilocarpine and a higher prevalence of central nervous system acting drugs use.

We performed multivariate analysis after adjusting for covariates such as menopause, Schirmer's test results, the presence of Raynaud's phenomenon, VAS scores for oral or eye dryness, depression, and fatigue, XI scores, initial ESSPRI scores, several SF-36 scores, and medication usage. But no significant predictive factor for favorable outcome was found.

DISCUSSION

The current study is the first to investigate longitudinal

changes in patient-oriented outcome measures including ESSPRI and SF-36 in Korean patients with pSS. In routine care, after a median of 6.6 years, clinically meaningful improvement in ESSPRI was observed in at most 25% of patients with pSS. Moreover, there was no significant improvement in quality-of-life measurements and subjective assessments of xerophthalmia and extraglandular symptoms, even though patient-derived measures for xerostomia and patient global assessment were significantly improved.

The number of published papers on pSS has grown exponentially in the last several decades but longitudinal patient-oriented outcomes have rarely been studied in patients with pSS. It was reported that salivary secretory function or sicca complaints in pSS were not markedly changed over a period of about 10 years [17,18]. In Swedish patients with pSS, symptoms of dry eye, dry mouth, and fatigue and health related quality of life did not change significantly over a period of 5 years [19]. In

Table 4. Comparison of overall medication usage between favorable (F) and unfavorable (UF) outcome subgroups during follow-up

Medication	F (n = 17)	UF (n = 24)	p-value*
Pilocarpine use	11 (64.7)	23 (95.8)	0.064
Cumulative duration (mo)	2 (0~70)	47.5 (33.0~66.5)	0.051
Cumulative dose (g)	0.14 (0~14.0)	13.1 (0.004~23.3)	0.022
Satisfactory refill adherence[†]	5 (29.4)	12 (50.0)	0.187
Glucocorticoids use	6 (35.3)	15 (62.5)	0.080
Cumulative duration (mo)	0 (0~9)	18 (0~41.7)	0.021
Cumulative dose (g)[†]	0 (0~0.8)	1.7 (0~3.1)	0.039
Hydroxychloroquine use	12 (70.6)	22 (91.7)	0.105
Cumulative duration (mo)	37 (0~60)	32.5 (11~58)	0.853
Cumulative dose (g)	207.3 (0~407.1)	319.7 (136.7~417.1)	0.340
Mizoribine use	4 (23.5)	10 (41.7)	0.321
Cumulative duration (mo)	0 (0~0)	0 (0~25.5)	0.462
Cumulative dose (g)	0 (0~0)	0 (0~91.2)	0.332
Mucolytic use	3 (17.6)	16 (66.7)	0.004
NSAID use	5 (29.4)	17 (70.4)	0.012
CNS acting xerostomic agents[§]	3 (17.6)	12 (50.0)	0.502

Values are presented as number (%) or median (interquartile range). NSAID: nonsteroidal anti-inflammatory drug, CNS: central nervous system. *Calculated using Mann–Whitney, chi-square, or Fisher's exact test when appropriate. [†]Dispensed refills covering > 75% of the follow up period of each patient; [‡]calculated by adding prednisolone equivalents; [§]included tricyclic agents, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, benzodiazepines, trazodone, and zolpidem.

another longitudinal study on temporal changes, self-reported fatigue levels were unchanged over a period of 5 years in Norwegian pSS patients [20]. Moreover, a recent study using salivary gland ultrasound outcomes revealed that abnormalities did not change significantly during a follow-up of nearly 2 years [21].

The current study also found no clinically meaningful changes in most patients with pSS; 85% and 73% did not experience clinically important improvement in ESSDAI and ESSPRI, respectively. Such stability of patient-oriented outcome measures or symptoms suggests that the current treatment modalities provide only very limited efficacy. In the current study, ESSPRI was not significantly reduced even in subjects with satisfactory refill adherence of pilocarpine although there was a tendency to decrease in VAS for sicca symptoms. It has been well established that pSS patients have significantly impaired quality of life and this may produce a floor effect. However, unlike the abovementioned studies, our participants reported significant improvement in xerostomia and global assessment of SS during the follow-up period. This can be explained by the finding that more patients (34/41, 82.9%) had taken cholinergics in our study when compared to previous studies (2/58 [4.4%] in the Swedish study) [19]. Moreover, diagnosis and education during regular visits can reduce the emotional impact of anxiety and depression, although mental component scores in the SF-36 were not improved.

Concerning laboratory parameters, we observed that only serum IgG levels were significantly decreased during the follow-up period. Theander et al. [19] previously reported that serum IgG levels were not changed over a period of 5 years, but Pertovaara et al. [18] reported that levels significantly decreased after a median of 9 years. Several treatments including abatacept and hydroxychloroquine reportedly decreased the serum IgG levels in pSS patients [22-24]. In the current study, 34 (82.9%) of 41 study subjects had taken hydroxychloroquine and 21 (51.2%) had received glucocorticoids during follow-up. These treatments could reduce serum IgG levels. However, the decrease in serum IgG levels was not associated with subjective improvement of xerostomia in our study.

Although pSS patients have a higher risk of non-Hodgkin lymphoma (NHL) than controls or patients with systemic lupus erythematosus, most have relatively chronic stable disease without rapid deterioration of exocrine function or dramatic changes in extra-exocrine clinical features [25-27]. Nevertheless, many researchers have focused only on the risk factors for NHL that develop in a small proportion of pSS patients (<2%) [28,29]. Until now, no study has investigated predictive factors for patient-oriented outcomes or longitudinal change in the

prevalent symptoms. In this context, we divided our pSS patients into favorable and unfavorable subgroups and compared clinical features between the two subgroups.

In the current study, about 40% showed a favorable course and even about 30% of pSS patients with baseline ESSPRI >5 achieved clinically meaningful improvement, although the F subgroup used less medication and tended to have low prevalence of satisfactory refill adherence of pilocarpine than the UF subgroup. Because of small sample size, multivariate analysis did not demonstrate an independent factor associated with favorable outcomes. However, in univariate analyses, better patient assessment of sicca symptoms and depression was associated with favorable outcomes. Therefore, the psychological attitude toward the disease or the background psychological profile may be an underlying factor associated with favorable outcomes, because ESSPRI is correlated with the mental health subdimension of SF-36 or depression [8,30].

Premenopausal status, the presence of extraglandular manifestations such as Raynaud's phenomenon, or residual lacrimal gland function at diagnosis was also associated with a favorable course. The prevalence of Raynaud's phenomenon was reported to be 16%~35% in a large case series of pSS patients, and Raynaud's phenomenon preceded the onset of sicca symptom in about half of pSS patients [31,32]. Several studies showed that the age at disease onset (defined as the first subjective experience of glandular or extraglandular symptoms) does not influence clinical features [33,34]. In the current study, disease duration was comparable between F and UF outcome subgroups. However, in a large Spanish cohort study, younger-onset pSS showed a lower prevalence of xerostomia and abnormal ocular findings [31]. Therefore, when considering the abovementioned findings together, a higher prevalence of premenopausal women in the F subgroup may suggest that early diagnosis without severe exocrine impairment could be associated with a favorable outcome in pSS. Unfortunately, we know little about the natural history of pSS as well as the transition from the preclinical phase into clinical disease. pSS-related autoantibodies can be detected at a median of 4~5 years before clinical diagnosis. In addition, immune-meditated glandular injury is considered to progress over several years and the delay between symptom onset and final diagnosis has been reported to range from 3~10 years [35,36]. Therefore, when the diagnosis of pSS is made after the development of sicca symptoms, the patient may already have irreversible exocrine dysfunction. Moreover, delayed diagnosis could increase the psychological distress caused by unexplained symptoms in pSS patients [10]. Thus, diagnosis in the state with lower scores on sicca symptoms or with residual exocrine function could be important to improve patient-oriented outcomes and to help decrease the local or systemic complications.

Our study has several limitations. First, the rate of loss to follow-up was high (about 60%). Those without symptomatic improvement were more likely to be lost to follow-up and the proportion of patients achieving clinically meaningful improvement could be overestimated in this study. However, we believe that the importance of early diagnosis in pSS is not overemphasized. Second, the sample size was inadequate for multivariate analysis. Hence, a larger number of patients with pSS is needed for study. Third, most patients had low-to-moderate disease activity and did not have severe systemic manifestations. However, the ESSDAI level (median 2.0) in our patients was similar to that in the French Assessment of Systemic Signs and Evolution in Sjögren's syndrome (ASSESS) cohort and in patients enrolled in a randomized clinical trial of hydroxychloroquine (the JOQUER trial) [37]. Therefore, our study subjects reflected general rather than unique features of pSS patients.

CONCLUSION

In summary, our study showed that 27% showed clinically important improvement in ESSPRI over a median of 6.6 years and 40% showed a favorable course based on ESSPRI in routine care. Favorable patient-derived outcome was associated with some clinical features, including premenopausal status, greater lacrimal flow, and fewer sicca or depressive symptoms at baseline.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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