Rheumatology International (2019) 39:991–999
https://doi.org/10.1007/s00296-019-04285-w

Rheumatology
INTERNATIONAL

COHORT STUDIES

ESSDAI activity index of the SJÖGRENSER cohort: analysis and comparison with other European cohorts

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Received: 3 February 2019 / Accepted: 13 March 2019 / Published online: 19 March 2019

Abstract

The objective of the study was to assess the ESSDAI index characteristics in the SJÖGRENSER cohort (Spanish Rheumatology Association's registry of patients with Primary Sjögren Syndrome [PSS]). SJÖGRENSER is a prospective multicentric study on a cohort of Spanish patients with PSS who meet the 2002 American–European consensus from rheumatology units. 298 variables were studied in patients for the inclusion of the study from an anonymous list from each department. The ESSDAI (EULAR Sjögren's syndrome disease activity index) includes 12 domains and measures systematic activity in PSS patients. Each domain is divided into 3–4 levels, (0: no activity; 1: low activity; 2: moderate activity; 3: high activity) and is attributed a weight. Each domain score is obtained by multiplying the activity level by the weight assigned. According to ESSDAI: low activity < 5; moderate activity 5–13, and high activity ≥ 14. ESSDAI was compared between several European PSS cohorts (EULAR, ASSES, GEAS, GRISS, Ducth). 437 patients were included from 33 Spanish rheumatology units. 95.2% were women with a median age of 58.63 years [p25–p75: 50.02–67.98 years] and average PSS evolution of 10.4 years (6–16 years). ESSDAI median on entering the study was 2 (0–4). 31% of patients had ESSDAI 0; low activity 49%, moderate activity 15%, and high activity 5%. Those with greater activity were the joint, haematological and biological domains, whereas the lung was the most affected organ with pleural and parenchymatous involvement. Unlike other European cohorts, the initial SJÖGRENSER cohort was characterised by low-zero systemic activity in 80% of patients, which differentiates it from other cohorts and provides a prospective study opportunity.

Keywords ESSDAI · Primary Sjögren syndrome · SJÖGRENSER · Cohort study

The members of the institutional author SJÖGRENSER Group, part of the Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER), are mentioned in Acknowledgements section.

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Introduction

Primary Sjögren syndrome (PSS) is a chronic autoimmune exocrinopathy with slow progression and unknown aetiology. It is characterised by dry mucosa, chiefly of the mouth (xerostomia) and eye (xerophthalmia), although it may frequently cause nasal, skin or vaginal dryness [1]. It is also called autoimmune epithelitis, since the glandular epithelial cells are the inflammatory response target due to lymphoplasmocytic infiltration, the presence of auto-antibodies and inflammation mediators [2].

Although in most patients the disease remains located in exocrine glands (glandular symptoms), in 30% of patients different organs or systems can be affected (extraglandular symptoms): joint, lung, nervous system, kidney or others, likewise non-exocrine glands such as the thyroid [1, 2]. Symptoms may appear before or after PSS diagnosis, together with typical PSS dryness characteristics or without accompanying dryness syndrome, thus frequently hindering diagnosis. Between 2.7% and 9.8% of patients may develop lymphoma [3].

The disease is more prevalent in women, with a ratio of 10.72 (CI 95% 7.35–15.62), and while it may appear at any age, it predominantly occurs during the fourth to fifth decades of life [4].

As with other systemic disease, indices have been developed for PSS to measure disease activity. The ESSDAI (EULAR Sjögren's syndrome disease activity index) is a clinical index measuring disease systemic activity in patients with PSS. It was developed in 2009 based on the consensus of 39 American and European experts in this disease under EULAR sponsorship [5, 6]. Today, it is used not only as a gold standard, but also as the main outcome measure in the majority of studies that measure systemic clinical activity in patients with PSS [7–11]. Moreover, it has been validated and proven itself highly reproducible and sensitive to changes [12].

There has been great interest in PSS in Spain in recent years, thanks to the initiative of research groups such as GEMESS that are interested in autoimmune and systemic pathologies [13, 14]. Such research enjoys the support of scientific associations like the Spanish Rheumatology Association (SER—Spanish acronym), particularly with the SJÖGRENSER registry.

The aim of this paper is to assess the baseline characteristics of ESSDAI in Spanish patients with PSS in the SJÖGRENSER, the registry being used at rheumatology units.

Methods

SJÖGRENSER

SJÖGRENSER is a prospective multicentric register of patients with PSS, who meet the 2002 American–European classification criteria and who were attended at Spanish Rheumatology outpatient centres [15]. This article presents the baseline results of ESSDAI.

The main aims of SJÖGRENSER are to describe patients with PSS: (1) clinical characteristics with special emphasis on activity and seriousness; (2) biological characteristics; (3) specific co-morbidities and their frequency; and (4) disease treatment, methodology and initial results, which have already been published [15].

SJÖGRENSER began in 2013 and included 437 patients diagnosed with PSS from 33 Spanish rheumatology units, according to the 2002 American–European consensus classification criteria [14]. Basic data were obtained by reviewing clinical records and doctor's interviews with patients. Researchers excluded those patients they considered might have difficulty attending appointments or completing the forms, as well as those individuals meeting the 2002 exclusion criteria.

Each participating centre anonymously sent a list of patients undergoing outpatient follow-up and meeting the SER selection criteria to the Research Unit (IU-SER). To obtain a representative sample and limit possible selection bias, a randomised sample was chosen from the patient list of each centre and remitted to each for recruitment. Finally, a percentage of those chosen at random were monitored in the participating centre [15].

Variables

298 variables were collected for the global registry which included the following data: epidemiological, disease co-morbidities at the clinical level, complications, treatment, etc.

The degree of cohort affectation, activity and damage were measured using different validated indexes, namely: SSDAI (Sjögren's syndrome disease activity index), SSDDI (Sjögren's syndrome disease damage index) and ESSDAI.

This paper has included all the study patients in its analysis, bearing in mind the following variables: demographic (age and gender), clinical (clinical symptoms) and pharmacological (treatments used by patients in the registry).

Table 1 Results of the ESSDAI domains in 437 patients from the SJÖGRENSER cohort

ESSDAI domains (weight)	SJÖGRENSER *N* (%)
Constitutional (×3)	37 (8.47)
Fever during the last visit	
≥ 37.5 and < 38 °C	3 (0.69)
≥ 38 < and ≤ 38.5 °C	2 (0.46)
> 38.5 °C	0 (0)
Night sweats	18 (4.12)
Involuntary weight loss	
< 5%	9 (2.06)
5–10%	5 (1.14)
> 10% (Infectious fever and voluntary weight loss excluded)	0 (0)
Lymphadenopathy (×4)	10 (2.29)
≥ 1 cm in any lymph node chain o ≥ 2 cm in the inguinal region	9 (2.06)
≥ 2 cm in any lymph node chain o ≥ 3 cm in the inguinal region and/or splenomegaly	0 (0)
Malignant B cell proliferative disorder (infection excluded)	1 (0.23)
Glandular (×2)	19 (4.35)
Parotid gland enlargement ≤ 3 cm	17 (3.89)
Parotid gland enlargement > 3 cm (stone and infection excluded)	2 (0.46)
Articular (×2)	154 (35.24)
Arthralgia in hands, carpal bones, elbows, feet, with morning stiffness > 30 min	141 (32.27)
Synovitis in 1 to 5 joints	13 (2.97)
Synovitis > 5 joints (arthrosis excluded)	0 (0)
Cutaneous (×3)	14 (3.14)
Erythaema multiforme	3 (0.69)
Skin limited vasculitis	8 (1.83)
Skin diffuse vasculitis (should be marked "inactive" if stable or long duration related to damage)	3 (0.69)
Muscular (×6)	1 (0.23)
EMG or biopsy-proven myositis, without weakness and normal or slightly raised CK (CK ≤ twice normal) (excluding weakness due to corticoids)	1 (0.23)
Pulmonary (×5)	25 (5.72)
Cough or bronchial problem with no radiological findings of disease or	8 (1.83)
shortness of breath and normal lung function test	
HRCT-proven interstitial disease with shortness of breath (NHYA II) or lung function test: 70%>DLCO ≥ 40% or 80%>FVC ≥ 60	14 (3.20)
HRCT-proven interstitial disease with shortness of breath (NHYA III-IV) or lung function test: DLCO < 40% or FVC < 60% (mark 'no activity' if stable or long evolution related to pulmonary damage or affectation if not disease related)	3 (0.69)
Renal (×5)	23 (5.26)
Increase in serum creatinine	14 (3.20)
Tubular acidosis without kidney failure, or glomerular affectation with proteinuria between 0.5 and 1 g/day and without haematuria or kidney failure	2 (0.46)
Tubular acidosis with kidney failure, or glomerular affectation with proteinuria between 0.5 and 1 g/day and without haematuria or kidney failure (GFR ≥ 60 ml/min), or histological evidence of extramembranous GN or important interstitial lymphoid infiltrate	5 (1.14)
Glomerular affectation with proteinuria > 1.5 g/day or haematuria or kidney failure of histological evidence of proliferative GN or kidney affectation due to cryoglobulinaemia (mark as "no activity" if stable or long evolution with kidney damage or affectation not related to the disease. If kidney biopsy performed, mark activity as per result.)	2 (0.46)
Central nervous system (×5)	7 (1.61)
Affectation of a cranial nerve with central origin, optical neuritis, MS-like solely with sensitive or cognitive symptoms	4 (0.92)
Cerebral vasculitis with stroke or transitory ischaemic attack, infarctions, transversal myelitis, lymphocytic meningitis, MS-like with motor deficit (mark as 'no activity' if stable or long evolution with central neurological damage or affectation not related to the disease)	3 (0.69)
Peripheral nervous system (×5)	15 (3.43)

Table 1 (continued)

ESSDAI domains (weight)	SJÖGRENSER *N* (%)
Sensorial axonal polyneuropathy objectified in ENG or trigeminal neuralgia	5 (1.14)
ENG objectified: motor-sensitive axonal neuropathy (max. deficit 4/5), pure sensorial axonal neuropathy with the presence of cryoglobulinaemic vasculitis, ganglionopathy (mild–moderate ataxia), mild inflammatory demyelinating polyneuropathy (deficit 4/5 or mild ataxia), affectation of cranial nerve with peripheral origin (except trigeminal)	7 (1.60)
ENG objectified: motor-sensitive axonal neuropathy (deficit ≤ 3/5), peripheral nerve affectation due to vasculitis (multiple mononeuritis, etc.), ganglionopathy with severe ataxia symptoms, severe demyelinating polyneuropathy (deficit ≤ 3/5 or severe ataxia) (mark as "no activity" if stable or long evolution with peripheral neurological damage or affectation not related to the disease)	3 (0.69)
Haematological (x2)	137 (44.62)
Anaemia	
Haemoglobin > 10 g/dl	54 (12.36)
Haemoglobin > 7 g/dl and < 11 g/dl	9 (2.06)
Haemoglobin < 8 g/dl	0 (0)
Lymphopaenia	
> 500/mm^3 and < 1001/mm^3	33 (13.47)
≤ 500/mm^3	1 (0.41)
Neutropaenia	
> 1000/mm^3 and < 1500/mm^3	14 (5.71)
> 499/mm^3 and < 1001/mm^3	4 (1.63)
< 500/mm^3	0 (0)
Thrombocytopaenia	
> 100.000/mm^3 and < 150.000/mm^3	13 (5.31)
> 49.000/mm^3 and < 101.000/mm^3	6 (2.45)
< 50.000/mm^3 (excluding iron and vitamin deficiency, likewise drug-related cytopaenia. Considering only immunological origin cytopaenia)	3 (1.22)
Biological (×1)	120 (27.46)
Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia and/or raised IgG (between 16 and 20 g/L)	102 (23.34)
Cryoglobulinaemia and/or hypergammaglobulinaemia and/or raised IgG > 20 g/L, and/or recent hypogammaglobulinaemia or recent reduced IgG (< 5 g/L)	18 (4.12)

ESSDAI Median Score (p25–p75): 2 (0–5)

ESSDAI EULAR Sjögren's syndrome disease activity index,*EMG* electromyography, *CK* creatinine kinase, *GN* glomerulonephritis, *HRCT* high resolution computer tomography, *NHYA* New York Heart Association, *DLCO* diffusing capacity of carbon monoxide, *FVC* forced vital capacity, *ENG* electroneurography

ESSDAI

ESSDAI includes 12 domains (Table 1), which reflect systemic activity in different organs and laboratory tests: constitutional, lymphadenopathy, glandular, haematological, biological, and organs: skin, joint, respiratory, kidney, muscular, central and peripheral nervous systems. Each domain is divided into 3–4 levels, according to degree of activity (0: no activity; 1: low activity; 2: moderate activity; 3: high activity) and the possible exclusion from the domain is defined in each. The weight of each level depends on the domain [5, 16].

The score per domain is obtained by multiplying the level of activity per weight assigned, which varies from 1 to 6. The final index score is the sum of all the domain scores. The result varies between 0 (no activity) and 123 maximum. To prevent chronic damage scoring per systemic activity, the score is considered 0 if the manifestation is due to irreversible damage that has remained unchanging for at least 12 months [5, 16].

Three disease activity grades are accepted according to the final ESSDAI scoring classification: (a) low activity: < 5 points; (b) moderate activity: 5–13 points; (c) high activity: ≥ 14 points (6). Minimum improvement as measured by ESSDAI is considered 3 points.

Statistical analysis

Descriptive statistics were used to analyse variables. The average, standard deviation or median and interquartile ranges were calculated [p25–p75] for continuous numerical variables. Frequencies were estimated as n percentages for

the different ESSDAI domains with a confidence interval of 95% (CI 95%).

Results

Of the 437 patients included, 416 were women (95.2%), with a mean age on entering the study of 58.63 years (p25–p75: 50.02–67.98 years). The average age for onset of the first symptom of the disease, and when diagnosed age of PSS diagnosis, was 46.58 years (36.48–54.47 years) and 50.24 years (42.99–58.29 years), respectively. The evolution of the disease was 10.4 years (range: 6–16 years).

The average 2002 PSS classification criteria was 5 [4, 5], of a possible 6. Most patients suffered from dry syndrome, i.e, 94% xerostomia or xerophthalmia symptoms. In 85% of the 371 patients who underwent the Schirmer test (normal value: ≤5 mm in 5 min) and 27% of the 119 patients who underwent the non-stimulated saliva flow (normal value: ≤1.5 ml in 15 min), the results were deemed pathological. Thirty-four percent of the patients had persistent or recurrent inflammation of the saliva glands.

In the 133 (30.44%) patients who underwent lip biopsy, the results were positive. Anti-Ro and anti-La presence was detected in 93.59% and 67.05% of the patients, respectively. The reduced number of lip biopsies performed contrasts with the large percentage of patients with anti-Ro, over 90%.

62% and 65% were positive for rheumatoid factor and antinuclear antibodies, respectively. 27% of patients had some kind of cytopaenia, 23% hypocomplementaemia, 22% raised microglobulin level and cryoglobulin was detected in 3%.

Regarding pharmacological treatment, 20% of patients received corticoids; the most commonly used DMARDs were: hydroxychloroquine ([HCQ] 28%), methotrexate ([MTX] 7%) and azathioprine ([AZA] 6%). Rituximab (RTX) was the most commonly administered biological drug (4.3%) (Table 2).

ESSDAI

The cohort ESSDAI median on entering the study was 2 [0–4]. The most frequent domain was articular (35%), followed by biological (28%) and haematological (27%). The domains present in at least 5% of patients or more were as follows: constitutional (8%) and pulmonary affectation (6%) and renal (5%). The other domains appeared in less than 5% of cases (Tables 1, 2).

Regarding ESSDAI activity grade, 31% of SJÖGRENSER patients had 0 activity, low activity (ESSDAI: 1–4) 49%, moderate activity (ESSDAI: 5–13) 15% and high activity (≥ 14) 5%. Table 2 compares the SJÖGRENSER ESSDAI results with the EULAR patient cohort [6], the French ASSES [17], Spanish GEAS [18], Italian GRISS [19] and Dutch groups [20]. On comparing these patient groups, the results largely depended on the percentage of those included with greater or lesser systemic activity; i.e. the ESSDAI average of the GEAS group was 9; 6 in the EULAR and GRIS groups, where domains with affected organs were predominant, against the medians of 2 in the ASSES and SJÖGRENSER groups; and 1.5 in the Dutch study, in which the biological and haematological domains predominated (Table 2).

Discussion

The Spanish SJÖGRENSER registry was designed to characterise a representative cohort of Spanish patients with PSS in regular clinical practice, to analyse the magnitude and distribution of its clinical symptoms, biological characteristics, disease activity and damaged accumulated, associated comorbidities and pharmacological and non-pharmacological treatments [15].

This paper shows the results of the first cross-sectional stage of the ESSDAI activity index in a cohort of patients with PSS, undergoing follow-up at Spanish rheumatology units in clinical practice without interference and an approximate disease evolution of 10 years. Stage 2 or evolution will be starting shortly with the collection of prospective data from this population at the 5 years mark.

In clinical practice, most PSS patients do not present systemic activity; however, at least 30% will develop it during evolution [15]. In the SJÖGRENSER cohort, over 90% suffered from dry eye and mouth, as with the majority of PSS patient cohorts published. A relevant SJÖGRENSER fact is that 31% of patients did not present any activity, with an ESSDAI 0 result of 0. Half of the patients had low activity and only 20% had moderate or high activity. In our patients, the most frequent domains at over 10% were as follows: articular, biological and haematological. Therefore, it will be interesting to check the evolution of these patients in clinical practice.

In recent years, several international cohorts have assessed the ESSDAI results and used this index to evaluate and compare drug response and efficacy, especially immunosuppressants and biological therapy in clinical trials and studies [6–11, 21–25].

The EULAR cohort is a collaborative project in itself and from 2009 to 2011 included 395 patients with PSS diagnosed as per the 2002 American–European consensus classification criteria, in which at least 50% of patients must have systemic pathology [6]. The aim was ESSDAI validation of a 6 month study. On inclusion, 61% of patients already had an ESSDAI ≥ 5, of moderate or high activity; therefore, they presented a systemic domain predominance unlike

Table 2 Comparison of ESSDAI domains and other relevant data among patient cohorts with PSS

	SJÖG-RENSER [15] *N*: 437	EULAR [5, 6] *N*: 395	ASSES [17] *N*: 395	GEAS [18] *N*: 921	GRISS [19] *N*: 826	Risselada [20] *N*: 195
ESSDAI Domains, %						
Constitutional	8	14	4	12	14	2 (1)
Lymphadenopathy	2	9	2	10	28	6 (3)
Glandular	4	29	12	34	28	15 (8)
Articular	35	37	19	56	61	10 (5)
Cutaneous	3	29	4	13	14	8 (4)
Muscular	0.2	5	3	1	1	1 (1)
Pulmonary	6	14	14	15	7	2 (1)
Renal	5	14	3	4	3	1 (1)
CNS	2	4	2	3	2	3 (2)
PNS	3	10	10	10	6	0 (0)
Haematological	27	24	16	12	28	35 (18)
Biological	28	55	17	12	54	120 (62)
ESSDAI	2 [0–5]	6 [2–12]	2 [0–7]	9 ± 2.0	6 (0–63)*	1.5 (0–43)*
ESSDAI = 0, *n* (%)	135 (31)	–	–	74 (8)	–	
Others						
PSS evolution, mean years	10 (6–16)*	6 [2–12]	5 [2–9]	6.8 (0.5–30)**	–	–
Positive biopsy, *n* (%)	133/437(30)	230/250 (96.5)	318/352 (88)	424/482 (88)	–	–
Anti-Ro, *n* (%)	409 (94)	313 (79)	233 (59)	666 (73)	580 (70)	–
Anti-La, *n* (%)	293 (67)	202 (48)	132 (33.5)	419 (46)	295 (36)	–
Cryoglobulins, *n* (%)	13 (3)	–	57 (17)	81 (12)	73 (9)	–
Low C3 or C4, *n* (%)	102 (23)	–	72 (19)	–	174 (21)	–
B2-Raised microglobulin, *n* (%)	97 (22)	–	–	–	–	–
Treatment, *n* (%)						–
Corticoids	88 (20)	96 (24)	94 (24)	353 (38)	–	–
Hydroxychloro-quine	122 (28)	115 (29)	121 (31)	225 (24)	–	–
Methotrexate	30 (7)	16 (4)	20 (5)	–	–	–
Leflunomide	7 (2)	–	2 (0.5)	–	–	–
Azathioprine	28 (6)	13 (3)	6 (1.5)	–	–	–
Mycophenolate	11 (2.5)	–	5 (1)	–	–	–
Cyclophosphamide	4 (1)	–	–	–	–	–
Anti-TNF	4 (0.9)	–	–	–	–	–
Rituximab	19 (4)	12 (3)	4 (1)	36 (4)	–	–
Abatacept	2 (0.5)	–	–	–	–	–
Tocilizumab	1 (0.2)	–	–	–	–	–

Results are expressed as: median [p25–p75]

EULAR: European League Against Rheumatism. ASSESS: Assessment of Systemic Signs and Evolution of SS. GEAS: Systemic Autoimmune Diseases Group. GRISS: Italian research group for Sjögren's syndrome. ESSDAI: EULAR Sjögren's syndrome disease activity index

Median and range (*), average ± DE, average and range (**), percentage (%)

SJÖGRENSER, except in the case of the articular domain, which is very similar. Furthermore, almost all of the EULAR cohort patients had undergone a lip biopsy, probably in accordance with protocol, and yet surprisingly the anti-Ro and anti-La percentages were lower than the SJÖGRENSER. The high positivity of anti-Ro in the SJÖGRENSER cohort most likely explains the low percentage of lip biopsies performed since, as the patients presented 3 of the classification criteria in addition to anti-Ro or anti-La positivity, the biopsy would be unnecessary for classification.

Regarding the therapy used, the percentage of patients being treated with corticoids and HCQ was similar in both. Nevertheless, despite presenting fewer systemic complications, a greater percentage of the SJÖGRENSER cohort patients were still being treated with MTX, AZA or other immunosuppressant and biological therapies including RTX. Immunosuppressants in general, and MTX in particular, as well as biological therapies are frequently prescribed in clinical practice by rheumatologists, e.g. in patients with chronic arthritis.

The French cohort ASSES (Assessment of Systemic Signs and Evolution in Sjögren's Syndrome) included 395 patients with PSS, 30% of whom had systemic complications [17]. A prospective multicentric study, ongoing since 2009, has sought to determine whether different biomarkers can predict systemic complications, including lymphoma. The patients were drawn from 15 rheumatology and internal medicine units, and ESSDAI was used to analyse the systemic activity of the disease. The ESSDAI median was 2 [0–7], which was very similar to that of the SJÖGRENSER patients. The glandular, muscular, pulmonary and peripheral nervous system domains had predominance. This contrasts with the SJÖGRENSER cohort, in which constitutional, articular, haematological and biological domains predominated, characterised yet again by the anti-Ro and anti-La percentages described previously. The percentage of patients treated with corticoids, MTX and HCQ was similar in both groups, although in the SJÖGRENSER cohort, a higher percentage of patients continue being treated with AZA or other immunosuppressant drug and biological therapy, including RTX.

The GEAS (Systemic Autoimmune Diseases Group) cohort, comprising 20 Spanish internal medicine units, included 921 patients diagnosed with PSS as (per the 2002 classification criteria), who were undergoing prospective follow-up in current clinical practice setting [18]. The average PSS evolution in this cohort was 6.8 years. ESSDAI was calculated according to the PSS diagnosis (basic), the onset of new systemic pathology during evolution (incident) and the last visit (accumulative). Although in calculating basic ESSDAI they included the 12 standard domains, when it came to the incident and accumulative ESSDAI, they excluded the biological and haematological domains. The average ESSDAI on diagnosis in the GEAS cohort was 5.81 and at the last follow-up appointment, it was 9.81, which is considerably higher than the results obtained in the EULAR, ASSES and SJÖGRENSER cohorts. This is likely due to the fact that the GEAS cohort was drawn from internal medicine departments. Thus, a significant percentage of patients can be admitted to hospital due to systemic manifestations, which would add at least 5 points in to the said domains. Another intriguing aspect that explains the GEAS cohort characteristics in relation to the SJÖGRENSER cohort is the percentage of patients with an ESSDAI = 0. In the GEAS cohort, 18% of patients had ESSDAI = 0 at diagnosis, which dropped to 8% with the last appointment included, and was 31% in the retrospective phases of the SJÖGRENSER cohort (this data was not described in the EULAR and ASSES cohorts). Thus, these two populations differ greatly, rendering the prospective phase of patients without activity or with low activity more interesting. As with the EULAR and ASSES cohorts, but unlike SJÖGRENSER, a large percentage of GEAS cohort patients underwent saliva gland biopsy, which was positive in 88% of the patients. However, the positive anti-Ro and/or anti-La were lower than those of SJÖGRENSER. An explanation for this aspect might be that we are unaware of the positivity level reached in these antibodies in the different cohorts, or it might be related to the sensitivity of the kits used and might include some false positive cases.

Various registries have recently been published essentially to describe the ESSDAI results. The Italian group GRISS (19) retrospectively assessed 825 patients with PSS from five centres. The median ESSDAI was 6, with a predominance of articular and biological domains in over half of the patients.

The British registry UKPSSR (UK Primary Sjögren´s Syndrome Registry) [26], included 665 patients with PSS recruited from 2009 and analysed in 2013. They observed that ESSDAI activity was low in 58% of patients, 0 in 17%, and high in 6%, results that are close to those obtained with SJÖGRENSER.

In the retrospective of a Dutch study [20], involving 195 patients with an average PSS evolution of 8 years, most patients presented low ESSDAI activity at the first (median: 2) and last (median: 1.5) appointments. Only 25% of patients had an ESSDAI ≥ 4. Biological and haematological domains predominated.

Regarding treatment, the percentage of patients treated with HCQ is similar among the cohorts described above. However, 38% of the GEAS cohort patients received corticoids versus 24% in the EULAR and ASSES cohorts, and 20% in SJÖGRENSER. The use of rituximab was similar to that of SJÖGRENSER and higher than that of the EULAR and ASSES cohorts. There are no specific data regarding MTX, other immunosuppressants or other biological

therapies. In the other studies analysed, there are no data regarding treatment administered.

The SJÖGRENSER cohort is apparently deemed the most representative of PSS patients who attended the Spanish rheumatology units in standard clinical practice settings, since it encompassed a large geographic area. Moreover, selection bias was mitigated due to its randomised design regarding patient inclusion and outsourced control of the participating units. In addition, data exploitation was supervised by the IU-SER. Nevertheless, this first stage suffers from some limitations, in that the primary information source consisted of the review of medical records and a patient interview. The latter was used to recover information regarding the use of treatments or past presentations or manifestations. With regard to laboratory results, different analytical techniques and procedures might have been used depending on the hospital.

In conclusion, SJÖGRENSER is characterised by low or absent systemic activity in 80% of patients, which differentiates it from other cohorts and, therefore, provides an opportunity for prospective study. ESSDAI is an appropriate clinical tool not only for assessing systemic activity in clinical practice in patients with PSS, but also for comparing results among different cohorts.

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Compliance with ethical standards

Conflict of interest None of the authors declare that they have conflict of interest in relation to this manuscript.

References

1. FoxX RI (2005) Sjögren's syndrome. Lancet 366:321–331
2. Moutsopoulos (1994) Sjögren's syndrome: autoimmune epithelitis. Clin Immunol Immunopathol 72:162–165
3. Aagyropoulou O, Valentini E, Ferro F et al (2018) One year in review 2018: Sjögren's syndrome. Clin Exp Rheumatol 36(Suppl 112):27–28
4. Qin B, Wang J, Yang Z et al (2015) Epidemiology of primary Sjögren's syndrome: A systematic review and meta-analysis. Ann Rheum Dis 74:1983–1989
5. Seror R, Ravaud P, Bowman SJ et al (2010) EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 69:1103–1109
6. Seror R, Bootsma H, Saraux A et al (2016) Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 75:382–389
7. Souza FB, Porfirio GJ, Andriolo BN et al (2016) Rituximab effectiveness and safety for treating primary Sjögren's Syndrome (pSS): systematic review and meta-analysis. PLoS One 11:e0150749
8. Carubbi F, Cipriani P, Marelli A et al (2013) Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther 15:R172
9. Mekinian A, Ravaud P, Hatron PY et al (2012) Efficacy of rituximab in primary Sjögren's syndrome with peripheral nervous system involvement: results from the AIR registry. Ann Rheum Dis 71:84–87
10. Gottenberg JE, Cinquetti G, Larroche C et al (2013) Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the autoimmune and Rituximab registry. Ann Rheum Dis 72:1026–1031
11. Meiners PM, Arends S, Brouwer E et al (2012) Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 71:1297–1302
12. Seror R, Mariette X, Bowman S et al (2010) Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. Arthritis Care Res (Hoboken) 62:551–558
13. Ramos-Casals M, Solans R, Rosas J et al (2008) Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine 87:210–219
14. Vitali C, Bombardieri S, Jonsson R et al (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61:554–558
15. Fernández Castro M, Andreu JL, Sánchez-Piedra C et al (2016) Sjögren-SER: National registry of the Spanish Society of Rheumatology of patients with primary Sjögren syndrome: objectives and methodology. Reumatol Clin 12:184–189
16. Seror R, Bowman SJ, Brito-Zerón P et al (2015) EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 1:e000022
17. Gottenberg JE, Seror R, Micelli-Richard C et al (2013) Serum levels of Beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's Syndrome. Data at enrollment in the prospective ASSESS Cohort. PLoS One 8:e59868. https://doi.org/10.1371/journal.pone.0059868

18. Ramos-Casals M, Brito-Zerón P, Solans R et al (2014) Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology 53:321–331
19. Quartuccio L, Baldini C, Priori R et al (2017) Cryoglobulinemia in Sjögren's Syndrome: a disease subset that links higher systemic disease activity, autoimmunity, and local B cell proliferation in mucosa-associated lymphoid tissue. J Rheumatol 44:1179–1183
20. Risselada AO, Kruize AA, Bijlsma JWJ (2012) Clinical applicability of the EULAR Sjögren's syndrome disease activity index: a cumulative ESSDAI score adds in describing disease severity. Ann Rheum Dis 71:631–632
21. Moerman RV, Arends S, Meiners PM et al (2014) EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomized controlled trial. Ann Rheum Dis 73:472–474
22. Mariette X, Roux S, Zhang J et al (2003) The level of BLyS (BAFF) correlates with the titer of autoantibodies in human Sjögren's syndrome. Ann Rheum Dis 62:168–171
23. De Vita S, Quartuccio L, Seror R et al (2015) Efficacy and safety of belimumab given for 12 months in primary Sjögren's syndrome: the BELISS open-label phase II study. Rheumatology. (Oxford) 54:2249–2256
24. Quartuccio L, Salvin S, Corazza L et al (2016) Efficacy of belimumab and targeting of rheumatoid factor-positive B-cell expansion in Sjögren's syndrome: follow-up after the end of the phase II open-label BELISS study. Clin Exp Rheumatol 34:311–314
25. Meiners PM, Vissink A, Kroese FG et al (2014) Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 73:1393–1396
26. Dumusc A, Wan-Fai NG, James K et al (2018) Comparison of ESSDAI and ClinESSDAI in potential optimization of trial outcomes in primary Sjögren's syndrome: examination of data from the UK Primary Sjögren's Syndrome Registry. Swiss Med Wkly 148:w14588