Comparative study between two European inception cohorts of patients with early systemic lupus erythematosus

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Abstract

Objective

To compare the main characteristics of two inception cohorts (Italian [ITC] and Spanish [SPC]) cohorts of patients with systemic lupus erythematosus (SLE) at the time of diagnosis and at one year of follow-up.

Methods

Demographic, clinical and immunological characteristics, and treatments at SLE diagnosis and at 12 months of follow-up of ITC and SPC were compared.

Results

One hundred and sixty-four patients in the ITC and 231 patients in the SPC were compared. the patients from ITC were younger at SLE diagnosis (41.1±15.0 years vs. 46.4±15.6 years; p<0.001) and had a higher prevalence of arthritis (62.8% vs. 45.5%; p=0.001), serositis (25.6% vs. 16.0%; p=0.026), neurological involvement (7.9% vs. 1.7%; p=0.006), and immunological abnormalities (anti-dsDNA, anti-Sm, antiphospholipid antibodies) (93.9% vs. 77.8%; p<0.001). Conversely, photosensitivity (29.5% in ITC vs. 45.9% in SPC; p=0.001) and oral ulcers (12.4% vs. 30.3%; p<0.001) were more frequent at onset of SLE in the Spanish patients. At the first 12 months of follow-up, these differences were maintained. At SLE onset, more Italian patients received glucocorticoids (85.4% vs. 50.2%; p<0.001) and immunosuppressive agents. At 12 months of follow-up, more Spanish patients were treated with antimalarials (75.6% in ITC vs. 90.0% in SPC; p<0.001). Conversely, the use of glucocorticoids was lower in SPC (89.0% in ITC vs. 57.1% in SPC; p<0.001).

Conclusion

These cohorts presented different profiles in terms of pattern of organ/system involvement and disease treatment, possibly as a consequence of patient selection or different disease management approaches between Italy and Spain.

Key words

systemic lupus erythematosus, inception cohort, clinical manifestations

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of autoimmune origin occurring in 90% of cases in women during the third/forth decade. As for other systemic autoimmune disorders, SLE can be associated to variable clinical manifestations and follows a relapsing and remitting course (1, 2).

Patients with SLE may present with variable combinations of more disease-specific clinical manifestations together with completely unspecific symptoms. Some dermatological and renal manifestations as well as anti-dsDNA antibodies can be considered as lupus-specific. However, these manifestations are often coupled to unspecific ones, such as constitutional symptoms, arthralgia, arthritis, serositis, and antinuclear antibody (ANA) positivity (3, 4).

Taking into account the complexity of clinical manifestations, SLE represents a true diagnostic challenge for physicians despite the improvements made in recent years in the knowledge of the disease pathogenesis. Furthermore, an early diagnosis is crucial to start prompt treatment, whereas a delay in diagnosis has been associated to a worse prognosis, decrease in survival rates and a worse quality of life (5, 6).

For these reasons, given the importance of a better knowledge of the clinical and immunologic characteristics of SLE patients at the beginning of their disease, we focused our attention on two inception cohorts of southern European lupus patients with a short disease duration (up to one year), coming from 9 Italian Rheumatology Departments (7) and 32 Spanish Internal Medicine Departments (8, 9).

The main objective of the present study was to describe and compare the general clinical and immunological characteristics of patients of the two cohorts at the time of the diagnosis of SLE and at one year of follow-up, both in terms of disease activity and therapeutic strategies.

Patients and methods

This is a comparative study between two inception cohorts of southern European SLE patients with short disease duration (less than 12 months). Early Lupus Project, named Italian cohort (ITC) henceforth, is a multicentre prospective study involving 9 Italian centres with longstanding experience in lupus management. All but one (San Camillo Hospital, tertiary referral centre) of the participating Italian hospitals are University centres. The study started in January 2012 (7). RELES (*Registro Español de pacientes con Lupus Eritematoso Sistémico* in Spanish) referred to as SPC in the present study, is a research project of the Spanish Group of Autoimmune Diseases (*Grupo de Enfermedades Autoinmunes, GEAS*) within the Spanish Society of Internal Medicine (*Sociedad Española de Medicina Interna, SEMI*). It is the first Spanish multicentric inception lupus cohort in which patients with a new diagnosis of SLE have been included since January 2009. Thirty-two Internal Medicine Departments from hospitals all over Spain participated in this study (8-10). The majority of participating Spanish hospitals are University centres of second and third level.

In both cohorts, the patients were recruited consecutively and all of them had a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) classification criteria (11) and disease duration (from diagnosis until study entry) was required to be less than 12 months. Only patients with available data of study inclusion visit and at 12 months were included. Written informed consent was obtained from each patient according to the declaration of Helsinki. In addition, all participating centres obtained approval from the local ethics committee.

Information on demographic characteristics, clinical manifestations, laboratory results, disease activity and damage at study entry and at 12 months were collected into specific forms and subsequently transferred into specific electronic databases. Global SLE disease activity was measured by European Consensus Lupus Activity Measurement (ECLAM) (12, 13) in the ITC and by Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) (14) in the SPC. Cumulative damage was scored in both cohorts according to the Systemic Lupus International

Collaborating Clinics (SLICC) Damage Index, a validated measure to assess damage in SLE (15).

Statistical analysis

The statistical analysis was performed by means of "R" statistical software. Conventional chi-square and Fisher exact test were used to analyse qualitative differences. Regarding age at SLE diagnosis and SDI between the Italian and Spanish cohorts Wilcoxon test was utilised because the values were not normally distributed (analysed by Shapiro test). Continuous variables are summarised as mean ± standard deviation (SD) or median and range, as appropriate. Wilcoxon's test was used to calculate the *p*-value.

Results

General characteristics

One hundred and sixty-four SLE patients in the ITC and 231 patients in the SPC fulfilled the inclusion criteria at the time of enrolment into the study. The majority of patients were female (84.8% in ITC and 90.5% in SPC; p=0.116) and of Caucasian ethnicity (93.9% in ITC and 87.9% in SPC; p=0.068) in both cohorts without significant differences. The prevalence of family history of SLE was similar between the two cohorts as well (6.7% in ITC and 6.1% in SPC; p=0.960). Patients from ITC were younger at SLE diagnosis (41.1±15.0 years in ITC *vs*. 46.4±15.6 years in SPC; p<0.001) (Table I).

Clinical manifestations and immunological features included in the ACR classification criteria at SLE diagnosis

Italian SLE patients had a higher prevalence of arthritis (62.8% *vs*. 45.5%; p=0.001), serositis (25.6% *vs*. 16.0%; p=0.026), neurological involvement (7.9% *vs*. 1.7%; p=0.006), and immunological abnormalities (anti-Sm, anti-dsDNA, antiphospholipid antibodies; 93.9% *vs*. 77.8% as a whole; p<0.001). Conversely, photosensitivity (29.5% in ITC *vs*. 45.9% in SPC; p=0.001) and oral ulcers (12.4% in ITC *vs*. 30.3% in SPC; p<0.001) were more frequent at onset of SLE in Spanish patients (Table II).

Table I. Comparison of demographic characteristics between Italian and Spanish SLE cohorts.

	Italian cohort (n=164)	Spanish cohort (n=231)	*p*-value
Sex (female)	139 (84.8)	209 (90.5)	NS
Race			
Caucasian	154 (93.9)	203 (87.9)	
African	4 (2.4)	2 (0.9)	
Indian	1 (0.6)	15 (6.5)	
Asian	2 (1.2)	2 (0.9)	
Others	3 (1.8)	9 (3.9)	0.008
Family history of SLE	11 (6.7)	14 (6.1)	NS
Smoke	71 (43.3)	77 (33.3)	NS
Age at SLE diagnosis (years)	41.1 ± 15.0	46.6 ± 15.6	<0.001

Values of categorical variables are expressed as number and percentage and those for continuous variables are presented as mean ± standard deviation. NS: not significant; SLE: Systemic Lupus Erythematosus.

Laboratory features, clinimetry and comorbidity at SLE diagnosis

Regarding immunological features, patients from ITC presented with higher prevalence of markers of lupus immunological activity such as low levels of C3 (70.2% *vs*. 52.6%; p=0.001), low C4 (86.3% *vs*. 46.9%; p<0.001), and positive anti-dsDNA antibody (78.6% *vs*. 59.3%; p<0.001). In addition, anticardiolipin antibodies were more frequent in Italian patients (27.7% *vs*. 18.3%; p=0.046) (Table II).

In both cohorts the majority of patients showed an active disease at study entry (89% of ITC and 97% of SPC had ECLAM or SLEDAI, respectively, greater than 0). However, a small proportion of patients had ECLAM or SLEDAI = 0 at baseline, and they were more represented in ITC (10.9% *vs*. 2.7%; p=0.002) (Table II).

Concerning comorbidities, osteoporosis was detected more frequently in the ITC (7.9% *vs*. 0.9%; p=0.001), whereas the prevalence of diabetes was similar in the two cohorts (2.4% in ITC and 3.9% in SPC) (Table III).

Clinical manifestations and immunological features included in the ACR classification criteria at 12 months of follow-up

Of note, no patients were lost in the first year of follow-up. Overall, most of the differences found at the time of SLE diagnosis were maintained at first 12 months of follow-up. Patients from ITC still had more arthritis (65.2% *vs*. 50.9%; p=0.006), and neurological involvement (9.1% *vs*. 1.7%; p=0.002) when compared with SPC (Table II). Conversely, Spanish patients had more frequently photosensitivity (31.7% in ITC versus 46.8% in SPC; p=0.004), oral ulcers (12.2% *vs*. 32.9%, respectively; p<0.001), and haematological involvement (57.3% *vs*. 69.1%, respectively; p=0.021). Immunological criteria (anti-Sm, anti-dsDNA, antiphospholipid antibodies) were similar between both cohorts (Table II).

Laboratory features, clinimetry and comorbidity at 12 months of follow-up

At 12 months of follow-up, Italian patients remained with higher immunological activity in form of higher prevalence of low levels of C3 (52.6% *vs*. 33.6%; p<0.001), C4 (75.7% *vs*. 26.6%; p<0.001), and positive anti-dsDNA (60.8% *vs*. 40.6%; p<0.001) (Table II). However, in both cohorts the prevalence of those patients with low C3, low C4 and positive anti-dsDNA antibody decreased when compared with baseline.

Of note, in both cohorts the majority of patients still showed an active disease at 12 months follow-up (65.2% in ITC and 79.8% in SPC). However, among patients with active disease at baseline (ECLAM >0 in ITC and SLEDAI-2k >0 in SPC) a higher percentage of patients in ITC (32.2%) than in SPC (18.9%) achieved disease remission (ECLAM or SLEDAI-2k = 0, respectively). Moreover, among patients with moderate disease at baseline (ECLAM >5 in ITC and SLEDAI >5 in SPC) a higher percentage of patients in ITC (25%) than in

Table II. Clinical manifestations and immunological features included in the ACR classification criteria at SLE diagnosis and at 12 months in both cohorts of SLE patients.

	At baseline			At 12 months		
	Italian cohort (n=164)	Spanish cohort (n=231)	*p*-value	Italian cohort (n=164)	Spanish cohort (n=231)	*p*-value
ACR criteria at baseline						
Malar rash	52 (31.7)	62 (26.8)	NS	59 (35.9)	70 (30.3)	NS
Discoid rash	12 (7.4)	23 (9.9)	NS	14 (8.6)	25 (10.8)	NS
Photosensitivity	48 (29.5)	106 (45.9)	0.001	52 (31.7)	108 (46.8)	0.004
Oral ulcers	20 (12.4)	70 (30.3)	<0.001	20 (12.2)	76 (32.9)	<0.001
Arthritis	103 (62.8)	105 (45.5)	0.001	107 (65.2)	117 (50.8)	0.006
Serositis	42 (25.6)	37 (16.0)	0.026	43 (26.2)	41 (17.8)	NS
Renal criteria	50 (30.5)	55 (23.8)	NS	53 (32.3)	65 (28.1)	NS
Neurological criteria	13 (7.9)	4 (1.7)	0.006	15 (9.2)	4 (1.7)	0.002
Haematological criteria	89 (54.3)	147 (63.6)	NS	94 (57.3)	159 (69.1)	0.021
Immunological criteria	154 (93.9)	179 (77.8)	<0.001	155 (94.5)	187 (89.1)	NS
Antinuclear antibodies	163 (99.4)	228 (98.7)	NS	163 (100)	228 (99.1)	NS
SLE activity						
ECLAM or SLEDAI-2K = 0 [a]	18 (10.9)	6 (2.7)	0.002	57 (34.8)	45 (20.2)	0.002
ECLAM or SLEDAI-2K mean (SD)	3.1 (2.4)	10 (8.1)	-	1.1 (1.4)	4.1 (3.9)	-
ECLAM or SLEDAI-2K median (IQR)	2.5 (1.4-5)	8 (4-14)	-	1 (0-3)	4 (2-5)	-
ECLAM or SLEDAI-2k >5 [b]	27 (16.5)	146 (65.4)	-	2 (1.2)	55 (24.7)	-
SLE damage						
SDI mean (SD)	0.23 ± 0.54	0.40 ± 0.87	NS	0.46 ± 1.10	0.54 ± 1.05	NS
SDI ≥1	22 (18)	57 (24.7)	NS	44 (26.8)	70 (30.3)	NS
Immunological features						
Low C3	113 (70.2)	121 (52.6)	0.001	80 (52.6)	76 (33.6)	<0.001
Low C4	139 (86.3)	108 (46.9)	<0.001	115 (75.7)	60 (26.6)	<0.001
Anti-dsDNA antibodies	125 (78.6)	137 (59.3)	<0.001	79 (60.8)	91 (40.6)	<0.001
Anti-SSA(Ro) antibodies	56 (37.8)	89 (38.7)	NS	33 (41.8)	55 (33.7)	NS
Anti-SSB(La) antibodies	23 (15.6)	37 (16.1)	NS	10 (12.7)	22 (13.4)	NS
Anti-Sm antibodies	29 (19.7)	48 (20.9)	NS	13 (16.5)	25 (15.2)	NS
Anti-RNP antibodies	36 (24.5)	43 (18.7)	NS	19 (24.4)	27 (16.7)	NS
Anticardiolipin antibodies	38 (27.7)	42 (18.3)	0.046	15 (21.4)	17 (10.3)	0.039
Anti-β2GPI antibodies	28 (21.4)	43 (20.5)	NS	11 (16.2)	22 (13.7)	NS
Lupus anticoagulant	26 (19.7)	51 (22.4)	NS	10 (14.3)	32 (19.6)	NS

Values of categorical variables are expressed as number and percentage.

[a] Number (and percentage) of SLE patients with ECLAM or SLEDAI-2K =0.

[b] Number (and percentage) of SLE patients with ECLAM or SLEDAI-2K >5.

Valid values:

Italian cohort at baseline: discoid rash and photosensitivity (n=163); oral ulcers (n=162); SLICC index (n=122); low C3 and C4 (n=161); anti-dsDNA (n=159); anti-SSA(Ro) (n=148); anti-SSB(La), anti-Sm and anti-RNP (n=147); anticardiolipin (n=137), anti-β2GPI (n=131), and lupus anticoagulant (132).

Italian cohort at 12 months: discoid rash and antinuclear antibodies (n=163); low C3 and C4 (n=152); anti-dsDNA (n=130); anti-SSA(Ro), anti-SSB(La) and anti-Sm (n=79), anti-RNP (n=78); anticardiolipin and lupus anticoagulant (n=70), anti-β2GPI (n=68).

Spanish cohort at baseline: Low C3, C4, anti-SSA(Ro), anti-SSB(La), anti-Sm, anti-RNP, and anticardiolipin (n=230); anti-β2GPI (n=210), lupus anticoagulant (n=228).

Spanish cohort at 12 months: arthritis, haematological involvement, and antinuclear antibodies (n=230); renal involvement (n=228); immunological involvement (n=179); low C3, C4 (n=226); anti-dsDNA (224), anti-SSA(Ro) and lupus anticoagulant (n=163), anti-SSB(La) (164); anti-Sm and anticardiolipin (n=165); anti-RNP (162); anti-β2GPI (n=161).

ACR: American College of Rheumatology; ECLAM; European Consensus Lupus Activity Measurement; IQR: interquartilic range; NS: not significant; SD: standard deviation; SDI: Systemic Lupus International Collaborating Clinics (SLICC) Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

SPC (17.7%) achieved disease remission (ECLAM or SLEDAI-2K = 0). There was no difference in SLE damage accrual between the two cohorts at 12 months of follow-up (Table II).

Osteoporosis was still more prevalent in ITC (8.6% *vs*. 1.8%; *p*=0.004), whereas the prevalence of diabetes did not differ (Table III).

Development of new clinical manifestations and immunological features included in the ACR classification criteria during the 12 months of follow-up

Further, we compared the development of new ACR classification criteria and immunological features at 12 months taking into account the difference between the two cohorts at baseline. For each analysis, the population was composed by the subjects devoid of that ACR specific criterion in the baseline analysis. During the 12-month follow-up period, patients of both cohorts developed new clinical manifestations and immunological features of those included in the ACR classification cri-

Table III. Treatments and comorbidities at baseline and at 12 months of follow-up in both cohorts of SLE patients.

	At baseline			At 12 months		
	Italian cohort (n=164)	Spanish cohort (n=231)	*p*-value	Italian cohort (n=164)	Spanish cohort (n=231)	*p*-value
Treatments						
Glucocorticoids	140 (85.4)	116 (50.2)	<0.001	146 (89.2)	132 (57.1)	<0.001
Antimalarials	104 (63.4)	116 (65.4)	NS	124 (75.6)	208 (90.0)	<0.001
Azathioprine	18 (10.9)	10 (4.3)	0.016	30 (18.3)	27 (11.7)	NS
Mycophenolate	16 (9.8)	16 (6.9)	NS	37 (22.6)	51 (22.1)	NS
Methotrexate	14 (8.5)	10 (4.3)	NS	17 (10.4)	21 (9.1)	NS
Cyclophosphamide	12 (7.3)	6 (2.6)	0.047	13 (7.9)	10 (4.3)	NS
Cyclosporine	5 (3.1)	0	NS	5 (3.1)	0	0.012
Biologics agents	3 (1.8)	0	NS	13 (7.9)	1 (0.4)	<0.001
Comorbidities						
Diabetes mellitus	4 (2.4)	9 (3.9)	NS	4 (2.4)	10 (4.4)	NS
Osteoporosis	13 (7.9)	2 (0.9)	0.001	14 (8.5)	4 (1.8)	0.004

Values of categorical variables are expressed as number and percentage.
Glucocorticoids included prednisone in the Italian cohort and prednisone, pulses of methylprednisolone and deflazacort in the Spanish cohort.
Antimalarials included hydroxychloroquine and mepacrine in the Italian cohort and hydroxychloroquine in the Spanish cohort.
Mycophenolate included mycophenolate mofetil and mycophenolate sodium in both cohorts.
Biologics agents included rituximab, belimumab, epratuzumab, and abatacept in Italian cohort and rituximab and belimumab in the Spanish cohort.
NS: not significant.

teria in a similar percentage, with the exception of oral ulcers and immunological manifestations (Table IV). In fact, the new appearance of oral ulcers (0% *vs*. 3.7%; $p<0.001$) were more frequent among the Spanish patients. Conversely, development of low C4 (31.6% *vs*. 5.8%; $p=0.003$) and anti-dsDNA antibody (66.7% *vs*. 5.6%; $p=0.014$) were more frequent in ITC.

Treatments at SLE diagnosis and at 12 months of follow-up

Once the diagnosis of lupus was made, more Italian patients received glucocorticoids (85.4% *vs*. 50.2%; $p<0.001$), azathioprine, cyclophosphamide, and cyclosporine (Table III). The most relevant finding at 12 months of follow-up was the difference in the percentage of patients treated with antimalarials, higher in Spanish patients (75.6% in ITC *vs*. 90.0% in SPC; $p<0.001$). In addition, the use of glucocorticoids was lower in Spanish patients (89.0% in ITC *vs*. 57.1% in SPC $p<0.001$). Of note, biologics agents were more often used in ITC (7.9% *vs*. 0.4%; $p<0.001$).

Table IV. Development of new clinical manifestations and immunological features included in ACR classification criteria during the 12 months of follow-up*.

	Italian cohort	Spanish cohort	*p*-value
New ACR criteria within 12 months			
Malar rash	7/112 (6.3)	8/169 (4.7)	NS
Discoid rash	2/150 (1.3)	2/208 (1)	NS
Photosensitivity	4/115 (3.5)	2/125 (1.6)	NS
Oral ulcers	0/142 (0)	6/161 (3.7)	<0.001
Arthritis	4/61 (6.6)	12/125 (9.6)	NS
Serositis	1/122 (0.8)	4/194 (2.1)	NS
Renal criteria	3/114 (2.6)	10/176 (5.7)	NS
Neurological criteria	2/151 (1.3)	0/227 (0)	NS
Haematological criteria	5/75 (6.7)	12/83 (14.5)	NS
Immunological criteria	0/10 (0)	7/51 (13.7)	NS
Antinuclear antibodies	0 (0)	0/2 (0)	NS
New immunological criteria within 12 months			
Low C3	8/45 (17.8)	15/106 (14.2)	NS
Low C4	6/19 (31.6)	7/120 (5.8)	0.003
Anti-dsDNA antibodies	2/3 (66.7)	5/90 (5.6)	0.014
Anti-SSA(Ro) antibodies	4/45 (8.9)	5/104 (4.8)	NS
Anti-SSB(La) antibodies	2/65 (3.1)	3/139 (2.2)	NS
Anti-Sm antibodies	0/59 (0)	4/132 (3.0)	NS
Anti-RNP antibodies	3/54 (5.6)	5/132 (3.8)	NS
Anticardiolipin antibodies	2/49 (4.1)	2/140 (1.4)	NS
Anti-ß2GPI antibodies	2/50 (4)	4/127 (3.2)	NS
Lupus anticoagulant	0/106 (0)	9/127 (7.1)	NS

* Number of subjects devoid of criteria at baseline.
ACR: American College of Rheumatology; NS: not significant.

Discussion

In the present study we compared the prevalence of the most relevant clinical and immunological features and therapies between two European cohorts of SLE patients with recent onset at disease SLE diagnosis and at 12 months of follow-up. In the two groups, as expected, ANA was the most prevalent ACR criteria. Considering clinical manifestations, arthritis and serositis were more prevalent as presenting manifestations in ITC whereas haematological manifestations, photosensitivity and arthritis were the predominant signs at SLE onset in SPC. Neurological disorders were more prevalent in patients from ITC, both at SLE onset and at 12 months. Finally, immunological involvement, as ACR criteria including anti-dsDNA, anti-Sm, and antiphospholipid antibodies was more prevalent in ITC at baseline. Patients from SPC more often presented with mucocutaneous involvement

at the beginning of their disease. The higher prevalence of arthritis in ITC could be a bias due to the medical departments contributing to each cohort, Rheumatology departments in the case of ITC and Internal Medicine departments for the SPC. In the two cohorts, aside arthritis and mucocutaneous involvement, the most frequent clinical manifestations at SLE onset were haematological and immunological abnormalities.

In general, the results of the present study are comparable with those described in other inception cohorts of SLE patients. Nossent *et al*. (16) described the early disease course of 200 SLE patients from 14 European centres. Similar to the current study, the most prevalent criteria were ANA presence (97%) followed by immunological involvement (74%), arthritis (69%), leukopenia as haematological disorder (54%) and malar rash (53%). The SLICC cohort reported in 2008 412 SLE patients recruited in 18 international academic centres. At enrolment the mean disease duration was only 5±4.2 months. Again, ANA followed by immunological and haematological disorders were the predominant presenting manifestations of SLE. Conversely to both ITC and SPC, serositis was present in up to 75% of patients from SLICC cohort (17). It is important to emphasise that the patients of SLICC cohort had a wide ethnic distribution although predominantly Caucasian (62.5%). Finally, 1214 SLE patients were recruited in GLADEL (Grupo Latinoamericano de Estudio del Lupus) cohort, corresponding to three main different ethnic groups, Mestizo (44%), Caucasian (42%), and African-Latin American (12%), respectively (18). Overall, median disease duration at study entry was 32 months. Unfortunately, GLADEL cohort cannot be completely compared with ITC and SPC due to different definitions of clinical variables. Of note, after controlling for clinical and sociodemographic variables as well as for country of origin, both mestizos and African-Latin American were statistically associated with a higher probability of lymphopenia, and mestizos with renal damage, than Caucasians. Therefore, different ethnic origin of patients is one of the reasons that could explain the discrepancies between studies and, probably, some of the differences between ITC and SPC (13% and 6% of patients were non-Caucasian in SPC and ITC, respectively). Another reason accounting for the differences in the prevalence of neurological involvement between ITC and SPC cohorts could be the different composition of the centres involved. In ITC rheumatologic centres that have particular expertise in the management of neurolupus are involved, leading to a more selected recruitment of patients with neuropsychiatric involvement. The very specialised Spanish departments of Internal Medicine in the management of SLE patients may explain the prevalence of different SLE criteria in SPC. It is possible that included Spanish SLE patients had more severe or infrequent clinical manifestations representing a selection bias. Considering the difference in treatments, it is important to highlight the higher proportion of patients who received glucocorticoids in the ITC at SLE onset and during follow-up. A more severe disease represented by the higher percentage of Italian patients with neurological involvement and higher prevalence of markers of SLE immunological activity such as low levels of C3 and anti-dsDNA antibody positivity could justify this difference. Another important point to highlight is the higher percentage of Spanish patients treated with antimalarials (up to 90%) at 12 months of follow-up. This could be an additional reason of the lower percentage of patients treated with glucocorticoids at 12 months.

Our study has some limitations. First, the activity index in the two cohorts was not the same, ECLAM in ITC and SLEDAI in SPC. However, we have tried to minimise this limitation comparing patients with inactive disease (ECLAM or SLEDAI=0) and those with moderate disease assuming a value of ECLAM and SLEDAI >5. Second, laboratory determinations were performed in each one of the Italian and Spanish participating hospitals with a wide variety of assays. However, we have used ordinal variables (yes/not) for anti-dsDNA antibodies and low complement values. Therefore, we consider that having used different laboratories should not be an important limitation. Moreover, 12 months of follow-up is not enough time to detect differences in damage index. Finally, as in all observational multicentric studies, the accuracy of the clinical manifestations as judged by the attending physician cannot be verified.

In conclusion, Italian patients with recent onset of SLE compared with Spanish patients with recent onset of SLE show different profile of pattern of organ/system involvement and disease treatment. These differences may as a consequence of patients' selection or different disease management approach between Italy and Spain.

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References

1. D'CRUZ DP, KHAMASHTA MA, HUGHES GRV: Systemic lupus erythematosus. *Lancet* 2007; 369: 587-96.
2. DI BATTISTA M, MARCUCCI E, ELEFANTE E *et al*.: One year in review 2018: systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 763-77.
3. GIACOMELLI R, AFELTRA A, ALUNNO A *et al*.: International consensus: What else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjögren's syndrome)?: The unmet needs and the clinical grey zone in autoimmune disease management. *Autoimmun Rev* 2017; 16: 911-24.
4. ZUCCHI D, ELEFANTE E, CALABRESI E, SIGNORINI V, BORTOLUZZI A, TANI C: One year in review 2019: systemic lupus erythematosus. *Clin Exp Rheumatol* 2019; 37: 715-22.
5. CERVERA R, KHAMASHTA MA, FONT J *et al*.; European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* (Baltimore) 2003; 82: 299-308.
6. UROWITZ MB, GLADMAN DD, IBAÑEZ D *et al*.: Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. *Arthritis Care Res* 2012; 64: 132-37.
7. SEBASTIANI GD, PREVETE I, PIGA M *et al*.: Early Lupus Project – A multicentre Italian study on systemic lupus erythematosus of recent onset. *Lupus* 2015; 24: 1276-82.
8. RUIZ-IRASTORZA G, GARCIA M, ESPINOSA G *et al*.: Patterns of drug therapy in newly diagnosed Spanish patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2016; 34: 466-72.
9. RUIZ-IRASTORZA G, GARCIA M, ESPINOSA G *et al*.: First month prednisone dose predicts prednisone burden during the following 11 months: an observational study from the RELES cohort. *Lupus Sci Med* 2016; 3: e000153.
10. CANORA J, GARCÍA M, MITJAVILA F *et al*.: Clinical characteristics during diagnosis of a prospective cohort of patients with systemic lupus erythematosus treated in Spanish Departments of Internal Medicine: The RELES study. *Rev Clin Esp* 2017; 217: 7-14.
11. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
12. VITALI C, BENCIVELLI W, ISENBERG DA *et al*.: Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. II. Identification of the variables indicative of disease activity and their use in the development of an activity score. The European Consensus Study Group for Disease Activity in SLE. *Clin Exp Rheumatol* 1992; 10: 541-47.
13. MOSCA M, BENCIVELLI W, VITALI C, CAR-

RAI P, NERI R, BOMBARDIERI S: The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. *Lupus* 2000; 9: 445-50.
14. GLADMAN DD, IBAÑEZ D, UROWITZ MB: Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29; 288-91.
15. GLADMAN D, GINZLER E, GOLDSMITH C *et al*.: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363-69.
16. NOSSENT J, KISS E, ROZMAN B, POKORNY G *et al*.: Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. *Lupus* 2010; 19: 949-56.
17. HANLY JG, UROWITZ MB, SIANNIS F *et al*.: Autoantibodies and neuropsychiatric events at diagnosis of SLE. Results from an international inception cohort study. *Arthritis Rheum* 2008; 58: 843-53.
18. PONS-ESTEL BA, CATOGGIO LJ, CARDIEL MH *et al*.: The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus. Ethnic and disease heterogeneity among ''Hispanics''. *Medicine* (Baltimore) 2004; 83: 1-17.