Sjögren SER: National registry of the Spanish Society of Rheumatology of patients with primary Sjögren syndrome: objectives and methodology

The Spanish Society of Rheumatology (SER (Sociedad Española de Reumatología) has promoted its first registry of Primary Sjögren's syndrome (pSS) patients (SJÖGREN'S-SER), an initiative of its working group on systemic autoimmune diseases (EAS-SER), with the methodological support and supervision of the SER research unit (RU-SER). SJÖGREN'S-SER is a descriptive, multicenter study of pSS patients who meet the consensus classification criteria of 2002. The 1-year cross-sectional phase, during which the patients were enrolled, has been completed.

Patients and methods

SJÖGREN'S-SER is a Spanish retrospective multicentre registry of pSS patients who meet the American-European classification criteria of 2002 being treated in Spanish rheumatology outpatient clinics. The data were obtained from the review of medical records and from interviews between physicians and patients, and were collected using an electronic format.

Objectives

The primary objectives of SJÖGREN'S-SER were to describe the pSS patients included in the registry, providing data on:

- Their clinical characteristics, with special reference to disease activity and severity,
- The biological characteristics.
- Specific comorbidities and their incidence.
- Disease management.

The secondary objectives of SJÖGREN'S-SER were:

- To establish a database including patients in the participating hospitals that could serve as a basis for future studies.
- Establish a consortium of centres interested in pSS that could take part in collaborative projects on the disease.

Patient selection

The study included pSS patients who met the 2002 American/European classification criteria, were at least 18 years old and in full command of their faculties in terms of their ability to formulate responses and participate in the collection of the requested data, and were being treated in rheumatology departments, mainly of hospitals, but also of tertiary care centres that take part in the EAS-SER group. It did not include patients who, in the opinion of the investigator, could find it difficult to keep appointments or complete forms, or those who met any ofthe exclusion criteria specified in the 2002 consensus classification criteria (head and neck radiation therapy, hepatitis C virus or human immunodeficiency virus infection, pre-existing lymphoma, sarcoidosis, graft-versus-host disease or the use of anticholinergic drugs).

The collaborating researchers were rheumatologists with extensive experience in the care and management of pSS patients. All the hospitals participating in the study created a database according to the model provided by the coordinators of the project, guaranteeing anonymity, in which they included all the pSS patients who were being seen in the department who met the inclusion criteria. For this, they used administrative databases or their own files. The list of patients fromeach center was sentto the RU-SER. To obtain a representative sample, without selection biases, the list of anonymous patients from each centre was subjected to randomised sampling and the resulting randomised list was sent to each rheumatology department for successive recruitment. Each researcher contacted the randomly selected patients in consecutive order according to the randomisation list provided, and proposed their participation in the study. Those patients who refused to participate were replaced by the next patient in the randomisation list and underwent a brief structured interview during which a series of minimum basic data was collected.

Data collection

To facilitate data collection, we developed an investigator's handbook and a quick guide to the questions to ask each patient on the day of his or her visit. The patients were asked to complete self-administered questionnaires on the day they were enrolled in the study. A software application was designed expressly for the registry and data storage. A user manual was prepared with instructions for the researchers. The software application has filters, ranges, menus and help dialogues to enhance data reliability. A member of the RU-SER was appointed as database administrator and monitor. Different strategies were employed to ensure adequate data quality control. First, a pilot study was conducted to evaluate difficulties and problems involving the electronic data collection notebook (DCN) and the web-based platform. The results of this study made it possible to introduce the modifications required to ensure the comprehensibility of the DCN and greater simplicity in its use. Second, an investigator's handbook was prepared to describe and standardise the processes involved in the study and to solve possible doubts that could arise when introducing data in the DCN. This handbook also included information on controlling lost data during follow-up and the processes of verification and quality control of the data. Third, in situ monitoring was carried out by monitors accredited in the RU-SER from a percentage of randomly selected centers. The filters of the DCN prevented the inclusion of values that fell out of the range and of lost values.

Variables

The primary objective of the registry is to obtain a characterisation as accurate and complete as possible of the clinical signs, features of the disease course and patterns in the development of comorbidities in our pSS patients, as well as their management. Thus, we did not define a specific main outcome variable in this study, with the limitations that this implies. We included 298 variables, which are provided below. For the description of the patients and to be able to analyse subgroups or modifiers and confounding factors, we included the following sociodemographic data: sex, race, level of education, date of birth, date of pSS symptom onset, date

Supplementary Table S1. Comparative study between pSS patients with and without biopsy-proven renal involvement.

	Patients with renal disease (n=9)	Patients without renal disease (n=428)	*p*
Age, years (mean ± SD)	61.8 ± 11.1	58.6 ± 12.9	0.466
Sex, woman/man, n (%)	8 (88.9%) / 1 (11.1%)	408 (95.3%) / 20 (4.7%)	0.371
Disease duration at inclusion, years (mean ± SD)	15 ± 12.3	5 ± 5.2	0.766
Histopathology in minor salivary gland*, n (%)	4 (44.4%)	170 (39.7%)	0.726
Glandular inflammation/Salivary gland enlargement, n (%)	3 (33.3%)	139 (32.5%)	0.957
Otorhinolaryngological involvement, n (%)	6 (66.7%)	201 (47%)	0.241
Upper airways involvement, n (%)	4 (44.4%)	80 (18.7%)	0.053
Urogenital manifestations, n (%)	6 (66.7%)	208 (48.6%)	0.283
Constitutional symptoms, n (%)	6 (66.7%)	72 (16.8%)	<0.001
Lymphadenopathy, n (%)	2 (22.2%)	67 (15.7%)	0.593
Splenomegaly, n (%)	0 (0%)	4 (0.9%)	0.771
Arthritis/Arthralgia, n (%)	4 (44.4%) / 8 (88.9%)	147 (34.3%) / 345 (80.6%)	0.528/0.533
Myopathy, n (%)	0 (0%)	10 (2.3%)	0.643
Raynaud's phenomenon, n (%)	2 (22.2%)	90 (21%)	0.931
Non vasculitic cutaneous involvement, n (%)	3 (33.3%)	11 (2.5)	<0.001
Annular erythema, n (%)	0 (0%)	5 (1.2%)	0.744
Multiform erythema, n (%)	3 (33.3%)	6 (1.4%)	<0.001
Vasculitis, n (%)	3 (33.3%)	37 (8.7%)	0.011
Lung involvement, n (%)	1 (11.1%)	42 (9.8%)	0.899
Gastrointestinal involvement, n (%)	2 (22.2%)	57 (13.3%)	0.439
Hepatitis, n (%)	1 (11.1%)	32 (7.5%)	0.683
Cardiac disease, n (%)	0 (0%)	13 (3%)	0.595
Peripheral neuropathy, n (%)	4 (44.4%)	35 (8.2%)	<0.001
Central nervous system involvement, n (%)	0 (0%)	34 (8%)	0.378
Haematologic abnormalities, n (%)	8 (88.9%)	236 (55.1%)	0.044
Lymphoma, n (%)	0 (0%)	7 (1.6%)	0.699
ESSDAI score (mean ± SD)	8.33 ± 6.7	7.67 ± 4.3	0.03
Positive antinuclear antibodies (ANA), n (%)	9 (100%)	415 (97%)	0.596
Positive test for anti-Ro/SSA, n (%)	9 (100%)	400 (93.5%)	0.428
Positive test for anti-La/SSB, n (%)	8 (88.9%)	285 (66.6%)	0.159
Positive rheumatoid factor, n (%)	9 (100%)	275 (65.8%)	0.031
Low C3 levels, n (%)	4 (44.4%)	61 (15.1%)	0.017
Low C4 levels, n (%)	2 (22.2%)	60 (14.9%)	0.543
Hypergammaglobulinaemia, n (%)	8 (88.9%)	222 (54%)	0.038
Positive cryoglobulins, n (%)	1 (16.7%)	13 (6.8%)	0.358
Antiphospholipid antibody (aPL) positivity, n (%)	0 (0%)	26 (6.1%)	0.240

* Focal lymphocytic sialoadenitis evaluated by an expert histopathologist, with a focus score ≥ 1.

of diagnosis of pSS and date of inclusion in the registry. Using these dates, we calculated different age-related variables (age at the time of diagnosis, at enrollment in the cohort and at disease onset) and the duration of the disease. Data were gathered on different aspects that make it possible to characterise the disease, including the presence of each of the 2002 classification criteria (oral and ocular symptoms and signs, histopathology and compatible antibodies), the presence of clinical manifestations of pSS (gland and genital involvement; ear, nose and throat involvement; fatigue; cachexia; splenomegaly; lymphadenopathy; joint, muscle and skin involvement; Raynaud's phenomenon; airway, pulmonary, renal, central and peripheral nervous system, haematological, gastrointestinal, cardiac and thyroid involvement); abnormal serological findings (erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, antinuclear antibodies, anti-Ro and anti-La antibodies, complement 3 and complement 4, immunoglobulins, cryoglobulins, 2-microglobulin, and anti-DNA, anti-Sm, anti-ribonucleoprotein and antiphospholipid antibodies); and hospital admissions and comorbidities (tobacco use, hypertension, diabetes mellitus, dyslipidemia, heart failure, ischaemic heart disease, peripheral arterial disease, stroke, multiple sclerosis, coeliac disease, fibromyalgia, osteoporosis, osteoporotic fracture, osteonecrosis and neoplasm). We included drug and non-drug therapies used for the management of pSS and its complications, categorised on the basis of oral, cutaneous, nasal or vaginal involvement, Raynaud's phenomenon, systemic involvement and eye surgery. The degree of involvement, activity and damage were measured using different validated indices. Some of these questionnaires are self-administered and were completed by the patients on the day they visited their rheumatologists, whereas others were calculated on the basis of the information gathered from the medical records and registered in the database developed specifically for this study. These indices were the Sjögren's Syndrome Disease Activity Index (SSDAI), the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the Sjögren's Syndrome Disease Damage Index (SSDDI).

Statistical analysis

Given that there is no single main outcome variable, we assume that we want an accuracy of 1.5% to detect signs of pSS for an expected prevalence of around 2.5%. Accepting a type I error of 0.05 for an accuracy of 0.015 percent units, in a two-sided test for an estimated proportion of 0.025, we would need a population size of 417 individuals, which, moreover, is a realistic prediction of the total number of patients that could be included.

Ethical aspects

The present study complies with the Declaration of Helsinki and its subsequent revisions. All the participating patients have been duly informed and have completed and signed in duplicate the informed consent form. The participating centers assigned an identification number to each patient to maintain the confidentiality of the data in accordance with the current legislation (Royal Decree 1720/2007, a further development of Organic Law 15/1999, dated December 13, regarding the protection of personal data). The project was approved by the ethics committee of the hospital of the principal investigators and by the ethics committees of the participating hospitals.