university of groningen

University Medical Center Groningen

University of Groningen

How immunological profile drives clinical phenotype of primary Sjogren's syndrome at diagnosis

Sjogren Big Data Consortium; Brito-Zeron, P.; Acar-Denizli, N.; Ng, W. F.; Zeher, M.; Rasmussen, A.; Mandl, T.; Seror, R.; Li, X.; Baldini, C.

Published in:
Clinical and Experimental Rheumatology

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Sjogren Big Data Consortium, Brito-Zeron, P., Acar-Denizli, N., Ng, W. F., Zeher, M., Rasmussen, A., Mandl, T., Seror, R., Li, X., Baldini, C., Gottenberg, J. -E., Danda, D., Quartuccio, L., Priori, R., Hernandez-Molina, G., Armagan, B., Kruize, A. A., Kwok, S. -K., Kvarnstrom, M., ... Wahren-Herlenius, M. (2018). How immunological profile drives clinical phenotype of primary Sjogren's syndrome at diagnosis: analysis of 10,500 patients (Sjogren Big Data Project). *Clinical and Experimental Rheumatology*, *36*(3), S102-S112. https://www.clinexprheumatol.org/abstract.asp?a=12899

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project)

P. Brito-Zerón[1,2], N. Acar-Denizli[3], W.F. Ng[4], M. Zeher[5], A. Rasmussen[6], T. Mandl[7], R. Seror[8], X. Li[9], C. Baldini[10], J.-E. Gottenberg[11], D. Danda[12], L. Quartuccio[13], R. Priori[14], G. Hernandez-Molina[15], B. Armagan[16], A.A. Kruize[17], S.-K. Kwok[18], M. Kvarnström[19], S. Praprotnik[20], D. Sène[21], E. Bartoloni[22], R. Solans[23], M. Rischmueller[24], Y. Suzuki[25], D.A. Isenberg[26], V. Valim[27], P. Wiland[28], G. Nordmark[29], G. Fraile[30], H. Bootsma[31], T. Nakamura[32], R. Giacomelli[33], V. Devauchelle-Pensec[34], A. Knopf[35], M. Bombardieri[36], V.-F. Trevisani[37], D. Hammenfors[38], S.G. Pasoto[39], S. Retamozo[40], T.A. Gheita[41], F. Atzeni[42], J. Morel[43], C. Vollenveider[44], I.-F. Horvath[5], K.L. Sivils[6], P. Olsson[7], S. De Vita[13], J. Sánchez-Guerrero[15], L. Kilic[16], M. Wahren-Herlenius[19], X. Mariette[8], M. Ramos-Casals[2], on behalf of the Sjögren Big Data Consortium*

Affiliations: see page S-110.

Pilar Brito-Zerón, Nihan Acar-Denizli, Wan-Fai Ng, Margit Zeher, Astrid Rasmussen, Thomas Mandl, Raphaele Seror, Xiaomei Li, Chiara Baldini, Jacques-Eric Gottenberg, Debashish Danda, Luca Quartuccio, Roberta Priori, Gabriela Hernandez-Molina, Berkan Armagan, Aike A. Kruize, Seung-Ki Kwok, Marika Kvarnström, Sonja Praprotnik, Damien Sène, Elena Bartoloni, Roser Solans, Maureen Rischmueller, Yasunori Suzuki, David A. Isenberg, Valeria Valim, Piotr Wiland, Gunnel Nordmark, Guadalupe Fraile, Hendrika Bootsma, Takashi Nakamura, Roberto Giacomelli, Valerie Devauchelle-Pensec, Andreas Knopf, Michele Bombardieri, Virginia-Fernandes Trevisani, Daniel Hammenfors, Sandra G. Pasoto, Soledad Retamozo, Tamer A. Gheita, Fabiola Atzeni, Jacques Morel, Cristina Vollenveider, Ildiko-Fanny Horvath, Kathy L. Sivils, Peter Olsson, Salvatore De Vita, Jorge Sánchez-Guerrero, Levent Kilic, Marie Wahren-Herlenius, Xavier Mariette, Manuel Ramos-Casals

**The members of the Sjögren Big Data Consortium are listed in Appendix 1.*

Please address correspondence to: Dr Manuel Ramos-Casals, Servei de Malalties Autoimmunes Sistèmiques, Hospital Clínic, C/Villarroel 170, 08036 Barcelona, Spain. E-mail: mramos@clinic.ub.es

Received on April 17, 2018; accepted on May 17, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 112): S102-S112.

© Copyright Clinical and Experimental Rheumatology 2018.

Key words: primary Sjögren's syndrome, salivary gland biopsy, Ro/La autoantibodies, hypocomplementaemia, cryoglobulinaemia, ESSDAI

Competing interests: none declared.

ABSTRACT

Objective. *To evaluate the influence of the main immunological markers on the disease phenotype at diagnosis in a large international cohort of patients with primary Sjögren's syndrome (SjS).*

Methods. *The Big Data Sjögren Project Consortium is an international, multicentre registry created in 2014. As a first step, baseline clinical information from leading centres on clinical research in SjS of the 5 continents was collected. The centres shared a harmonised data architecture and conducted cooperative online efforts in order to refine collected data under the coordination of a big data statistical team. Inclusion criteria were the fulfillment of the 2002 classification criteria. Immunological tests were carried out using standard commercial assays.*

Results. *By January 2018, the participant centres had included 10,500 valid patients from 22 countries. The cohort included 9,806 (93%) women and 694 (7%) men, with a mean age at diagnosis of primary SjS of 53 years, mainly White (78%) and included from European countries (71%). The frequency of positive immunological markers at diagnosis was 79.3% for ANA, 73.2% for anti-Ro, 48.6% for RF, 45.1% for anti-La, 13.4% for low C3 levels, 14.5% for low C4 levels and 7.3% for cryoglobulins. Positive autoantibodies (ANA, Ro, La) correlated with a positive result in salivary gland biopsy, while hypocomplementaemia and especially cryoglobulinaemia correlated with systemic activity (mean ESSDAI score of 17.7 for cryoglobulins, 11.3 for low C3 and 9.2 for low C4, in comparison with 3.8 for negative markers). The immunological markers with a great number of statistically-significant associations ($p<0.001$) in the organ-by-organ ESSDAI evaluation were cryoglobulins (9 domains), low C3 (8 domains), anti-La (7 domains) and low C4 (6 domains).*

Conclusion. *We confirm the strong influence of immunological markers on the phenotype of primary SjS at diagnosis in the largest multi-ethnic international cohort ever analysed, with a greater influence for cryoglobulinaemic-related markers in comparison with Ro/La autoantibodies and ANA. Immunological patterns play a central role in the phenotypic expression of the disease already at the time of diagnosis, and may guide physicians to design a specific personalised management during the follow-up of patients with primary SjS.*

Introduction

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease that mainly affects middle-aged women with a frequency in general population ranging between 0.01 and 0.72% (1). Etiopathogenically, the disease targets the exocrine glands that are infiltrated by lymphocytes (focal sialadenitis) (2). More than 95% of patients present with oral and/or ocular dryness (3), although

they may also develop a wide number of systemic (extraglandular) manifestations, which may be the first clinical manifestation of the disease (4).

Patients with primary SjS produce a wide variety of circulating autoantibodies directed to antigens either nuclear or cytoplasmic; in some cases, the target antigen is present within specific tissues. B lymphocyte hyperactivation, the most typical immunopathogenic peripheral abnormality of primary SS, accounts for these autoantibodies (5, 6). Immunological markers play a central role not only in the diagnosis of the disease, but also in predicting their outcome as prognostic markers (7). The key immunological markers are anti-Ro antibodies, as the most specific SjS-related autoantibody, and cryoglobulins and hypocomplementaemia, as the main prognostic markers (8). Among the variety of immunological markers, rheumatoid factor (RF) and anti-La antibodies are found in nearly half the patients with primary SjS, and although not included in the recent ACR/EULAR set of classification criteria (9), they should clinically be considered as key immunological markers of the disease (10, 11). Previous studies in large multicentre national registries have analysed the association between immunological markers and the clinical disease phenotype (3, 11-13), with heterogeneous results, although most identified patients carrying anti-Ro/La antibodies as the subset with the most clinically and immunologically "active" phenotype (14).

The objective of this study was to evaluate the influence of the main immunological markers on the disease phenotype at diagnosis in a large international cohort of patients with primary SjS.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry established in 2014 to take a "high-definition" picture of the main features of primary SjS following a worldwide data-sharing cooperative merging of pre-existing clinical SjS databases from leading centres on clinical research in SjS of the 5 continents (15). The centres share a harmonised data infrastructure and conduct cooperative online efforts in order to refine already collected data in each centre. Inclusion criteria were the fulfilment of the 2002 classification criteria (16). Exclusion criteria for considering SjS as a primary disease were chronic HCV/HIV infections, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SjS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group (17). The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

Disease diagnosis was defined as the time when the attending physician confirmed fulfilment of the 2002 criteria. At this time, the main features of the disease were retrospectively collected and analysed. The following clinical variables were selected in order to be harmonised and further refined: age, gender, ethnicity, country of residence, fulfilment of the 2002 criteria items, antinuclear antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and organ-by-organ ESSDAI scores. By January 2018, the participant centres had included 10,500 valid patients from 22 countries. Systemic involvement at diagnosis was retrospectively classified and scored according to the ESSDAI (18), which evaluates 12 domains or organ systems, and clinESSDAI (19), which evaluates the same domains but excluding the last (biological domain). Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity). Immunological tests were carried out using standard commercial assays (>95% of cases), using indirect immunofluorescence to detect ANA, ELISA to detect Ro/La antibodies, nephelometry for measuring RF and complement levels, and serum cryoglobulins by standard measure as previously described (20). We divided the results obtained according to the following two immunological subsets: patients with autoantibodies (ANA, Ro, La) and those presenting with cryoglobulin-related markers (RF, complement levels, cryoglobulins).

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. The Chi-square test was used to study the association between immunological markers with gender, diagnostic tests for SjS and systemic involvement. T-test was used to compare the mean age at diagnosis. All significance tests were two-tailed. *P*-values were adjusted for multiple comparisons using the false discovery rate (FDR) correction and values of $p<0.001$ were considered significant to avoid false positive significant results. A heatmap was constructed to represent the association pattern between immunological markers and disease phenotype. All analyses were conducted using the R V. 3.2.3 for Windows statistical software package (https://www.R-project.org/).

Results

The baseline characteristics of the cohort are summarised in Table I. The cohort included 9,806 (93%) women and 694 (7%) men (female: male ratio, 14:1), with a mean age at diagnosis of primary SjS of 53.1 (SD 14.1) years, mainly White (78%) and included predominantly from European countries (71%). Dry mouth was reported by 9,832 (94%) of patients, dry eyes by 9,684 (92%), abnormal ocular tests in 8,167/9,745 (84%), abnormal oral tests in 6,373/8,115 (78%) and positive salivary gland biopsy in 6,368/7,777 (82%) patients.

a) Phenotype of patients carrying autoantibodies

ANA+ patients: ANA were tested in 9,784 patients, and were positive in 7,749 (79%). ANA-positive patients had a lower mean age at diagnosis (52 *vs*. 56 yrs), a higher frequency of abnormal ocular tests (86% *vs*. 82%), positive biopsy (84% *vs*. 79%), mean

Table I. Baseline characteristics of 10,500 patients with primary Sjögren's syndrome.

Variable	Patients (%)
Gender (female)	9806 (93.4)
Age at diagnosis	53.1 ± 14.1
Dry eye	9684 (92.2)
Dry mouth	9832 (93.6)
Abnormal ocular tests	8167/9745 (83.8)
Schirmer's test	6668/8606 (77.5)
Rose bengal score/other ocular dye score	2916/3996 (73)
Positive minor salivary gland biopsy	6368/7777 (81.9)
Abnormal oral diagnostic tests	6373/8115 (78.5)
Unstimulated whole salivary flow	4727/6290 (75.2)
Parotid sialography	1718/2157 (79.6)
Salivary scintigraphy	1701/2084 (81.6)
Positive anti-Ro/La antibodies	7917/10420 (76)
Anti-Ro antibodies	7617/10417 (73.1)
Anti-La antibodies	4662/10362 (45)
ANA-positive	7749/9784 (79.2)
RF-positive	4245/8758 (48.5)
C3 low	1146/8573 (13.4)
C4 low	1234/8556 (14.4)
Positive cryoglobulins	342/4732 (7.2)
Ethnicity	
White	7862/10100 (78.0)
Asian	1345/10100 (13.3)
Hispanic	556/10100 (5.4)
Black/African-American	144/10100 (1.4)
Others	193/10100 (1.9)
Number of patients per continent	
Europe	7413 (70.6)
America	1445 (13.8)
Asia	1410 (13.4)
Africa	65 (0.6)
Australia	167 (1.6)
Number of countries per continent	
Europe	12
America	4
Asia	4
Africa	1
Australia	1

ESSDAI score (6.7 *vs*. 4.5) and a higher frequency of activity in the lymphadenopathy (10% *vs*. 5%), cutaneous (11% *vs*. 4%), haematological (25% *vs*. 11%) and biological (57% *vs*. 31%) ESSDAI domains in comparison with ANA-negative patients (Table II).

Ro+ patients: Ro autoantibodies were tested in 10,417 patients and were positive in 7,617 (73%). Ro-positive patients had a lower mean age at diagnosis (52 *vs*. 57 yrs), had a lower frequency of dry mouth (92% *vs*. 95%) and dry eyes (91% *vs*. 97%), a lower frequency of positive biopsy (74% *vs*. 96%), a higher mean ESSDAI score (6.7 *vs*. 4.7) and a higher frequency of activity in the constitutional (10% *vs*. 7%), cutaneous (11% *vs*. 5%), renal (5% *vs*. 2%), haematological (26% *vs*. 13%) and biological (58% *vs*. 31%) ESSDAI domains in comparison with Ro-negative patients (Table II).

La+ patients: La autoantibodies were tested in 10,362 patients and were positive in 4,662 (45%). La-positive patients had a lower mean age at diagnosis (51 *vs*. 54 yrs), had a higher frequency of ocular (86% *vs*. 82%) and oral (81% *vs*. 76%) diagnostic tests, a lower frequency of positive biopsy (73% *vs*. 87%), a higher mean ESSDAI score (7.2 *vs*. 4.3) and a higher frequency of activity in the constitutional (11% *vs*. 7%), lymphadenopathy (10% *vs*. 8%), glandular (24% *vs*. 19%), cutaneous (12% *vs*. 7%), renal (6% *vs*. 3%), muscular (3% *vs*. 2%), haematological (28% *vs*. 18%) and biological (65% *vs*. 40%) ESSDAI domains in comparison with La-negative patients (Table II).

Ro/La combination patterns: The 3 different combination patterns of anti-Ro/La antibodies (isolated Ro, isolated La and combined Ro and La) were associated with differentiated phenotypes (Table III). Patients with isolated La+ had the highest frequency of dry eye (p=0.001) and active glandular and muscular domains (p<0.001), while patients carrying both autoantibodies showed the highest frequency of abnormal ocular and oral (p<0.001) diagnostic tests, and the highest frequencies of systemic activity in the lymphadenopathy, cutaneous, renal, haematological and biological ESSDAI domains (p<0.001).

b) Phenotype of patients with cryoglobulin-related markers

RF+ patients: RF was tested in 8,758 patients and was positive in 4,245 (48.5%). RF-positive patients had a lower mean age at diagnosis (51 *vs*. 54 yrs), had a higher frequency of abnormal ocular (88% *vs*. 83%) and oral (82% *vs*. 76%) tests, a higher mean ESSDAI score (7.3 *vs*. 5.6) and a higher frequency of activity in the glandular (26% *vs*. 19%), articular (44% *vs*. 37%), cutaneous (12% *vs*. 8%), haematological (29% *vs*. 18%) and biological (66% *vs*. 39%) ESSDAI domains in comparison with RF-negative patients (Table IV).

Cryoglobulinaemic patients: Cryoglobulins were tested in 4,732 patients, and were positive in 342 (7%). Cryoglobulinaemic patients had a higher frequency of abnormal oral tests (87% *vs*. 76%), a higher mean ESSDAI score (17.7 *vs*. 7.2) and a higher frequency of activity in the constitutional (25% *vs*. 11%), lymphadenopathy (23% *vs*. 10%), glandular (39% *vs*. 28%), cutaneous (38% *vs*. 11%), renal (15% *vs*. 5%), muscular (8% *vs*. 3%), PNS (24% *vs*. 7%), CNS (6% *vs*. 2%), haematological (44% *vs*. 25%) and biological (91% *vs*. 50%) ESSDAI domains in comparison with non-cryoglobulinaemic patients (Table IV).

C4 hypocomplementaemic patients: C4 values were measured in 8,556 patients and were low in 1,234 (14%). C4-hypocomplementaemic patients had a lower mean age at diagnosis (51 *vs*. 53 yrs), had a lower frequency of positive

Table II. Association of antinuclear antibodies (ANA), anti-Ro and anti-La autoantibodies with epidemiological characteristics, glandular involvement, systemic involvement and immunological profile in patients with primary Sjögren's syndrome.
Each column shows the results of patients with positive marker.

Variable	ANA Positive (n=7749)	Ro positive (n=7617)	La positive (n=4662)
Epidemiology			
Gender (female)	7245 (93.5)	7115 (93.4)	4342 (93.1)
Age at diagnosis	**52.1 ± 14.4**	**51.8 ± 14.4**	**51.4 ± 14.5**
Glandular involvement			
Dry eye	7108 (91.7)	**6942 (91.1)**	4300 (92.2)
Dry mouth	7223 (93.2)	**7045 (92.5)**	4338 (93.1)
Abnormal ocular tests	**6152/7183 (85.6)**	5919/7018 (84.3)	**3702/4296 (86.2)**
Abnormal oral diagnostic tests	4674/5875 (79.6)	4640/5879 (78.9)	**2956/3634 (81.3)**
Positive minor salivary gland biopsy	**4505/5387 (83.6)**	**3720/5016 (74.2)**	**2221/3026 (73.4)**
Systemic involvement			
Mean ESSDAI	**6.7 ± 8.1**	**6.7 ± 8**	**7.2 ± 8.7**
Mean clinESSDAI	**6.8 ± 8.8**	**6.7 ± 8.7**	**7.2 ± 9.5**
ESSDAI domains (activity >0)			
Constitutional	687/7359 (9.3)	**748/7248 (10.3)**	**490/4404 (11.1)**
Lymphadenopathy	**725/7359 (9.9)**	666/7248 (9.2)	**454/4404 (10.3)**
Glandular	1665/7359 (22.6)	1622/7248 (22.4)	**1081/4404 (24.5)**
Articular	2925/7359 (39.7)	2770/7248 (38.2)	1635/4404 (37.1)
Cutaneous	**811/7359 (11)**	**807/7248 (11.1)**	**552/4404 (12.5)**
Pulmonary	772/7359 (10.5)	775/7248 (10.7)	502/4404 (11.4)
Renal	365/7359 (5)	**388/7248 (5.4)**	**278/4404 (6.3)**
Muscular	171/7359 (2.3)	180/7248 (2.5)	**133/4404 (3)**
Peripheral nervous system (PNS)	439/7359 (6)	440/7248 (6.1)	275/4404 (6.2)
Central nervous system (CNS)	149/7359 (2)	128/7248 (1.8)	80/4404 (1.8)
Haematological	**1842/7224 (25.5)**	**1847/7144 (25.9)**	**1228/4336 (28.3)**
Biological	**3987/7006 (56.9)**	**4106/7021 (58.5)**	**2767/4284 (64.6)**

In bold, statistically significant differences (adjusted *p* values for multiple comparisons with false discovery rate correction <0.001) in comparison with patients with negative marker.

biopsy (75% *vs*. 81%), a higher mean ESSDAI score (9.2 *vs*. 6.0) and a higher frequency of activity in the constitutional (13% *vs*. 10%), lymphadenopathy (13% *vs*. 8%), cutaneous (18% *vs*. 9%), renal (7% *vs*. 4%), PNS (12% *vs*. 5%), haematological (37% *vs*. 21%) and biological (85% *vs*. 47%) ESSDAI domains in comparison with C4-normocomplementaemic patients (Table IV).

C3 hypocomplementaemic patients: C3 values were measured in 8,573 patients and were low in 1,146 (13%). C3-hypocomplementaemic patients had a lower mean age at diagnosis (49 *vs*. 53 yrs), had a lower frequency of dry mouth (89% *vs*. 94%) and dry eyes (89% *vs*. 92%), a higher mean ESSDAI score (11.3 *vs*. 5.7) and a higher frequency of activity in the constitutional (17% *vs*. 9%), lymphadenopathy (18% *vs*. 8%), cutaneous (22% *vs*. 8%), pulmonary (15% *vs*. 10%), renal (11% *vs*. 4%), PNS (14% *vs*. 5%), CNS (3% *vs*. 2%), haematological (43% *vs*. 21%) and biological (86% *vs*. 48%) ESSDAI domains in comparison with C3-normocomplementaemic patients (Table IV).

Discussion

In the three last internationally-accepted classification criteria for primary SjS (9, 16, 17), autoantibodies have always been one of the included criteria and always the only laboratory criterion. However, the number of autoantibodies accepted as criteria has been reduced progressively. The 1993 European Criteria included 4 antibodies (ANA, RF, Ro/SS-A, and/or La/SS-B), the 2002 Criteria 2 (anti-Ro/SS-A and anti-La/SS-B) and the 2016 ACR/EULAR, only one (Ro/SS-A) (9, 16, 17), in the search for a significant improvement of sensitivity and especially specificity. However, the figures for sensitivity/specificity obtained in the three sets of criteria are quite similar (0.93/0.94 for the 1993 criteria, 0.96/0.94 for the 2002 criteria, and 0.96/0.95 for the 2016 criteria). In contrast, other immunological markers (cryoglobulins, hypocomplementaemia) that are strongly associated with disease prognosis and outcomes have been never included in the criteria. In this worldwide study, we have confirmed the close association of all these immunological markers with the phenotype of the disease at the time of diagnosis in the largest cohort of primary SjS patients ever studied.

We found ANA in 80% of patients with primary SjS, and as much the immunological marker most frequently detected. ANA+ patients had a specific phenotype (higher frequency of abnormal diagnostic tests, higher mean ESSDAI and a higher frequency of activity in the lymphadenopathy, cutaneous and laboratory-related domains) (Table II). Some of these features may be related to a late diagnosis (enhanced frequency of diagnostic and laboratory tests) in comparison with patients with negative ANA, who are often diagnosed earlier on the basis of systemic features and positive anti-Ro (21) (nearly 10% of Ro+ patients may be ANA negative (22)). However, the figures for the main systemic features are quite similar to that found in patients with anti-Ro antibodies, suggesting that a positive ANA result does not add specific value to the phenotype observed in anti-Ro carriers. Probably, the key usefulness of testing ANA would be the early suspicion of the disease in non-specialised healthcare settings. Since ANA are the most frequent autoantibodies in primary SjS and their detection is overwhelmingly available in standard healthcare settings, a positive result in a patient presenting with sicca features could help primary care physicians and other specialists to suspect an autoimmune origin of sicca symptoms and therefore, to refer the patient to the autoimmune specialist to discard the disease.

We found anti-Ro antibodies in 73% of our patients, a figure very close to that found for ANA. This is a logical consequence of the strong weight of these autoantibodies in the classification criteria used (2002), as mandatory criteria together with salivary biopsy. Various studies have correlated the presence of anti-Ro with most of the SjS-relat-

Table III. Association of the three combinations of anti-Ro/La antibodies (classification without missing values) with epidemiological characteristics, glandular involvement, systemic involvement and immunological profile in patients with primary Sjögren's syndrome.

Variable	Isolated Ro (n=3152)	Ro and La (n=4412)	Isolated La (n=248)	Adjusted *p*
Epidemiology				
Gender (female)	2961 (93.9)	4103 (93)	237 (95.6)	0.126
Age at diagnosis	52.6 ± 14.1	51.3 ± 14.6	52.2 ± 13.7	0.002
Glandular involvement				
Dry eye	2833 (89.9)	4064 (92.1)	236 (95.2)	**0.001**
Dry mouth	2893 (91.8)	4104 (93)	232 (93.5)	0.126
Abnormal ocular tests	2395/2919 (82)	3497/4055 (86.2)	203/239 (84.9)	**<0.001**
Abnormal oral diagnostic tests	1849/2447 (75.6)	2770/3404 (81.4)	184/228 (80.7)	**<0.001**
Positive minor salivary gland biopsy	1578/2113 (74.7)	2107/2858 (73.7)	113/166 (68.1)	0.179
Systemic involvement				
Mean ESSDAI	5.8 ± 6.7	7.3 ± 8.7	5.9 ± 7	**<0.001**
Mean clinESSDAI	6 ± 7.4	7.3 ± 9.6	6.2 ± 7.8	**<0.001**
ESSDAI domains (activity >0)				
Constitutional	275/3034 (9.1)	467/4161 (11.2)	23/242 (9.5)	0.015
Lymphadenopathy	234/3034 (7.7)	429/4161 (10.3)	25/242 (10.3)	**0.001**
Glandular	633/3034 (20.9)	986/4161 (23.7)	95/242 (39.3)	**<0.001**
Articular	1186/3034 (39.1)	1565/4161 (37.6)	69/242 (28.5)	0.006
Cutaneous	263/3034 (8.7)	541/4161 (13)	11/242 (4.5)	**<0.001**
Pulmonary	304/3034 (10)	469/4161 (11.3)	33/242 (13.6)	0.115
Renal	119/3034 (3.9)	268/4161 (6.4)	10/242 (4.1)	**<0.001**
Muscular	68/3034 (2.2)	112/4161 (2.7)	21/242 (8.7)	**<0.001**
Peripheral nervous system (PNS)	173/3034 (5.7)	265/4161 (6.4)	10/242 (4.1)	0.239
Central nervous system (CNS)	53/3034 (1.7)	75/4161 (1.8)	5/242 (2.1)	0.932
Haematological	650/2998 (21.7)	1188/4093 (29)	39/242 (16.1)	**<0.001**
Biological	1430/2927 (48.9)	2659/4043 (65.8)	107/240 (44.6)	**<0.001**

In bold, statistically significant associations (adjusted *p* values for multiple comparisons with false discovery rate correction <0.001).

Table IV. Association of rheumatoid factor (RF), low C3 levels, low C4 levels and cryoglobulins (Cryog) with epidemiological characteristics, glandular involvement, systemic involvement and immunological profile in patients with primary Sjögren's syndrome. Each column shows the results of patients with positive marker.

Variable	RF positive (n=4245)	Cryog positive (n=342)	Low C4 levels (n=1234)	Low C3 levels (n=1146)
Epidemiology				
Gender (female)	3942 (92.9)	312 (91.2)	1156 (93.7)	1077 (94)
Age at diagnosis	**50.8 ± 14.6**	53.5 ± 14.2	**51.3 ± 14.7**	**48.9 ± 14.2**
Glandular involvement				
Dry eye	3890 (91.6)	320 (93.6)	1125 (91.2)	**1019 (88.9)**
Dry mouth	3958 (93.2)	321 (93.9)	1138 (92.2)	**1018 (88.8)**
Abnormal ocular tests	**3471/3920 (88.5)**	300/326 (92)	1006/1174 (85.7)	944/1090 (86.6)
Abnormal oral diagnostic tests	**2668/3238 (82.4)**	**244/279 (87.5)**	772/972 (79.4)	763/930 (82)
Positive minor salivary gland biopsy	2538/2921 (86.9)	209/241 (86.7)	**658/875 (75.2)**	606/747 (81.1)
Systemic involvement				
Mean ESSDAI	**7.3 ± 8.3**	**17.7 ± 17.4**	**9.2 ± 10.9**	**11.3 ± 12.5**
Mean clinESSDAI	**7.3 ± 9.1**	**17.7 ± 19.1**	**9.1 ± 11.9**	**11.4 ± 13.7**
ESSDAI domains (activity >0)				
Constitutional	396/3972 (10)	**81/321 (25.2)**	**162/1202 (13.5)**	**192/1104 (17.4)**
Lymphadenopathy	417/3972 (10.5)	**74/321 (23.1)**	**157/1202 (13.1)**	**197/1104 (17.8)**
Glandular	**1033/3972 (26)**	**125/321 (38.9)**	311/1202 (25.9)	302/1104 (27.4)
Articular	**1739/3972 (43.8)**	160/321 (49.8)	486/1202 (40.4)	480/1104 (43.5)
Cutaneous	**474/3972 (11.9)**	**122/321 (38)**	**220/1202 (18.3)**	**247/1104 (22.4)**
Pulmonary	469/3972 (11.8)	61/321 (19)	153/1202 (12.7)	**166/1104 (15)**
Renal	188/3972 (4.7)	**47/321 (14.6)**	**84/1202 (7)**	**124/1104 (11.2)**
Muscular	89/3972 (2.2)	**25/321 (7.8)**	28/1202 (2.3)	45/1104 (4.1)
Peripheral nervous system (PNS)	239/3972 (6)	**76/321 (23.7)**	**145/1202 (12.1)**	**156/1104 (14.1)**
Central nervous system (CNS)	63/3972 (1.6)	**18/321 (5.6)**	26/1202 (2.2)	**38/1104 (3.4)**
Haematological	**1122/3888 (28.9)**	**140/321 (43.6)**	**447/1198 (37.3)**	**471/1103 (42.7)**
Biological	**2519/3817 (66)**	**291/321 (90.7)**	**1015/1193 (85.1)**	**935/1086 (86.1)**

In bold, statistically significant differences (adjusted *p* values for multiple comparisons with false discovery rate correction <0.001) in comparison with patients with negative marker.

ed features, including parotidomegaly, lymphadenopathy, cutaneous vasculitis, neurologic disease and serologic hallmarks such as the presence of hypergammaglobulinaemia, rheumatoid factor and cryoglobulins (10). Our results confirm a specific phenotype consisting of patients diagnosed at younger age, with a lower frequency of sicca syndrome and positive salivary gland biopsy, and a higher frequency of activity in the constitutional, cutaneous and laboratory ESSDAI domains. A recent study by Quartuccio *et al*. compared Ro/La+ and Ro/La- patients (23) and found a younger age at diagnosis and a higher frequency of glandular swelling, purpura, leukopenia, lymphoma, low C3, low C4, hypergammaglobulinaemia, rheumatoid factor and serum cryoglobulins in Ro/La+ patients, while we have recently reported that anti-Ro/SS-A and anti-La/SS-B antibodies were also associated with global systemic activity, especially anti-Ro/SS-A, whose positivity at diagnosis also correlated with a higher activity score in the articular, cutaneous and renal domains in a Spanish multicentre study (3).

Anti-La antibodies were detected in 45% of our patients and overwhelmingly associated with the presence of anti-Ro antibodies (95% of cases). Probably for this reason, the phenotype of La carriers was very similar to that reported for Ro carriers. However, when we analysed the phenotype of Ro/La patients according to the different antibody combinations, we found that the most striking phenotypic differences were found in patients carrying the two antibodies in comparison with those who carried only a single antibody, with a higher frequency of abnormal diagnostic tests, the highest mean ESSDAI score among the three groups, and the highest frequency of systemic activity in nearly all the ESSDAI domains (especially in the constitutional, lymphadenopathy, cutaneous, renal and haematological domains) (Table III). In a previous study, Locht *et al*. (24) reported a higher frequency of internal organ involvement in patients carrying anti-La and anti-Ro in comparison with those carrying anti-Ro alone, and other studies also reported similar results (25, 26). In contrast, recent studies have reported a lower frequency of abnormal diagnostics tests (Schirmer test, UWSF and salivary gland biopsy) in isolated La carriers (27, 28). The influence of Ro/La on the phenotypic expression of primary SjS at diagnosis could be driven by immunogenetic differences. The presence of these autoantibodies has been significantly linked with specific HLA-D epitopes (B1*03 and QB1*02, an association even more prominent and extended to QA1*0501 when patients were stratified according to the presence of La/SSB autoantibodies (29), suggesting a similar (but not identical) genetic susceptibility for Ro and La carriers.

Rheumatoid factor was detected in nearly half our patients, who also showed a specific phenotype consisting of a young age at diagnosis, a higher frequency of abnormal diagnostic tests, a high mean ESSDAI score, and a high frequency of systemic activity in the glandular, articular, cutaneous and haematological domains (Fig. 1). Previous studies reported that RF has an independent association with the main clinical and immunological features of the disease (10), and we found recently that RF was associated with a higher ESSDAI score both at diagnosis and at the end of follow-up (30). Thus, RF detection in primary SjS is clinically useful, especially for the diagnosis of some subsets of patients with primary SS, such as those with extraglandular manifestations or with circulating cryoglobulins.

Cryoglobulinaemia had no influence on the glandular disease expression for both subjective and objective glandular features (except for an increased frequency of abnormal oral diagnostic tests), but play a key role in driving a multi-systemic phenotype with statistically-significant higher frequencies in all ESSDAI domains but two (articular and pulmonary) (Fig. 1). In fact, pa-

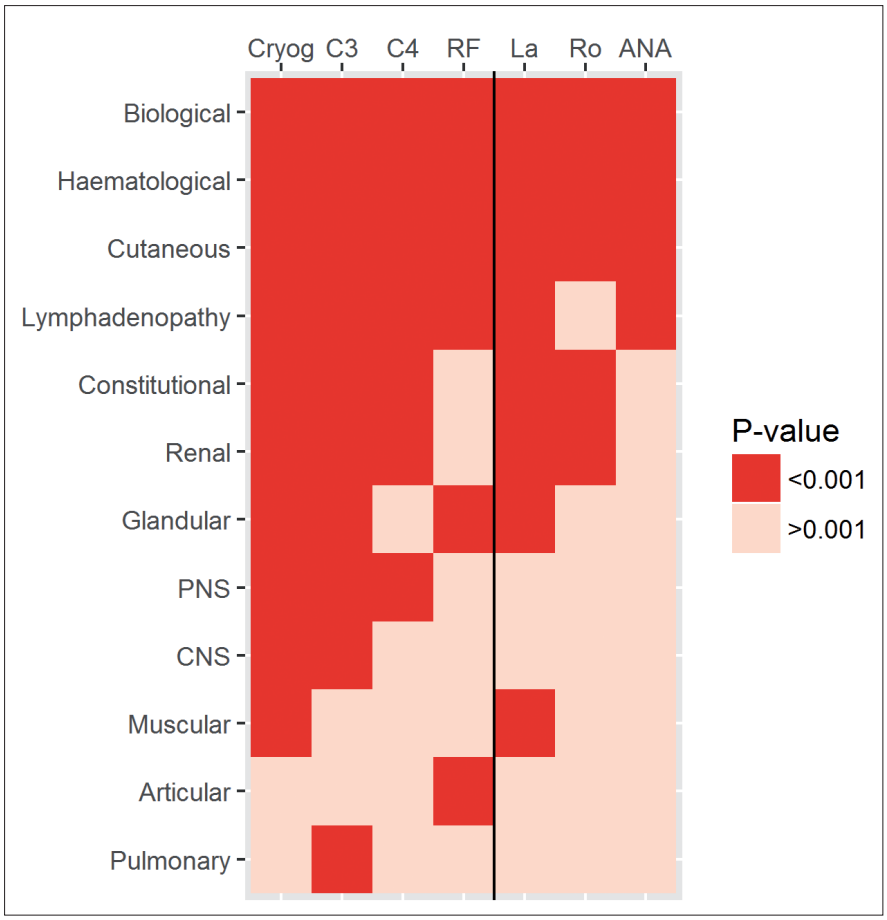

Fig. 1. Heat map of the main statistically-significant associations (adjusted *p* values <0.001) between immunological markers and disease phenotype.

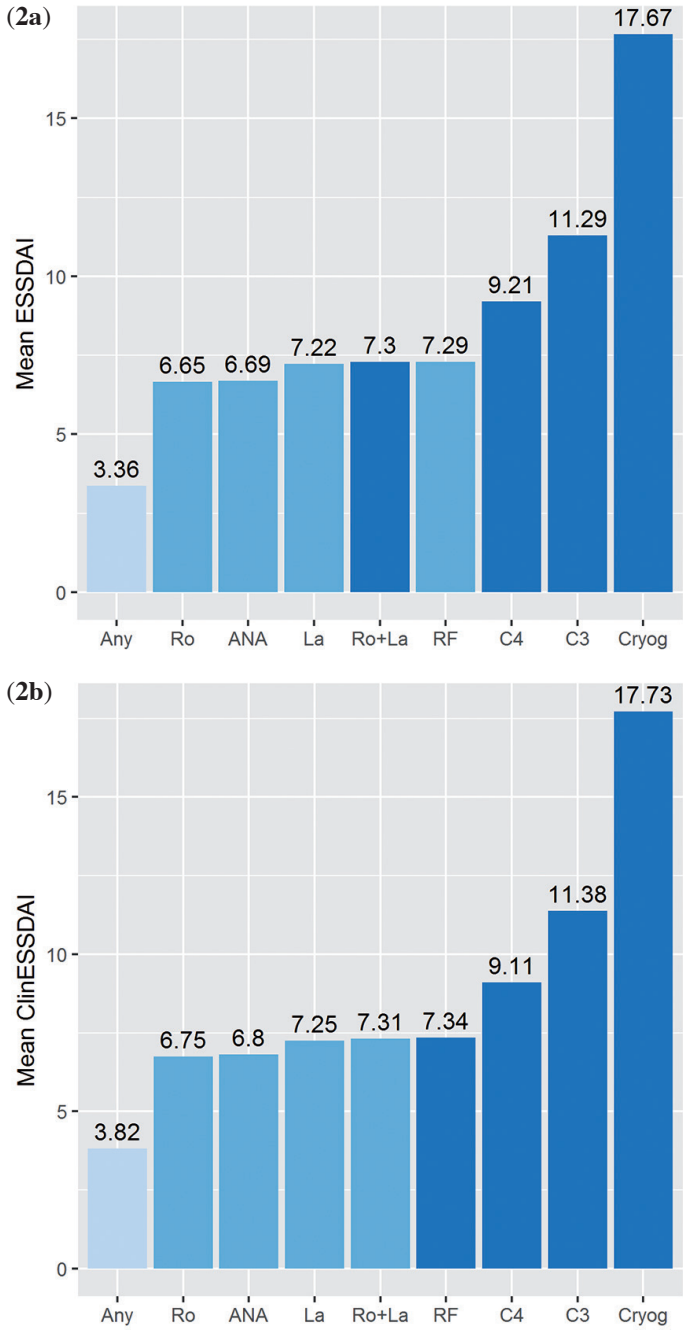

Fig. 2. Mean ESSDAI score (**2a**) and clinESSDAI score (**2b**) according to each immunological marker.

tients with cryoglobulinaemia showed the highest mean ESSDAI among all the immunological subsets, being 4-fold higher than the mean score found in patients with no immunological markers and 3-fold higher than that found in ANA+ or Ro+ patients (Fig. 2). This is closely related to the presence of a systemic vasculitic process, since although many patients with cryoglobulinaemia remain asymptomatic, the percentage of patients with circulating cryoglobulins who develop vasculitic symptoms in primary SjS is 35% (20). The presence of cryoglobulinaemic vasculitis at the diagnosis of primary SS is independently associated with mortality, and is closely linked with a higher baseline ESSDAI score (31).

In previous studies in multicentre national cohorts, we found a significant association between low complement levels and the main systemic SS features, including both extraglandular disease (fever, articular involvement, cutaneous vasculitis, and peripheral neuropathy) and immunological markers (cryoglobulinaemia, rheumatoid factor) (7, 32), and recently Shiboski *et al*. (33) have reported that sicca patients with hypocomplementaemia were 6 times more likely to progress to definite SjS. In addition, hypocomplementaemia is also closely associated with the two main adverse outcomes of primary SS (lymphoma development and death) (34), although two studies (7, 35) reported a predominant role for low C4. This study is the first to analyse separately the phenotype associated with either low C4 or low C3 values, and we found significant differences. Patients with C4-hypocomplementaemia were older and had an enhanced frequency of positive salivary gland biopsy, while those with C3-hypocomplementaemia were younger and had a lower frequency of sicca symptoms. Both subsets of patients showed higher mean ESSDAI scores (Fig. 2) and a close association with systemic activity in the ESSDAI domains, although systemic activity was more pronounced in C3-hypocomplementaemic patients (Fig. 1). This is a new finding, in contrast with previous studies carried out in more geographically-homogeneous populations that showed a predominant role for low C4 levels. Probably, the different degree of association between hypocomplementaemia and cryoglobulinaemia (cryoglobulinaemia is more frequently associated with consumption of C4 factor) could explain these differences with previous studies, since the frequency of cryoglobulinaemia is strongly influenced by geographical and ethnicity determinants (15).

The results of this study, however, should be interpreted with caution, and some limitations should be pointed out. Studies including clinical big data may detect some differences which, although statistically significant, may not be clinically relevant, and further studies are necessary to confirm their clinical relevance in smaller, but more homogeneous, populations. This was the reason why we considered statistically-significant *p*-values less than 0.001 after adjusting for multiple comparisons using the false discovery rate. The predominant presence of European patients could also limit the generalisation of the results in other ethnic subpopulations

less frequently reported. Other sources of heterogeneity may include the variable amount of missing data for some variables and the immunological assays used by the different centres, although all are commercial tests and more than 80% used the same technique (ELISA) to test for Ro/La autoantibodies and ANA were overwhelmingly tested for by indirect immunofluorescence.

In summary, we confirm a strong influence of immunological markers on the phenotype of primary SjS at diagnosis in the largest multi-ethnic international cohort ever analysed, with a greater influence for cryoglobulinaemic-related markers in comparison with Ro/La autoantibodies and ANA. Immunological patterns play a central role in the phenotypic expression of the disease already at the time of diagnosis, and may guide physicians to design a specific personalised management during the follow-up of patients with primary SjS.

Appendix

Members of the EULAR-SS Task Force Big Data Consortium:

a) Members of the EULAR-SS Task Force

P. Brito-Zerón, C. Morcillo (Autoimmune Diseases Unit, Dept. of Medicine, Hospital CIMA-Sanitas, Barcelona, Spain); P. Brito-Zerón, A. Flores-Chavez, M. Ramos-Casals (Sjögren Syndrome Research Group AGAUR, Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Dept. of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain); N. Acar-Denizli (Dept. of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey); W.F. Ng (Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK); M. Zeher, I.-F. Horvath (Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary); A. Rasmussen, K. Sivils, H. Scofield (Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA); R. Seror, X. Mariette (Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France); T. Mandl, P. Olsson (Dept. of Rheumatology, Malmö University Hospital, Lund University, Sweden); X. Li (Dept. of Rheumatology and Immunology, Anhui Provincial Hospital, China); C. Baldini (Rheumatology Unit, University of Pisa, Italy); J.E. Gottenberg (Dept. of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France); D. Danda, P. Sandhya (Dept. of Clinical Immunology & Rheumatology, Christian Medical College & Hospital, Vellore, India); L. Quartuccio, L. Corazza, S. De Vita (Clinic of Rheumatology, Dept. of Medical and Biological Sciences, University Hospital "Santa Maria della Misericordia", Udine, Italy); R. Priori, (Dept. of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Italy); G. Hernandez-Molina, J. Sánchez-Guerrero (Immunology and Rheumatology Dept., Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico); A.A. Kruize, E. van der Heijden (Dept. of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands); V. Valim (Dept. of Medicine, Federal University of Espírito Santo, Vitória, Brazil); M. Kvarnstrom, M. Wahren-Herlenius (Dept. of Medicine, Solna, Unit of Experimental Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden); D. Sene (Service de Médecine Interne 2, Hôpital Lariboisière, Université Paris VII, Assistance Publique-Hôpitaux de Paris, 2, Paris, France); R. Gerli, E. Bartoloni (Rheumatology Unit, Dept. of Medicine, University of Perugia, Italy); S. Praprotnik (Dept. of Rheumatology, University Medical Centre, Ljubljana, Slovenia); D.A. Isenberg (Centre for Rheumatology, Division of Medicine , University College London , UK); R. Solans (Dept. of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain); M. Rischmueller, S. Downie-Doyle (Dept. of Rheumatology, School of Medicine, The University of Western Australia, Crawley, Australia); S-K. Kwok, S-H. Park (Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea); G. Nordmark (Rheumatology, Dept. of Medical Sciences, Uppsala University, Uppsala, Sweden); Y. Suzuki, M. Kawano (Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan); R. Giacomelli, F. Carubbi (Clinical Unit of Rheumatology, University of l'Aquila, School of Medicine, L'Aquila, Italy); V. Devauchelle-Pensec, A. Saraux (Rheumatology Dept., Brest University Hospital, Brest, France); M. Bombardieri, E. Astorri (Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, UK); B. Hofauer, A. Knopf (Hals-Nasen-Ohrenklinik und Poliklinik, Technische Universität München, Germany); H. Bootsma, A. Vissink (Dept. of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, the Netherlands); J.G. Brun, D. Hammenfors (Dept. of Rheumatology, Haukeland University Hospital, Bergen, Norway); G. Fraile (Dept. of Internal Medicine, Hospital Ramón y Cajal, Madrid, Spain); S.E. Carsons (Division of Rheumatology, Allergy and Immunology Winthrop-University Hospital, Stony Brook University School of Medicine, Mineola, NY, USA); T.A. Gheita (Rheumatology Dept., Kasr Al Ainy School of Medicine, Cairo University, Egypt); H.M. Khalil (Ophthalmology Dept., Faculty of Medicine, Beni Suef University, Egypt); J. Morel (Dept. of Rheumatology, Teaching Hospital and University of Montpellier, France); C. Vollenveider (German Hospital, Buenos Aires, Argentina); F. Atzeni (IRCCS Galeazzi Orthopaedic Institute, Milan, and University of Messina, Italy); S. Retamozo (Hospital Privado Universitario de Córdoba, Institute University of Biomedical Sciences University of Córdoba, Córdoba, Argentina); V. Moça Trevisano (Federal University of São Paulo, Brazil); B. Armagan, L. Kilic (Dept. of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey); T. Nakamura (Dept. of Radiology and Cancer Biology, Nagasaki University Graduate School of Biomedical Sci-

ences, Nagasaki, Japan); A. Sebastian, P. Wiland (Dept. of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland); S. Pasoto (Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo USP, Brazil); B. Kostov, A. Sisó-Almirall (Primary Healthcare Transversal Research Group, IDIBAPS, Primary Care Centre Les Corts, CAPSBE, Barcelona, Spain).

b) Members of the French ASSESS Cohort

J. Sibilia (Rheumatology Centre National de Référence des Maladies Auto-Immunes Rares, Institut National de la Santé et de la Recherche Médicale UMRS_1109, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University Hospital, Université de Strasbourg, France); C. Miceli-Richard, G. Nocturne (Rheumatology, Bicetre Hospital, Institut National de la Santé et de la Recherche Médicale U-1012, Université Paris Sud, Assistance Publique des Hôpitaux de Paris, France); J. Benessiano (Centre de Ressources Biologiques, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, France); P. Dieude (Rheumatology, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, France); J-J. Dubost (Rheumatology, Clermont-Ferrand Hospital, France); A-L. Fauchais (Internal Medicine, Limoges Hospital, France); V. Goeb (Rheumatology, Amiens University Hospital, France); E. Hachulla, Pierre Yves Hatron (Internal Medicine, Lille University Hospital, France); C. Larroche (Internal Medicine, Avicenne Hospital, Assistance Publique des Hôpitaux de Paris, Bobigny, France); V. Le Guern, X. Puéchal (Internal Medicine, Cochin Hospital, Assistance Publique des Hôpitaux de Paris, France); J. Morel (Rheumatology, Montpellier University Hospital, France); A. Perdriger (Rheumatology, Rennes University Hospital, France); S. Rist (Rheumatology, Orléans Hospital, France); O. Vittecoq (Rheumatology, Rouen University Hospital, France); P. Ravaud (Centre of Clinical Epidemiology, Hotel Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale U378, University of Paris Descartes, Faculty of Medicine, Paris, France).

c) Members of the Spanish GEAS Cohort (SS Study Group, Autoimmune Diseases Study Group GEAS, Spanish Society of Internal Medicine SEMI)

B. Díaz-López (Dept. of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo), C. Feijoo, (Dept. of Internal Medicine, Hospital Parc Taulí, Sabadell), L. Pallarés (Dept. of Internal Medicine, Hospital Son Espases, Palma de Mallorca), M. López-Dupla (Dept. of Internal Medicine, Hospital Joan XXIII, Tarragona), R. Pérez-Alvarez (Dept. of Internal Medicine, Hospital do Meixoeiro, Vigo), M. Ripoll (Dept. of Internal Medicine, Hospital Infanta Sofía, Madrid), B. Pinilla (Dept. of Internal Medicine, Hospital Gregorio Marañón, Madrid), M. Akasbi (Dept. of Internal Medicine, Hospital Infanta Leonor, Madrid), B. Maure (Dept. of Internal Medicine, Complejo Hospitalario Universitario, Vigo), E. Fonseca (Dept. of Internal Medicine, Hospital de Cabueñes, Gijón), J. Canora (Dept. of Internal Medicine, Hospital Universitario de Fuenlabrada, Madrid), G de la Red (Dept. of Internal Medicine, Hospital Espíritu Santo, Barcelona), A.J. Chamorro (Dept. of Internal Medicine, Complejo Hospitalario de Ourense, Ourense), I. Jiménez-Heredia (Dept. of Internal Medicine, Hospital de Manises, Valencia, Spain), P. Fanlo (Complejo Universitario de Navarra), P. Guisado-Vasco (Hospital Quirón, Madrid), M. Zamora (Hospital Virgen de las Nieves, Granada).

Affiliations

[1]Autoimmune Diseases Unit, Dept. of Medicine, Hospital CIMA-Sanitas, Barcelona, Spain;
[2]Sjögren's Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Dept. of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain;
[3]Dept. of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey;
[4]Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK;
[5]Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Hungary;
[6]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA;
[7]Dept. of Rheumatology, Skane University Hospital Malmö, Lund University, Malmö, Sweden;
[8]Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique - Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France;
[9]Dept. of Rheumatology and Immunology, Anhui Provincial Hospital, Hefei, China;
[10]Rheumatology Unit, University of Pisa, Italy;
[11]Dept. of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France;
[12]Dept. of Clinical Immunology and Rheumatology, Christian Medical College & Hospital, Vellore, India; [13]Clinic of Rheumatology, Dept. of Medical Area (DAME), University Hospital "Santa Maria della Misericordia", Udine, Italy;
[14]Dept. of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Italy;
[15]Immunology and Rheumatology Dept., Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico;
[16]Dept. of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey;
[17]Dept. of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, The Netherlands;
[18]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea;
[19]Dept. of Medicine, Solna, Unit of Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden;
[20]Dept. of Rheumatology, University Medical Centre, Ljubljana, Slovenia;
[21]Dept. of Internal Medicine, Lariboisière Hospital, Assistance Publique-

Hôpitaux de Paris, Paris Diderot University, France;
[22]Rheumatology Unit, Dept. of Medicine, University of Perugia, Italy;
[23]Dept. of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain;
[24]Dept. of Rheumatology, School of Medicine, The University of Western Australia, Crawley, Australia;
[25]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan;
[26]Centre for Rheumatology, Division of Medicine, University College London, UK;
[27]Dept. of Medicine, Federal University of Espírito Santo and University Hospital HUCAM/EBSERH, Vitória, Brazil;
[28]Dept. of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland;
[29]Rheumatology, Dept. of Medical Sciences, Uppsala University, Sweden;
[30]Dept. of Internal Medicine, Hospital Ramón y Cajal, Madrid, Spain;
[31]Dept. of Rheumatology & Clinical Immunology, University of Groningen, University Medical Centre Groningen, The Netherlands;
[32]Dept. of Radiology and Cancer Biology, Nagasaki University Graduate School of Biomedical Sciences, Japan;
[33]Clinical Unit of Rheumatology, University of l'Aquila, School of Medicine, L'Aquila, Italy;
[34]Rheumatology Dept., Brest University Hospital, Brest, France;
[35]Otorhinolaryngology/Head and Neck Surgery, Klinikum rechts der Isar, Technical University Munich, Germany;
[36]Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, UK;
[37]Federal University of São Paulo, Brazil;
[38]Dept. of Clinical Science, University of Bergen; and Dept. of Rheumatology, Haukeland University Hospital, Bergen, Norway;
[39]Rheumatology Division, Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), Brazil;
[40]Hospital Privado Universitario de Córdoba, Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Instituto De Investigaciones En Ciencias De La Salud (INICSA), Universidad Nacional de Córdoba (UNC), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Córdoba, Argentina;
[41]Rheumatology Dept., Kasr Al Ainy School of Medicine, Cairo University, Egypt;
[42]IRCCS Galeazzi Orthopaedic Institute, Milan, and Rheumatology Unit, University of Messina, Italy
[43]Dept. of Rheumatology, Montpellier University Hospital and University of Montpellier, France;
[44]German Hospital, Buenos Aires, Argentina.

References

1. BRITO-ZERÓN P, BALDINI C, BOOTSMA H *et al*.: Sjögren's syndrome. *Nat Rev Dis Prim* 2016; 2: 16047.
2. MOUTSOPOULOS HM, KORDOSSIS T: Sjögren's syndrome revisited: autoimmune epithelitis. *Br J Rheumatol* 1996; 35: 204-6.
3. RAMOS-CASALS M, BRITO-ZERÓN P, SOLANS R *et al*.: Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 spanish patients (GEAS-SS registry). *Rheumatology* 2014; 53: 321-31.
4. BRITO-ZERÓN P, THEANDER E, BALDINI C *et al*.: Early Diagnosis of primary Sjögren's Syndrome: EULAR-SS Task Force Clinical Recommendations. *Expert Rev Clin Immunol* 2016; 12: 137-56.
5. KROESE FGM, ABDULAHAD WH, HAACKE E, BOS NA, VISSINK A, BOOTSMA H: B-cell hyperactivity in primary Sjögren's syndrome. *Expert Rev Clin Immunol* 2014; 10: 483-99.
6. VITALI C, BOMBARDIERI S: Sjögren's syndrome, mixed cryoglobulinaemia and the monoclonal gammopathies. *Clin Exp Rheumatol* 1996; 14 (Suppl. 14): S59-63.
7. BRITO-ZERON P, RAMOS-CASALS M, BOVE A, SENTIS J, FONT J: Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. *Rheumatology* 2007; 46: 1359-62.
8. RAMOS-CASALS M, BRITO-ZERÓN P, SISÓ-ALMIRALL A, BOSCH X: Primary Sjögren syndrome. *BMJ* 2012; 344: e3821.
9. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. *Ann Rheum Dis* 2017; 76: 9-16.
10. RAMOS-CASALS M, BRITO-ZERÓN P, PEREZ-DE-LIS M *et al*.: Sjögren syndrome or Sjögren disease? The histological and immunological bias caused by the 2002 criteria. *Clin Rev Allergy Immunol* 2010; 38: 178-85.
11. NOCTURNE G, VIRONE A, NG W-F *et al*.: Rheumatoid Factor and Disease Activity Are Independent Predictors of Lymphoma in Primary Sjögren's Syndrome. *Arthritis Rheumatol* (Hoboken) 2016; 68: 977-85.
12. QUARTUCCIO L, ISOLA M, BALDINI C *et al*.: Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. *J Autoimmun* 2014; 51: 75-80.
13. BALDINI C, PEPE P, QUARTUCCIO L *et al*.: Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology* 2013; 53: 839-44.
14. HERNANDEZ-MOLINA G, LEAL-ALEGRE G, MICHEL-PEREGRINA M: The meaning of anti-Ro and anti-La antibodies in primary Sjögren's syndrome. *Autoimmun Rev* 2011; 10: 123-5.
15. BRITO-ZERON P, ACAR-DENIZLI N, ZEHER M *et al*.: Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. *Ann Rheum Dis* 2017; 76: 1042-50.
16. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
17. VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al*.: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36: 340-7.
18. SEROR R, THEANDER E, BRUN JG *et al*.: Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 2015; 74: 859-66.
19. SEROR R, MEINERS P, BARON G *et al*.: Development of the ClinESSDAI: A clinical score without biological domain. A tool for biological studies. *Ann Rheum Dis* 2016; 75: 1945-50.
20. RETAMOZO S, GHEITASI H, QUARTUCCIO L *et al*.: Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjögren syndrome: Analysis of 515 patients. *Rheumatology* 2016; 55: 1443-51.
21. BRITO-ZERON P, THEANDER E, BALDINI C *et al*.: Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. *Expert Rev Clin Immunol* 2016; 12: 137-56.
22. RETAMOZO S, AKASBI M, BRITO-ZERON P *et al*.: Anti-Ro52 antibody testing influences the classification and clinical characterisation of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2012; 30: 686-92.
23. QUARTUCCIO L, BALDINI C, BARTOLONI E *et al*.: Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev* 2015; 14: 1019-22.
24. LOCHT H, PELCK R, MANTHORPE R: Clinical manifestations correlated to the prevalence of autoantibodies in a large (n=321) cohort of patients with primary Sjögren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the America. *Autoimmun Rev* 2005; 4: 276-81.

25. TER BORG EJ, KELDER JC: Lower prevalence of extra-glandular manifestations and anti-SSB antibodies in patients with primary Sjögren's syndrome and widespread pain: evidence for a relatively benign subset. *Clin Exp Rheumatol* 2014; 32: 349-53.
26. VENABLES PJ, SHATTLES W, PEASE CT, ELLIS JE, CHARLES PJ, MAINI RN: Anti-La (SS-B): a diagnostic criterion for Sjögren's syndrome? *Clin Exp Rheumatol* 1989; 7: 181-4.
27. BAER AN, MCADAMS DEMARCO M, SHIBOSKI SC *et al*.: The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjögren's syndrome. *Ann Rheum Dis* 2015; 74: 1557-61.
28. DANDA D, SHARMA R, TRUONG D *et al*.: Anti-La positive, anti-Ro negative subset of primary Sjögren's syndrome: anti-La is a reality but is the disease? *Clin Exp Rheumatol* 2017; 35: 438-44.
29. TZIOUFAS AG, WASSMUTH R, DAFNI UG *et al*.: Clinical, immunological, and immunogenetic aspects of autoantibody production against Ro/SSA, La/SSB and their linear epitopes in primary Sjögren's syndrome (pSS): a European multicentre study. *Ann Rheum Dis* 2002; 61: 398-404.
30. BRITO-ZERON P, KOSTOV B, SOLANS R *et al*.: Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. *Ann Rheum Dis* 2016; 75: 348-55.
31. QUARTUCCIO L, BALDINI C, PRIORI R *et al*.: Cryoglobulinemia in Sjögren syndrome: a disease subset that links higher systemic disease activity, autoimmunity, and local B cell proliferation in mucosa-associated lymphoid tissue. *J Rheumatol* 2017; 44: 1179-83.
32. RAMOS-CASALS M, BRITO-ZERÓN P, YAGÜE J *et al*.: Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. *Rheumatology* 2005; 44: 89-94.
33. SHIBOSKI CH, BAER AN, SHIBOSKI SC *et al*.: Natural History and Predictors of Progression to Sjögren's Syndrome Among Participants of the Sjögren's International Collaborative Clinical Alliance Registry. *Arthritis Care Res* 2018; 70: 284-94.
34. THEANDER E, MANTHORPE R, JACOBSSON LTH: Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. *Arthritis Rheum* 2004; 50: 1262-9.
35. IOANNIDIS JPA, VASSILIOU VA, MOUTSOPOULOS HM: Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum* 2002; 46: 741-7.