Anti-Ro52 antibody testing influences the classification and clinical characterisation of primary Sjögren's syndrome

S. Retamozo[1], M. Akasbi[1,5], P. Brito-Zerón[1], X. Bosch[2], A. Bove[1], M. Perez-De-Lis[5], I. Jimenez[7], M.-J. Soto-Cardenas[8], M. Gandía[8], C. Diaz-Lagares[1], O. Viñas[3], A. Siso[4], R. Perez-Alvarez[6], J. Yague[3], M. Ramos-Casals[1]

[1]Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Autoimmune Diseases, and [2]Department of Internal Medicine, ICMiD, and [3]Department of Immunology, CDB, Hospital Clínic, Barcelona; [4]Primary Care Research Group, IDIBAPS, Centre d'Assistència Primària ABS Les Corts, GESCLINIC, Barcelona; [5]Department of Internal Medicine, Hospital Infanta Leonor, Madrid; [6]Department of Internal Medicine, Hospital do Meixoeiro, Vigo; [7]Department of Internal Medicine, Hospital de Manises, Valencia; [8]Department of Internal Medicine, University of Cádiz, Hospital Puerta del Mar, Cádiz, Spain.

Abstract

Objectives

To evaluate how determination of antibodies against the Ro52 antigen influences the classification and clinical characterisation of patients with suspected primary Sjögren's syndrome (SS).

Methods

The cohort study included 187 patients who fulfilled at least four of the six 1993 SS classification criteria, including positive autoantibodies (antinuclear antibodies [ANA], rheumatoid factor [RF], anti-Ro/SSA and/or anti-La/SS-B antibodies) as mandatory criterium. Anti-Ro/SSA antibodies were tested by qualitative ELISA using a commercial assay. Anti-Ro52 antibodies were detected by a semiquantitative ELISA.

Results

Anti-Ro52 antibodies were found in 70/187 (37%) patients. A significant percentage of patients with anti-Ro/SSA antibodies were negative for anti-Ro52 antibodies (22%), while 13 patients (12%) were negative for anti-Ro/SSA antibodies but positive for anti-Ro52 antibodies, meaning that they fulfilled the 2002 SS criteria while avoiding the need for a salivary biopsy. Higher mean titers of anti-Ro52 antibodies were associated with severe scintigraphic involvement, positive salivary gland biopsy, parotid enlargement, anaemia, leukopenia and RF. A statistical correlation was found between anti-Ro52 titers and age, gammaglobulin levels, RF titers and serum IgA and IgG. Patients with positive anti-Ro/SSA and anti-Ro52 antibodies had a higher frequency of positive salivary gland biopsy, parotid enlargement and positive RF, and higher levels of serum IgG and IgA levels in comparison with patients with positive anti-Ro/SSA but negative anti-Ro52 antibodies.

Conclusion

Anti-Ro52 antibodies were closely associated with the main clinical, histopathological and immunological features of primary SS. Anti-Ro52 autoantibody testing may help to identify a specific subset of SS patients with more aggressive disease, in whom a closer follow-up and earlier, more robust therapeutic management may be necessary.

Key words

Sjögren's syndrome, anri-Ro/SSA antibodies, anti-Ro52 antibodies

*Soledad Retamozo, MD**
*Miriam Akasbi, MD**
Pilar Brito-Zerón, MD, PhD
Xavier Bosch, MD, PhD
Albert Bove, MD PhD
Marta Perez-De-Lis, MD PhD
Iratxe Jimenez, MD
Maria-José Soto-Cardenas, MD, PhD
Miriam Gandía, MD
Candido Diaz-Lagares, MD
Odette Viñas, MD
Antoni Siso, MD, PhD
Roberto Perez-Alvarez, MD
Jordi Yague, MD
Manuel Ramos-Casals, MD, PhD

**These authors made an equal contribution to the study.*

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

Received on August 2, 2011; accepted in revised form on December 13, 2011.

Funding: this study was supported by Grants La Marató de TV3 (071810) and Fondo de Investigaciones Sanitarias (080103).

Competing interests: none declared.

Introduction

Sjögren syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosa surfaces (1) and whose spectrum extends from sicca symptoms to systemic involvement (2-3). Antinuclear antibodies (ANA) are present in the sera of 90% of patients with primary SS (4). Of these antibodies, two are directed against two ribonucleoprotein antigens known as Ro or SS antigen A (SSA) and La or SS antigen B (SSB) (5). Anti-Ro/SSA antibodies appear to play a role in the local autoimmune response in the exocrine glands and represent a key immunological disease marker (6). Recent studies, including cohorts of more than 400, 700 and 1000 primary SS patients (7-9), respectively, have demonstrated that anti-Ro+ patients have a higher frequency of systemic manifestations and analytical abnormalities.

Clinical studies evaluating the fine specificity of the autoimmune response against the Ro antigen (autoantibodies against the Ro52 and Ro60 subunits) in primary SS are limited to a few small descriptive studies (10, 11). Peene *et al*. (12) demonstrated that the standard anti-Ro/SSA serological assays predominantly detect anti-Ro60 antibodies, and suggested that anti-Ro52 antibodies are systematically missed by the standard anti-Ro/SSA detection techniques. Because the 2002 criteria limit included patients with positive salivary gland biopsy or positive anti-Ro/La antibodies (13), determination of antibodies against the Ro antigen currently plays a crucial role in the diagnosis of primary SS.

The aim of this study was to evaluate how determination of antibodies against the Ro52 antigen influences the classification and clinical characterisation of patients with a suspected primary SS.

Patients and methods

Patients

The study cohort included 545 patients consecutively evaluated by our unit between January 1995 and July 2010 who fulfilled the 1993 classification criteria for primary SS (14). All patients were considered to have well-established primary SS defined as fulfillment of at least four of the six 1993 criteria, including either positive autoantibodies (antinuclear antibodies [ANA], rheumatoid factor [RF], anti-Ro/SSA and/or anti-La/SS-B antibodies) or salivary biopsy as a mandatory criterion. Patients with other possible causes of sicca syndrome (infiltrative processes, infections or neoplasia) and other concomitant systemic autoimmune diseases were excluded. The entire cohort was retrospectively evaluated to determine fulfillment of the 2002 classification criteria (15). Extraglandular involvement was evaluated according to the 2010 EULAR SS disease activity index (16). The study was approved by the Ethics Committee of the Hospital Clinic, Barcelona, Spain. Due to the anonymous nature of the study, informed patient consent was not required.

Anti-Ro/SSA and anti-Ro52 detection

Anti-Ro/SSA antibodies were tested using a commercial assay (Captia™ SSA-Ro, Trinity Biotech, Bray, Ireland); this test is an ELISA intended for the detection of IgG, IgA and IgM antibodies to Ro/SSA antigens. A patient index value ≥1.00 was considered as a positive result for Ro/SSA antibodies (sensitivity 100%, specificity 99.2%).

Anti-Ro52 antibodies were tested using a commercial assay (SSA 52 KD and SSA 60 KD Kits, Orgentec, Mainz, Germany); those tests are semi-quantitative solid phase ELISA intended to screen for the presence of anti-Ro60 and anti-Ro52 IgG antibodies using specifically purified autoantigens including Ro52 and Ro60. Anti-Ro52 and anti-Ro60 reactivity >10 U/mL was considered as a positive result for anti-Ro52 or anti-Ro60 antibodies, respectively (sensitivity 97.8%, specificity 97.9%).

Statistical analysis

Categorical data were compared using the χ^2 test. Fisher's exact test was used to confirm statistical differences where sample sizes were small. Continuous variables were analysed with the Student's *t*-test in large samples of similar variance and with the non-parametric

Mann-Whitney U-test for small samples, with results indicated as mean ± standard error of the mean (SEM). A two-tailed value of $p<0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a multiple logistic regression analysis was performed. The correlation between anti-Ro52 levels and quantitative variables was analysed using Pearson's correlation test. The statistical analysis was performed with the SPSS programme (SPSS, Chicago, IL, USA).

Results

Of the 545 patients, 506 (93%) were female and 39 (7%) male, with a mean age at the time of fulfillment of the 1993 classification criteria of 57.11 years (SEM 0.63). Four hundred and fifty-six (84%) patients had positive ANA, 238 (44%) positive RF, 198 (36%) positive anti-Ro/SSA, 156 (29%) anti-La/SSB antibodies and 163/209 (78%) had a positive salivary gland biopsy. A total of 327 (60%) patients fulfilled the 2002 classification criteria retrospectively.

a) Comparison of patients according to Ro52 autoantibody positivity

Anti-Ro52 antibodies were tested in 187 consecutive patients, of whom 76 (41%) had positive anti-Ro/SSA antibodies and 70 (37%) positive anti-Ro52 antibodies. There were 59 patients positive for both anti-Ro/SSA and anti-Ro52 antibodies, 17 patients with positive anti-Ro/SSA and negative anti-Ro52 antibodies, and 11 with negative anti-Ro/SSA and positive anti-Ro52 antibodies.

Table I compares the main epidemiological, clinical and immunological features according to anti-Ro52 antibody status. Patients with anti-Ro52 antibodies had a higher frequency of severe involvement in parotid scintigraphy – grades III/IV – (73% *vs*. 56%, $p=0.042$), parotid enlargement (29% *vs*. 11%, $p=0.019$), positive salivary gland biopsy (100% *vs*. 64% $p=0.001$), autoimmune liver disease (17% *vs*. 7%, $p=0.048$), anaemia (37% *vs*. 20%, $p=0.014$), leukopenia (19% *vs*. 8%, $p=0.039$), ANA (93% *vs*. 81%, $p=0.032$) and RF (74% *vs*. 26%, $p<0.001$), and higher levels of ESR (47.17 *vs*. 24.31 mm/h, $p<0.001$) and serum IgG (18.65 *vs*. 11.07 g/L, $p<0.001$) and IgA levels (3.14 *vs*. 2.32 g/L, $p<0.001$). In contrast, Ro52+ patients had a lower frequency of neurological involvement (9% *vs*. 22%, $p=0.017$) in comparison with patients with negative anti-Ro52 antibodies. Multivariate analysis showed that parotid enlargement, ESR value, serum IgG and RF were significantly associated with anti-Ro52 antibodies.

Patients with positive anti-Ro/SSA and negative anti-Ro52 antibodies had a lower frequency of positive salivary gland biopsy (50% *vs*. 100%, $p=0.024$), parotid enlargement (6% *vs*. 30%, $p=0.05$) and RF (25% *vs*. 78%, $p<0.001$), and lower levels of serum IgG (12.11 *vs*. 19.25 g/L, $p=0.001$) and IgA levels (2.24 *vs*. 3.23 g/L, $p=0.05$) in comparison with patients positive for both anti-Ro/SSA and anti-Ro52 antibodies.

Table I. Comparison of the main epidemiological, clinical and immunological features of patients with primary SS according to anti-Ro52 antibody status.

	Anti-Ro52 (-) n=117	Anti-Ro52 (+) n=70	Bilateral *p*-value
Gender (male)	10 (8%)	1 (1%)	0.055
Age (mean ± SEM)	56.91 ± 1.15	53.06 ± 1.93	0.068
Xerostomia	116 (99%)	69 (99%)	1.000
Xerophthalmia	116 (99%)	69 (99%)	1.000
Positive ocular tests	103/108 (95%)	62/63 (98%)	0.416
Parotid scintigraphy >= III	61/109 (56%)	40/55 (73%)	**0.042**
Positive salivary gland biopsy	20/31 (64%)	22/22 (100%)	**0.001**
Fever	6 (5%)	9 (13%)	0.092
Parotid enlargement	13 (11%)	20 (29%)	**0.005***
Arthralgias	67 (57%)	37 (53%)	0.648
Arthritis	12 (10%)	15 (21%)	0.052
Raynaud phenomenon	19 (16%)	17 (24%)	0.185
Cutaneous vasculitis	5 (4%)	5 (7%)	0.505
Ro-associated cutaneous lesions	3 (3%)	5 (7%)	0.153
Interstitial lung disease	7 (6%)	5 (7%)	0.765
Autoimmune liver disease	8 (7%)	12 (17%)	**0.048**
Renal involvement	2 (2%)	2 (3%)	0.631
Neurological involvement	26 (22%)	6 (9%)	**0.017**
Mean ESR (mm/h)	24.31 ± 1.94	47.17 ± 3.88	**<0.001***
Anaemia (Hb <110 g/L)	23 (20%)	25 (37%)	**0.014**
Leukopenia (<4000/mm^3)	10 (8%)	13 (19%)	**0.039**
Thrombocytopenia (<150000/ mm^3)	8 (7%)	9 (13%)	0.185
Serum IgG levels (g/L)	11.07 ± 0.27	18.65 ± 0.95	**<0.001***
Serum IgM levels (g/L)	2.43 ± 0.87	1.64 ± 0.13	0.504
Serum IgA levels (g/L)	2.32 ± 0.10	3.14 ± 0.22	**<0.001**
Antinuclear antibodies	95 (81%)	65 (93%)	**0.032**
Rheumatoid factor	30 (26%)	52 (74%)	**<0.001***
Anti-La antibodies	15 (13%)	47 (67%)	**<0.001**
Monoclonal gammopathy	16/100 (16%)	11/61 (18%)	0.829
Cryoglobulins	4/115 (3%)	7/65 (11%)	0.059
Low C3	10 (8%)	8/65 (12%)	0.444
Low C4	4 (3%)	5/65 (8%)	0.285

*Statistically significant in the multivariate analysis.

b) Comparison of patients according to anti-Ro52 titers

In the 70 patients with positive anti-Ro52 antibodies, mean anti-Ro52 titers were 50.76±5.64 U/mL. Higher mean titers of anti-Ro52 antibodies were associated with severe scintigraphic involvement (52 *vs*. 29 U/mL, $p=0.042$), positive salivary gland biopsy (71 *vs*. 1.6 U/mL, $p=0.007$), parotid enlargement (98 *vs*. 39 U/mL, $p<0.001$), anemia (71 *vs*. 41 U/mL, $p=0.015$), leukopenia (82 *vs*. 44 U/mL, $p=0.02$), positive RF (91 *vs*. 17 U/mL, $p<0.001$) and low C4 levels (94 *vs*. 45 U/mL, $p=0.047$); in addition, patients with CNS involvement had lower mean titers than those without neurological involvement (14 *vs*. 53 U/mL, $p=0.049$) (Table II). A statistical correlation was found between anti-

Table II. Mean titers of anti-Ro52 antibodies according to the main epidemiological, clinical and immunological features of patients with primary SS.

	Mean titer of anti-Ro52 antibodies (mean ± SEM)	*p*-value
Gender		0.071
- Female	51.92 ± 5.73	
- Male	10.00 ± 8.75	
Parotid scintigraphy classification		**0.042**
- III-IV	52.73 ± 7.68	
- I-II	29.32 ± 7.67	
Salivary gland biopsy		**0.007**
- Positive	71.08 ± 12.67	
- Negative	10.64 ± 0.45	
Parotid enlargement		**<0.001**
- Presence	98.36 ± 15.17	
- Absent	38.89 ± 5.44	
Ro-associated cutaneous lesions		0.220
- Presence	81.12 ± 31.57	
- Absence	48.01 ± 5.53	
Autoimmune liver disease		0.071
- Presence	77.87 ± 8.67	
- Absence	46.02 ± 5.57	
CNS involvement		**0.049**
- Presence	14.34 ± 7.78	
- Absence	52.75 ± 5.88	
Hemoglobin		**0.015**
- <110 g/L	70.99 ± 11.79	
- ≥110 g/L	40.94 ± 6.94	
White cells count		**0.020**
- <4000/mm^3	82.24 ± 18.40	
- ≥4000/mm^3	43.99 ± 5.59	
Rheumatoid factor		**<0.001**
- >25 UI/L	91.17 ± 9.27	
- ≤25 UI/L	17.41 ± 4.51	
Anti-La antibodies		**<0.001**
- Positive	103.47 ± 10.33	
- Negative	54.95 ± 4.91	
C4 values		**0.047**
- <0.11 g/L	94.06 ± 31.58	
- ≥0.11 g/L	44.67 ± 5.39	

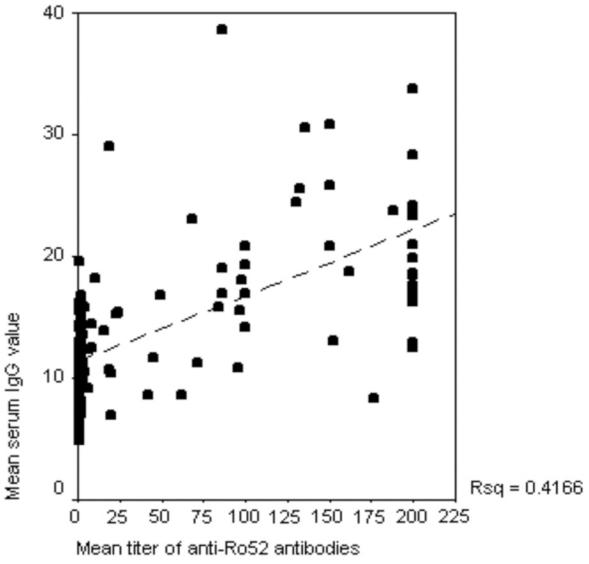

Fig. 1. Statistical correlation between anti-Ro52 titers and serum IgG levels (p<0.01).

Ro52 titers and age, gammaglobulin levels, RF titers and serum IgA and IgG levels (p<0.01, Fig. 1).

Forty-nine patients were positive for both anti-Ro52 and anti-Ro60 antibodies. Nine (18%) patients had higher anti-Ro52 titers than anti-Ro60 titers, while the remaining 40 patients had anti-Ro52 titers lower or equal to anti-Ro60 titers. Table III compares the main epidemiological, clinical and immunological features according to the predominance of anti-Ro52 or anti-Ro60 antibodies. Patients with higher anti-Ro52 titers had a higher mean age (62.67 *vs*. 48.28 years, p=0.012), a higher frequency of Raynaud phenomenon (56% *vs*. 20%, p=0.043) and autoimmune liver disease (44% *vs*. 15%, p=0.07), a lower frequency of positive RF (22% *vs*. 77%, p=0.003) and lower levels of serum IgG (9.67 *vs*. 19.59 g/L, p=0.002) and IgA levels (2.12 *vs*. 3.58 g/L, p=0.039) in comparison with patients with ant-Ro52 titers lower than or equal to anti-Ro60 antibodies.

Discussion

Anti-Ro antibodies are the most frequent ANA identified in patients with primary SS (4). Four molecular forms of the human autoantigen Ro complex have been described: two Ro-lymphocyte peptides of 60 kDa and 52 kDa, and two Ro-erythrocyte equivalent peptides of 60 kDa and 54 kDa. Although Ro52 and Ro60, which are encoded by different genes (17), were initially suggested to be closely related, a direct interaction of the proteins could not be conclusively proven. The Ro60 and La proteins have been shown to be components of the same ribonucleoprotein complex, but it remains uncertain whether the Ro52 protein is also a component of this complex (12). Anti-Ro antibodies play a key role in the clinical expression of primary SS. In a series of 1010 patients with primary SS, we found that the main differences in the clinical expression were associated with the anti-Ro status, since Ro+ patients fulfilled the criteria at a younger age and had a higher frequency of the main extraglandular features and analytical abnormalities in comparison with Ro negative patients (9). These differences

Table III. Comparison of the main epidemiological, clinical and immunological features of patients with primary SS according to higher titers of anti-Ro52 or anti-Ro60 antibodies.

	Higher titers of anti-Ro52 n=9	Equal or higher titers of anti-Ro60 n=40	Bilateral *p*-value
Gender (male)	0 (0%)	1 (2%)	1.000
Age (mean ± SEM)	62.67 ± 4.22	48.28 ± 2.43	**0.012**
Xerostomia	9 (100%)	40 (100%)	NC
Xerophthalmia	9 (100%)	39 (97%)	1.000
Positive ocular tests	8/8 (100%)	38/38 (100%)	NC
Parotid scintigraphy >= III	5/7 (71%)	19/32 (59%)	0.686
Positive salivary gland biopsy	3/3 (100%)	11/11 (100%)	NC
Fever	1 (11%)	7 (17%)	1.000
Parotid enlargement	2 (22%)	11 (17%)	1.000
Arthralgias	4 (44%)	26 (65%)	0.282
Arthritis	2 (22%)	11 (27%)	1.000
Raynaud phenomenon	5 (56%)	8 (20%)	**0.043**
Cutaneous vasculitis	1 (11%)	3 (7%)	0.569
Ro-associated cutaneous lesions	0 (0%)	5 (12%)	0.569
Interstitial lung disease	2 (22%)	3 (7%)	0.224
Autoimmune liver disease	4 (44%)	6 (15%)	**0.070**
Renal involvement	1 (11%)	1 (2%)	0.337
Neurological involvement	1 (11%)	4 (10%)	1.000
Mean ESR (mm/h)	20.75 ± 1.96	55.31 ± 4.91	**0.003**
Anaemia (Hb < 110g/L)	3 (33%)	16 (41%)	1.000
Leukopenia (<4000/mm^3)	0 (0%)	9 (23%)	0.176
Thrombocytopenia (<150000/ mm^3)	1 (11%)	4 (10%)	1.000
Mean serum IgG levels (mg/L)	9.67 ± 0.55	19.59 ± 1.21	**0.002***
Mean serum IgM levels (mg/L)	1.21 ± 0.10	1.61 ± 0.17	0.327
Mean serum IgA levels (mg/L)	2.12 ± 0.29	3.58 ± 0.28	**0.039**
Antinuclear antibodies	9 (100%)	38 (95%)	1.000
Rheumatoid factor	2 (22%)	31 (77%)	**0.003**
Anti-La antibodies	2 (22%)	34 (85%)	**<0.001**
Monoclonal gammopathy	0/8 (0%)	7/37 (19%)	0.321
Cryoglobulins	2 (22%)	5/39 (13%)	0.601
Low C3	1 (11%)	7/39 (18%)	1.000
Low C4	0 (0%)	1/39 (3%)	1.000

NC: not calculated. *Statistically significant in the multivariate analysis.

were first described by Alexander *et al*. in 1983 (18) and were confirmed by subsequent studies (19-21).

Traditionally, anti-Ro antibodies were screened by indirect immunofluorescence (IIF) on HEp-2 cells, and detected, or confirmed, by immunodiffusion with cell or tissue extracts, which included SS-A or both Ro-60 and Ro52 autoantigens. When Ro/SS-A, Ro60 and Ro52 purified autoantigens became available, immunoblot and ELISA autoantibody-specific immunedetection techniques were developed. However, Peene *et al*. (12) found that most anti-Ro/SSA antibodies detection kits were limited to Ro60 autoantigen specificity detection. In the mid-nineties it was reported that a significant number of sera with anti-Ro52 reactivity may have a negative IIF result (22), suggesting the need for testing antibodies against Ro52 separately. However, the prevalence and clinical significance of anti-Ro52 autoantibodies in patients with systemic autoimmune diseases has been little studied. Anti-Ro52 antibodies have been reported in 10–60% of patients with systemic sclerosis, dermatomyositis and rheumatoid arthitis (23-28), although the main studies have been carried out in patients with SLE or SS. These studies have suggested that the predominant response against Ro consists of anti-Ro52 antibodies in primary SS and anti-Ro60 antibodies in SLE (29-31). Peene *et al*. (12) found that triple reactivity (anti-Ro52, anti-Ro60 and anti-La) and anti-Ro60 (with or without anti-Ro52 reactivity) were mainly associated with SLE, while isolated anti-Ro52 reactivity was seen predominantly in primary SS. Other studies suggested a close association between anti-Ro60 and SLE with or without associated SS (32, 33). However, the scarcity of studies in large series of patients with primary SS, which is the disease most closely related to anti-Ro/SSA antibodies and the only disease in which they are included in the classification criteria, is somewhat surprising.

We found a prevalence of anti-Ro52 antibodies of 37% in a large cohort of immunopositive patients diagnosed with primary SS using the 1993 criteria. This percentage rose to 61% in patients fulfilling the 2002 criteria. Garberg *et al*. (11) tested 100 SS patients fulfilling the 1993 criteria (66% fulfilled the 2002 criteria) and found anti-Ro52 antibodies in 62% of patients and anti-Ro60 antibodies in 24%. These percentages increased to 71% and 33%, respectively, in patients fulfilling the 2002 criteria. Song *et al*. (10) found anti-Ro52 antibodies in 67% and anti-Ro60 antibodies in 52% of 96 SS patients (2002 criteria), while Aguilera *et al*. (34) found anti-Ro52 antibodies in 65% and anti-Ro60 antibodies in 59% of 46 SS patients (2002 criteria). These authors also found a high prevalence of anti-Ro52 and anti-Ro60 antibodies (36–50%) in 14 patients who tested positive for ANA/RF but negative for anti-Ro antibodies by ELISA (34). These studies, taken together, suggests a prevalence of 36–62% for anti-Ro52 antibodies and 24–35% for anti-Ro60 antibodies in patients fulfilling the 1993 criteria, and 61–71% and 33–61%, respectively, in patients fulfilling the 2002 criteria.

This study confirms the close association of anti-Ro52 antibodies with the main clinical and immunological features of a large series of patients with primary SS. A close association was found with severe scintigraphic involvement and parotid enlargement, suggesting that autoimmune response against these autoantigens plays a key role in the autoimmune damage to salivary glands, as several experimental studies have suggested (6, 35). Furthermore, all 35 patients with positive Ro52 and Ro60 antibodies who were biopsied had a positive result, which

indicates a strong correlation between autoantibody positivity in serum and histopathological SS-related changes. Patients with positive anti-Ro52 antibodies also showed a higher prevalence of extraglandular manifestations, especially cutaneous, articular, hematological and hepatic involvement. The few studies that have analysed the association of these autoantibodies with extraglandular features in patients with primary SS found a higher frequency of liver involvement (10), muscular involvement (10) and cutaneous lesions similar to SCLE (annular erythema) (12). The close association between positive anti-Ro52 antibodies and immunological markers found in our study (serum IgG/IgA levels, ANA, RF) has also been reported in previous studies in small series of patients (24, 36). Our results in a large series of patients confirmed that anti-Ro52 antibodies identify a specific subset of SS patients who present with more-pronounced systemic and autoimmune expression, and who may share a specific etiopathogenic mechanism (local production of Ro antigens, severe glandular damage, and B-cell hyperactivity) (18, 37-42).

Our study reports some new findings. Firstly, we found that a significant percentage of Ro/SSA+ patients (18–22%) have negative results for anti-Ro52 and anti-Ro60 antibodies (22% and 18%, respectively), and that these patients have less-pronounced systemic and autoimmune expression. Secondly, 13 patients (12%) had negative Ro/SSA antibodies but positive anti-Ro52 antibodies, meaning that they fulfilled the 2002 criteria while avoiding the need for a salivary biopsy. Thirdly, we found that some features are more-specifically linked to anti-Ro52 antibodies and others to anti-Ro60 antibodies. For these reasons, specific determination of antibodies to Ro52 antigen seems to have additional benefits with respect to standard techniques testing for anti-Ro/SSA antibodies.

In summary, we found a prevalence of anti-Ro52 antibodies of 61% in patients with primary SS fulfilling the 2002 criteria. Anti-Ro52 antibodies were closely associated with the main clinical, histopathological and immunological features of primary SS. Twelve per cent of patients had negative anti-Ro/SSA antibodies but were positive for anti-Ro52 antibodies, meaning that they fulfilled the 2002 criteria while avoiding the need for a salivary biopsy. The prevalence and clinical significance of anti-Ro52 and anti-Ro60 antibodies was similar. Our results suggest that specific determination of antibodies to the Ro52 antigen seems to have additional benefits with respect to standard techniques testing for anti-Ro/SSA antibodies in patients with primary SS.

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