**Comprehensive Description of Clinical Characteristics of a Large Systemic Lupus Erythematosus Cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) With Emphasis on Complete Versus Incomplete Lupus Differences**

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**Abstract:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiple organ involvement and pronounced racial and ethnic heterogeneity. The aims of the present work were (1) to describe the cumulative clinical characteristics of those patients included in the Spanish Rheumatology Society SLE Registry (RELESSER), focusing on the differences between patients who fulfilled the 1997 ACR-SLE criteria versus those with less than 4 criteria (hereafter designated as incomplete SLE (iSLE)) and (2) to compare SLE patient characteristics with those documented in other multicentric SLE registries.

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METHODS

RELESSER-T is a cross-sectional study, recording cumulative clinical data until the last medical visit and the status of the disease and treatments at this time. Its design and the methods have been described in detail elsewhere. In short, 45 Rheumatology Units throughout Spain participated in the study. All of the participating centers belong to the same national public healthcare system and thus have the same resources at their disposal. All clinicians involved in the study were expert rheumatologists in SLE. They were asked to include subjects 16 years of age or older, and who met 4 or more of the 1997 ACR SLE criteria and those who did not (“incomplete SLE”): iSLE). We also compared these cross-sectional data from RELESSER with those from other large cohorts around the world.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease with multiple organ involvement and remains one of the most frequent systemic rheumatic diseases. In Spain, it has a prevalence of 9 per 10,000 persons. SLE is a remarkably heterogeneous disease with very different symptoms and outcomes. In recent years, considerable efforts have been made to gain a deeper understanding of the disease and how to best manage it. One such effort involves the setting up of SLE patient registries similar to those that have been active in North and South America, as well as in Europe, since the seventies. These registries contain a large number of subjects and reflect a real-world setting for lupus patients. Data obtained from these lupus registries are essential for planning, designing, and conducting clinical lupus studies.

The severity of SLE may vary considerably from one population to another and the Task Force of the EULAR Standing Committee for International Clinical Studies has included this topic in its suggested research agenda. With the aim of obtaining a more representative, accurate information database about SLE in the southern European population, the Spanish Rheumatology Society (SER) has established a multicenter registry of patients with SLE known as RELESSER (Spanish Rheumatology Society SLE Registry), which is the largest European SLE registry mounted thus far. It offers comprehensive, reliable, and updated information about this complex disease, and is being carried out in two phases. The first part of the registry (RELESSER-T), with cross-sectional data recording has already completed the enrolment process.

There was, however, a subgroup of patients that did not meet the 1997 ACR SLE criteria but that presented symptoms and/or laboratory results which often led to the clinician diagnosing them as SLE patients. As there are relatively few studies concerning these types of patients, it was considered worthwhile to include them in the Spanish registry. The availability of a large and well-characterized SLE population via RELESSER provides an excellent opportunity to compare, in detail, both of the patient groups included in the register.

The purposes of the present analysis were to describe the demographic features, cumulative clinical manifestations, severity, treatments, and complications of RELESSER patients at the time of the last medical visit, focusing on the differences between patients who fulfilled 4 or more of the 1997-ACR SLE criteria and those who did not (“incomplete SLE”: iSLE). We also compared these cross-sectional data from RELESSER with those from other large cohorts around the world.

Abbreviations: Ab = antibodies, ACR = American College of Rheumatology, ANA = antinuclear antibodies, BILAG = British Isles Lupus Assessment Group, CI = confidence intervals, CVC = cyclophosphamide, DM = diabetes mellitus, iSLE = incomplete SLE, OR = odds ratio, PHT = pulmonary hypertension, SD = standard deviation, SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-SLEDAI, SER = Spanish Rheumatology Society, SKI = Severity Katz Index, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLICC/ACR DI = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

RELESSER is a multicenter hospital-based registry, with a collection of data from a large, representative sample of adult patients with SLE (1997 ACR criteria) seen at Spanish rheumatology departments. The registry includes demographic data, comprehensive descriptions of clinical manifestations, as well as information about disease activity and severity, cumulative damage, comorbidities, treatments and mortality, using variables with highly standardized definitions.

A total of 4,024 SLE patients (91% with >4 ACR criteria) were included. Ninety percent were women with a mean age at diagnosis of 35.4 years and a median duration of disease of 11.0 years. As expected, most SLE manifestations were more frequent in SLE patients than in iSLE ones and every one of the ACR criteria was also associated with SLE condition; this was particularly true of malar rash, oral ulcers and renal disorder. The analysis—adjusted by gender, age at diagnosis, and disease duration—revealed that higher disease activity, damage and SLE severity index are associated with SLE [OR: 1.14; 95% CI: 1.08–1.20 (P < 0.001); 1.29; 95% CI: 1.15–1.44 (P < 0.001); and 2.10; 95% CI: 1.83–2.42 (P < 0.001), respectively]. These results support the hypothesis that iSLE behaves as a relative stable and mild disease. SLE patients from the RELESSER register do not appear to differ substantially from other Caucasian populations and although activity hypothesis that iSLE behaves as a relative stable and mild disease.

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Variables and Definitions

Three hundred fifty-nine variables per patient were collected. Variables were divided into several groups:

1. Demographic data: age, gender, and ethnicity.
2. Chronology: time of first symptom and diagnosis of SLE, follow-up.
3. Cumulative manifestations as defined in (1) the ACR classification criteria for SLE,8,11 (2) the activity index SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)12 in the BILAG (British Isles Lupus Assessment Group) Index,13,14 and (3) the SLICC/ACR DI (Systemic Lupus International Collaborative Clinics/Armed Forces Institute of PathologyDamage Index).15
4. SLE status, using the activity index SELENA-SLEDAI (Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-SLEDAI)16; damage, using the SLICC/ACR Damage Index (SLICC/ACR/DI)15; and severity, using the Katz Index (SKI), range 0 to 13.17
5. Coexistence of antiphospholipid syndrome, as defined by the Sydney classification criteria18; mixed connective tissue disease, as defined by Alarcón-Segovia criteria19; or Sjögren syndrome if the patient presented sicca syndrome and a positive Schirmer test, as well as typical changes in scintigraphy or a positive labial biopsy.
6. Comorbidities, including severe infections and conditions described in the Charlson Comorbidity Index.20
7. Laboratory findings, imaging or pathological studies.
8. Any treatments undergone and the reason for discontinuation, if applicable.
9. Refractory SLE: defined as inefficacy of cyclophosphamide (CYC), use of rituximab, splenectomy, or inefficacy of 2 or more immunosuppressives (methotrexate, leflunomide, abatacept, anti-TNF, azathioprine, mycophenolate mofetil, and/or mycophenolic acid).

A clinical or laboratory finding was considered noteworthy if the patient presented it at any time during the course of the disease.

Statistical Analysis

Relative and absolute frequencies for qualitative variables were calculated, as were mean and standard deviations or median and interquartile ranges for the quantitative variables, depending on whether the distribution was normal or not. Differences between values due to the number of ACR criteria fulfilled (<4 or ≥4) were analyzed using a Student’s t test for normal quantitative variables and a Mann–Whitney test for abnormal variables. Chi-square was calculated for qualitative independent variables, with corrections made with a Yates or Fisher’s exact test for dichotomous variables.

Finally, to investigate the risk factors associated with an iSLE status, we used a case–control design. An analysis based on the estimation of simple and adjusted (by gender, age at onset, and disease duration, for all of the variables studied) odds ratios (ORs) by means of logistic regression with 95% confidence intervals (95% CI) was carried out; P values <0.05 were considered significant. The analysis was performed using the statistical package SPSS 21.0 for Windows (SPSS, Chicago, IL).

Ethical Issues

RELESSER adheres to the principles established by the Declaration of Helsinki21 and the Protocol of Oviedo.22 Confidentiality was respected in full accordance with Spanish law.23 In addition, the study was approved by the local ethics committees.

RESULTS

A total of 4024 patients were included; 3679 (91.4%) patients were SLE and 345 (8.5%) iSLE. Ninety percent were women, the mean age at diagnosis was 35.4 (SD: 15.1) years, and the median duration of disease was 11.0 years with an interquartile range (IQ) of 6.0 to 19.0 years. The rest of the demographic and chronological data contained in the RELESSER registry is described elsewhere.10

In the RELESSER registry, SLE patients experienced their first symptom at a younger age and were also typically younger when the diagnosis was first made. However, the delay between the first symptom’s appearance and diagnosis was similar in both groups. Disease duration and follow-up were longer in SLE subjects than iSLE ones (Table 1). The ACR criteria frequencies are shown in Table 2. The most common SLE clinical manifestation in both groups (SLE and iSLE) was arthritis. All ACR criteria had a higher

### Table 1. Demographic and Chronological Characteristics of iSLE and SLE Patients (Bivariate and Multivariate Analyses)

| Variable                        | N  | iSLE    | SLE     | P      | OR [95% CI]   | OR* [95% CI] | P    |
|---------------------------------|----|---------|---------|--------|---------------|--------------|------|
| Female, N (%)                   |    | 4016    | 292 (84.9) | 3315 (90.3) | 0.002 | 1.65 [1.21–2.27] | —   | —   |
| Caucasians, N (%)               |    | 3905    | 312 (94.0) | 3326 (93.1) | 0.617 | 1.16 [0.72–1.85] | 1.20 [0.2–1.99] | 0.490 |
| Age at diagnosis mean (SD)      |    | 3990    | 42.9 (16.8) | 34.6 (14.6) | <0.001 | 0.97 [0.96–0.97] | 0.92 [0.90–0.96] | <0.001 |
| Age at first symptom mean (SD)  |    | 3919    | 41.0 (SD: 17.2) | 32.6 (SD: 14.5) | <0.001 | 0.97 [0.9–0.97] | —   | —   |
| Diagnostic delay1 median (p25–p75) |    | 3923    | 7.0 (2.0–26.0) | 5.0 (1.0–24.0) | 0.467 | 1.00 [1.00–1.00] | 0.99 [0.99–1.00] | <0.001 |
| Follow-up2 median (p25–p75)     |    | 3827    | 67.0 (23.3–125.0) | 102.0 (46.0–170.0) | <0.001 | 1.00 [1.00–1.00] | 1.00 [1.00–1.00] | 0.439 |
| Disease duration median (p25–p75) |    | 3846    | 8.0 (3.0–13.0) | 12.0 (6.0–19.0) | <0.001 | 1.07 [1.05–1.08] | —   | —   |

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
1 Adjusted odds ratio by gender, age at first symptom, and disease duration.
2 Delay between first symptom and diagnosis, months.
3 Follow-up at a rheumatology unit, months.
prevalence among SLE patients. Moreover, although all of the ACR criteria were associated with SLE, this association was remarkably high in cases of malar rash, oral ulcers, and renal disorder. The presence of antiphospholipid syndrome also correlated with an SLE status (OR: 1.54; 95% CI: 1.03–2.32; *P* < 0.04), as well as pregnancy morbidity (OR: 2.19; 95% CI: 1.11–4.34; *P* < 0.03) and anticardiolipin IgM or IgG antibodies (Ab) (OR: 1.36; 95% CI: 1.02–1.82; *P* < 0.04). However, there were no differences between the two groups in terms of arterial, venous or small vessel thrombosis, anti-beta 2 glycoprotein Ab, and lupus anticoagulant.

Most SLE manifestations were more often found in SLE patients (Table 3). Osteoarticular and mucocutaneous manifestations, excepting cutaneous ulcers, were all associated with SLE.

If considered individually, the frequency of respiratory manifestations such as pleuritis, interstitial alveolitis, alveolar hemorrhage, pulmonary hypertension (PHT), as defined by SLICC/ACR/DI criteria or PTH in echocardiography, lung or pleural fibrosis, and shrinking lung syndrome was no different between the two groups. When general respiratory involvement (any of the above manifestations) was globally considered, however, it was more prevalent in SLE patients. This was similarly true of cardiac and vascular involvement. In general, although such respiratory complications were more frequent in SLE subjects, when these manifestations were analyzed individually, only valvular dysfunction (OR: 3.49; 95% CI: 1.09–11.22; *P* < 0.04) and Raynaud (OR: 1.74; 95% CI: 1.29–2.35; *P* < 0.01) were associated with SLE (adjusted OR). Lupus nephritis, as defined by clinical or laboratory alterations with or without renal biopsy, was much more prevalent in SLE patients. In fact, 30.3% of SLE subjects present it versus 6.3% iSLE patients. In terms of the relative frequencies of the different patterns of pathological findings, however, there were no differences between the two groups. Class IV (WHO) glomerular disease was the most frequently occurring form of lupus nephritis in renal biopsies (29.4% in iSLE and 48.6% in SLE patients). The association of end-stage renal disease, as defined by SLICC/ACR/DI and SLE status, did not reach statistical significance (adjusted OR: 2.04; 95% CI: 0.63–6.56; *P* = 0.23) (Table 3).

Neuropsychiatric involvement as a whole and seizures in particular were both associated with SLE. Ophthalmological symptoms others than keratoconjunctivitis sicca, such as visual alteration, cataracts, retinopathy or uveitis, were all associated with SLE. They were found in 15% of SLE patients and in nearly 10% of iSLE patients. Most laboratory manifestations, such as hematological alterations, low complement levels, and above all the presence of autoantibodies were also associated with SLE status (Table 3).

Hospitalizations, refractoriness, and mortality were associated with SLE. Furthermore, SLE patients died younger than iSLE ones (55.8 (18.0) vs 71.7 (9.0) years), although deaths due to SLE activity did not differ between the two groups (Table 4).

Differences in comorbidity were also explored. Severe infection was associated with SLE. The proportion of patients that smoked or had smoked in the past exceeded 40% in both groups. Although the prevalence of arterial hypertension was higher in SLE patients, there were no differences regarding cardiovascular events or dyslipoproteinemia. Diabetes mellitus (DM) was associated with iSLE. The proportion of patients who received corticosteroids (88.9% in SLE vs 69.1% in iSLE) and lupus anticoagulant.

An analysis of the various treatments used showed that although the majority of patients in both groups received or had received corticosteroids (88.9% in SLE vs 69.1% in iSLE) and antimalarials (83.3 vs 69.4%), all such treatments were more commonly associated with SLE (Table 6). One-third of SLE subjects were, or had been on, azathioprine versus just 13.2% of iSLE patients. Statistical differences were also found in terms of treatments involving CYC, mycophenolate mofetil, and rituximab. Approximately 15% of patients received methotrexate, without differences being noted between the two groups.

Treatment with angiotensin-converting enzyme inhibitors, statins, diuretics, and anti-osteoerotic agents were all associated with SLE, while acetylsalicylic acid, oral anticoagulants, and oral hypoglycemic agents were not (Table 5).

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**TABLE 2. ACR SLE Criteria Fulfilled in iSLE and SLE Patients**

|                                | iSLE, N (%) | SLE, N (%) | *P*   | OR [95% CI]        | OR* [95% CI]        | *P*   |
|--------------------------------|-------------|------------|-------|--------------------|---------------------|-------|
| Malar rash                      | 3963        | 37 (11.0)  | 2004  | 55.2               | 9.94 [7.02–14.07]   | 0.001 |
| Discoid rash                    | 3928        | 24 (7.1)   | 753   | 21.0               | 3.45 [2.26–5.26]    | 0.001 |
| Photosensitivity                | 3901        | 68 (20.5)  | 2172  | 60.8               | 6.00 [4.56–7.91]    | 0.001 |
| Oral ulcers                     | 3898        | 24 (7.3)   | 1645  | 46.1               | 10.91 [7.16–16.61]  | 0.97   |
| Arthritis                       | 3963        | 148 (44.2) | 2827  | 77.9               | 4.46 [3.54–5.61]    | 0.001 |
| Serositis                       | 3875        | 29 (8.8)   | 997   | 28.1               | 4.06 [2.76–5.99]    | 0.001 |
| Renal disorder                  | 3783        | 14 (4.3)   | 1112  | 32.1               | 10.49 [6.11–18.01]  | 0.001 |
| Neurological disorder           | 3918        | 4 (1.2)    | 294   | 8.2                | 7.30 [2.70–19.70]   | 0.001 |
| Hematological disorder          | 3764        | 131 (43.5) | 2762  | 79.8               | 5.11 [4.01–6.52]    | 0.001 |
| Immunological disorder          | 3359        | 145 (55.1) | 2657  | 85.8               | 4.93 [3.79–6.41]    | 0.001 |
| ANA                             | 4012        | 323 (94.7) | 3637  | 99.1               | 5.96 [3.33–10.67]   | 0.001 |

Bivariate and multivariate analyses. iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.

* OR adjusted by gender, age at first symptom, and disease duration.

† 20.1% of values lost.
**DISCUSSION**

RELESSER is a large multicenter registry of SLE patients from the European population, created by SER, with high quality and homogeneous data.\(^1\)\(^2\) The narrow confidence intervals in the results presented here underscore the reliability and accuracy of the data drawn from this register. In this study, we have carried out a detailed cross-sectional description of the patients included in the RELESSER registry, focusing on the differences between SLE and iSLE, and providing the largest iSLE cohort assembled now available. We consider this a very pertinent exercise, since iSLE is not a rare condition. In our registry, nearly 10% of the patients diagnosed with SLE by experts should be more properly classified as iSLE. In fact, in the only epidemiologic population-based study published to date, the prevalence of iSLE was about one-quarter that of SLE and this was a very pertinent exercise, since iSLE is not a rare condition. In our study, there were differences between the two groups with respect to sex and age. It is known that both age at onset and gender modify disease expression.\(^1\)\(^2\) In addition, in our study, there were differences between the two groups with respect to sex and age. It is known that both age at onset and gender modify disease expression.

### TABLE 3. Organ Involvement in iSLE and SLE Patients

| N | iSLE, N (%) | SLE, N (%) | \(P\) | **OR [95% CI]** | **OR\(^*\) [95% CI]** | **P** |
|---|-------------|------------|-----|-----------------|------------------|-----|
| Weight loss | 3952 | 18 (5.4) | 358 (9.9) | 0.009 | 1.93 [1.19–3.15] | 2.03 [1.22–3.39] | 0.006 |
| Adenopathy | 3945 | 11 (3.3) | 374 (10.4) | <0.001 | 3.39 [1.84–6.25] | 2.96 [1.60–5.48] | 0.001 |
| Inflammatory rash | 3962 | 92 (27.2) | 2390 (65.9) | <0.001 | 5.18 [4.04–6.64] | 4.38 [3.36–5.72] | <0.001 |
| Alopecia | 3933 | 54 (16.2) | 1291 (35.9) | <0.001 | 2.90 [2.15–3.91] | 2.23 [1.62–3.06] | <0.001 |
| Cutaneous ulcers | 3966 | 3 (0.9) | 104 (2.9) | 0.047 | 3.32 [1.05–10.51] | 3.83 [0.93–15.80] | 0.064 |
| Any osteoarticular manifestation\(^*\) | 3917 | 160 (49.1) | 2877 (80.1) | <0.001 | 4.18 [3.32–5.27] | 3.74 [2.92–4.78] | <0.001 |
| Avascular necrosis | 3948 | 3 (0.9) | 151 (4.2) | 0.004 | 4.89 [1.51–15.42] | 4.65 [1.14–19.02] | 0.033 |
| Any respiratory manifestation\(^1\) | 3958 | 3 (14.3) | 1065 (30.6) | <0.001 | 2.46 [1.79–3.38] | 2.55 [1.82–3.58] | <0.001 |
| Any cardiac manifestation\(^1\) | 3850 | 5 (17.3) | 943 (28.2) | <0.001 | 1.88 [1.38–2.55] | 1.73 [1.25–2.39] | 0.001 |
| Myocardial infarction | 3962 | 12 (3.5) | 71 (2) | 0.001 | 5.05 [0.29–10.02] | 0.68 [0.35–1.33] | 0.257 |
| Peripheral vascular disease\(^1\) | 3863 | 75 (22.9) | 1329 (37.6) | <0.001 | 2.02 [1.55–2.64] | 1.65 [1.24–2.19] | 0.001 |
| Raynaud | 3879 | 69 (19.1) | 1200 (33.9) | <0.001 | 2.17 [1.64–2.87] | 1.74 [1.29–2.35] | 0.001 |
| Lupus nephritis | 3930 | 21 (6.3) | 1101 (30.6) | <0.001 | 6.60 [4.22–10.33] | 5.69 [3.53–9.16] | <0.001 |
| End-stage renal disease | 3872 | 3 (0.9) | 99 (2.8) | 0.059 | 3.17 [1.00–10.04] | 2.04 [0.63–6.56] | 0.232 |

\(\text{iSLE} = \text{incomplete Systemic Lupus Erythematosus, SLE} = \text{complete Sistemic Lupus Erythematosus.}\)

\(^*\) Adjusted odds ratio by gender, age at first symptom and disease duration.

### TABLE 4. Bivariate and Multivariate Analyses of Mortality and Other Variables Related to Complications in SLE and iSLE Patients

| N | iSLE N (%) | dSLE N (%) | \(P\) | **OR [95% CI]** | **OR\(^*\) [95% CI]** | **P** |
|---|-------------|------------|-----|-----------------|------------------|-----|
| Hospitalization by SLE activity | 3932 | 94 (28.0) | 1965 (44.6) | <0.001 | 3.10 [2.42–3.97] | 2.79 [2.15–3.63] | <0.001 |
| Deaths | 3695 | 15 (4.7) | 211 (6.3) | 0.314 | 1.36 [0.80–2.33] | 2.25 [1.24–4.08] | 0.008 |
| Death due to SLE activity | | 5 (33.3) | 55 (26.1) | 0.551 | 0.71 [0.23–2.15] | 0.40 [0.09–1.70] | 0.212 |
| Age at death (mean (SD)) | | 71.7 (9.0) | 55.8 (18.0) | <0.001 | 0.94 [0.90–0.98] | 0.62 [0.43–0.88] | 0.007 |
| Refractory SLE | 4024 | 25 (7.2) | 900 (23.0) | <0.001 | 4.15 [2.74–6.27] | 3.04 [1.98–4.68] | <0.001 |

\(\text{iSLE} = \text{incomplete Sistemic Lupus Erythematosus, SLE} = \text{complete Sistemic Lupus Erythematosus.}\)

\(^*\) Adjusted odds ratio by gender, age at first symptom and disease duration.

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disease duration has a significant impact on various parameters such as accrual of clinical manifestations, damage and rate of complications. To avoid these confounding factors, adjusted analyses by gender, age at onset, and disease duration, for all of the variables studied, were carried out. Although disease duration was longer in the SLE population, that of the RELES- iSLE patients was similarly long; that is, 8 years, which allowed for an adequate characterization of this patient

| TABLE 5. Differences in Comorbidities Between iSLE and SLE Patients |
|----------------|----------------|----------------|----------|----------|----------|----------|
|                | iSLE, N (%)    | SLE, N (%)     | P        | OR [95% CI] | OR* [95% CI] | P        |
| Smoking        | 3610           | 139 (46.6)     | 1362     | 41.1      | 0.073     | 0.80 [0.63–1.01] | 0.80 [0.62–1.04] | 0.092 |
| DM             | 3962           | 29 (8.5)       | 179 (4.9)| 0.007     | 0.56 [0.37–0.84] | 0.68 [0.44–1.06] | 0.09 |
| DL             | 3859           | 99 (30.3)      | 1106 (31.3) | 0.745     | 1.05 [0.82–1.34] | 1.16 [0.89–1.52] | 0.269 |
| HTN            | 3983           | 70 (20.7)      | 1069 (29.3) | 0.001     | 1.59 [1.21–2.09] | 1.88 [1.38–2.56] | <0.001 |
| Cardiovascular events† | 3916          | 30 (9.1)       | 368 (10.3) | 0.550     | 1.15 [0.78–1.70] | 1.53 [0.98–2.38] | 0.062 |
| Severe infection | 3795          | 30 (9.6)       | 725 (20.8)    | <0.001    | 2.49 [1.69–3.66] | 2.16 [1.45–3.23] | <0.001 |
| Malignancy     | 3961           | 18 (5.4)       | 209 (5.8)    | 0.875     | 1.07 [0.65–1.76] | 1.21 [0.71–2.06] | 0.484 |
| Lymphoma       | 3961           | 1 (0.3)        | 20 (0.6)     | 0.99      | 1.85 [0.25–13.80] | 2.08 [0.27–15.95] | 0.482 |

DL = dyslipoproteinemia, DM = diabetes mellitus, HTN = hypertension, iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* OR adjusted by gender, age at onset, and disease duration.
† Stroke or heart attack or peripheral arteriopathy.
iSLE patients were never prescribed antimalarials, and it is well known that these drugs have beneficial and protective effects on survival. In any case, the relatively low number of deaths precludes the drawing of firm conclusions.

In regards to comorbidity—another topic not previously studied in patients with iSLE—it is worth noting that no differences were noted in the Charlson Index, which was low in both groups. Perhaps this index is not sufficiently sensitive to identify all of the potential comorbidities in SLE and thus was unable to detect any differences between the two groups. iSLE patients suffer less severe infections, which may reflect the milder disease states they experience, as well as the fact that they receive less immunosuppressive drugs. In terms of cardiovascular complications, the rates of angina or by-pass and heart attack were numerically higher in iSLE subjects, although without reaching statistical significance. iSLE patients were typically older, and presented a higher rate of certain risk factors for coronary disease (eg, smoking and DM), although, again, in the multivariate analysis, such differences lost their statistical significance. Besides, iSLE patients received less statins than those with SLE, even though there were no differences with respect to the prevalence of dyslipoproteinemia between the two groups. This may reflect the lack of tight control over cardiovascular risk factors in a subgroup assumed to have a milder form of the disease. As described previously, in the RELESSER registry patients with hypertension were more often SLE, which presumably reflects the higher incidence of lupus nephritis found in these individuals.

Consistent with our own results, several authors have suggested that incomplete SLE may be a frequent, mild, and relatively stable or benign form of the disease, apparently with a relatively low number of deaths precludes the drawing of firm conclusions. In any case, the relatively low number of deaths precludes the drawing of firm conclusions.

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Consistent with our own results, several authors have suggested that incomplete SLE may be a frequent, mild, and relatively stable or benign form of the disease, apparently with a minority of patients gradually evolving to SLE or other rheumatic disease. Other groups, however, have obtained results consistent with the hypothesis that iSLE patients encompass a subset that is likely to experience progressive organ damage or to develop complete SLE. Swaak et al studied a multicenter European cohort of patients with incomplete SLE.

### TABLE 6. Treatments Received by iSLE and SLE Patients

|                | iSLE, N(%) | SLE, N (%) | P     | OR [95% CI] | OR* [95% CI] | P     |
|----------------|-----------|------------|-------|-------------|-------------|-------|
| Corticosteroids| 3823      | 224 (69.1) | <0.001| 3.59 [2.77–4.65] | 3.22 [2.43–4.25] | <0.001|
| Methotrexate   | 3798      | 44 (13.8)  | 0.027 | 1.25 [0.90–1.74] | 1.22 [0.86–1.74] | 0.268 |
| Leflunomide    | 3657      | 8 (2.5)    | 0.360 | 1.48 [0.72–3.06] | 1.22 [0.58–2.55] | 0.596 |
| Azathioprine   | 3785      | 42 (13.2)  | <0.001| 3.25 [2.33–4.52] | 2.46 [1.73–3.50] | <0.001|
| Cyclophosphamide| 3793    | 20 (6.3)   | <0.001| 4.35 [2.74–6.88] | 3.47 [2.12–5.67] | <0.001|
| Mycophenolate mofetil | 3774 | 13 (4.0)  | <0.001| 4.25 [2.42–7.46] | 3.45 [1.91–6.25] | <0.001|
| Antimalarials  | 3806      | 225 (69.4) | <0.001| 2.19 [1.70–2.82] | 1.91 [1.45–2.51] | <0.001|
| Intravenous immunoglobulin | 3755 | 10 (3.1) | 0.326 | 1.45 [0.76–2.78] | 1.14 [0.59–2.23] | 0.693 |
| Rituximab      | 3791      | 5 (1.6)    | <0.001| 4.38 [1.79–10.70] | 3.34 [1.36–8.23] | 0.009 |
| Acetylsalicylic acid | 3222 | 88 (32.6) | 0.154 | 1.22 [0.94–1.60] | 1.16 [0.88–1.54] | 0.289 |
| Oral anticoagulants | 3764 | 37 (11.6) | 0.193 | 1.29 [0.90–1.83] | 1.37 [0.93–2.02] | 0.113 |
| Plasmapheresis | 3801      | 1 (0.3)    | 0.087 | 5.23 [0.72–37.93] | 4.22 [0.57–31.04] | 0.157 |
| Dialysis       | 3774      | 2 (0.6)    | <0.021| 4.98 [1.22–20.26] | 3.33 [0.81–13.70] | 0.095 |
| Statins        | 3645      | 58 (18.8)  | 0.013 | 1.47 [1.09–1.97] | 1.43 [1.04–1.95] | <0.026|
| Angiotensin-converting enzyme inhibitors | 3635 | 48 (15.4) | <0.001| 2.51 [1.83–3.45] | 2.58 [1.85–3.61] | <0.001|
| Diuretics      | 3604      | 25 (11.5)  | <0.001| 2.20 [1.53–3.16] | 2.41 [1.65–3.53] | <0.001|
| Anti-osteoporotic agents | 3682 | 55 (17.5) | 0.006 | 1.54 [1.14–2.09] | 1.63 [1.17–2.28] | 0.004|

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.

1 Adjusted odds ratio by gender, age at onset, and disease duration.

1 Multivariate analysis was not possible due to the small number of cases.
Besides RELESSER, this is the only multicenter study available on iSLE. This study included 122 patients with mean disease duration of 4.5 years. Consistent with our results and with virtually all of the studies completed to date, renal and central nervous system involvement was low (16% and 3%, respectively). Interestingly, even when patients eventually met the ACR-SLE criteria in longitudinal studies, renal and neuropsychiatric manifestations remained low.6,8 Median basal SLE activity, as measured by SLEDAI, was 2.6 (4.5) in the Swaak study. The figure was higher than in RELESSER iSLE patients;38 38% of Swaak patients were on corticosteroids and another 17% were on antimalarials vs RELESSER subjects (69% on corticosteroids and another 69% on antimalarials). This suggests a significant variability in clinical practice, although disease duration at the time of enrollment was higher in RELESSER patients. As with our patients, the low rate of damage accrual in iSLE patients, compared to those with SLE, has been previously reported.6,30

We have attempted to compare RELESSER SLE patient characteristics not only with those from the EUROLUPUS cohort, but also with the baseline characteristics of Caucasian patients from the LUMINA and GLADEL cohorts. However, it should be emphasized that differences in patient selection, design, period of time when was conducted, and variable definitions limits the validity of such comparison among these various cohorts. The EUROLUPUS cohort included patients from different European countries; specifically from the internal medicine, rheumatology and nephrology units of only 4 Spanish referral centers. In contrast, RELESSER patients were enrolled at 45 different rheumatology units spread across the country, and thus more comprehensively reflects the current reality of SLE in Spain and likewise a large southern European area. Ninety-three percent one percent of RELESSER patients were Caucasian, reflecting the current demographics in Spain, where most of the native population is Caucasian.31 In contrast, the EUROLUPUS PROYECT, which was carried out in the 1990s, reported 97% of the Spanish population as Caucasian.32 RELESSER patients were 33.3 (14.9) and 35.4 (15) years old at onset and diagnosis, respectively, which is quite similar to the EUROLUPUS data. In the LUMINA cohort, the mean age at diagnosis varied with ethnicity, Caucasians tending to be older than African-Americans and Hispanics [41.2 (14) vs 33.6 (12) vs 32.4 (13) years, respectively].33 GLADEL is an inception cohort in which fulfillment of 4 SLE ACR criteria was not mandatory. Here, patients were of similar age at first symptom [29.5 (12) years] and at diagnosis [31.1 (12) years] for the Caucasian subjects group.34 The median time between first symptom and diagnosis in the RELESSER group was 5.0 (0–618) months, which is similar to the GLADEL registry figure of 6.0 (0.4–301) months. In contrast, in the EUROLUPUS cohort the mean time between first manifestation and final classification as SLE was 2 years.32 This difference could be explained by differences in the set of criteria used for case definition (ie, ACR-1997 vs ACR-1982).

Musculoskeletal and hematological manifestations are the most frequent symptoms in both RELESSER and GLADEL patients, which means that these types of symptoms are the most common at disease onset, as well as during disease evolution, taking into account that median disease duration in the GLADEL cohort was 34.2 (range: 0.9–333.0) months and in the RELESSER cohort 148.0 (0–640) months. In EUROLUPUS patients, who experienced a mean disease duration of 101 ± 96 months, arthritis—followed by malar rash and fever—were the most frequent symptoms.35 Thirty percent of RELESSER patients present some kind of renal involvement, which was very similar to the Caucasian population in the LUMINA cohort (32% of patients)30 and somewhat lower than in the EUROLUPUS and GLADEL registries (39% and 43.6%, respectively). These differences may have stemmed from differences in ethnicity and/or patients sources.

There are striking differences in the prevalence of ocular manifestations. After 5 years of follow-up, only 1.7% of EUROLUPUS patients continued to suffer retinopathy and 2.9% cataracts. One point one percent of GLADEL subjects experienced uveitis, episcleritis, or scleritis. These manifestations were more prevalent in the RELESSER group (15% of SLE subjects), despite the fact that they were not actively recruited; in fact, the incidence rate here is perhaps more in keeping with what is commonly described in ophthalmological consultations.37 Ocular manifestations of SLE are a reflection of systemic disease38 and can lead to severe sight impairment, including blindness.37 This signifies that ophthalmological complaints, frequently overlooked, should be actively investigated.

Global activity has been evaluated using the SELENA-SLEDAI index in RELESSER patients, and baseline S-SLEDAI was low: 2.6 (3.6). The LUMINA cohort was subject to a different index for assessment of disease activity at baseline: the SLAM (Systemic Lupus Activity Measure) index. Using the SLAM index, Caucasians in the LUMINA cohort scored 8.5 (3.7).35 Although the scoring tools used differed, most likely differences in baseline activity between the two groups was insignificant.

Among the cumulative treatments administered in the GLADEL cohort, corticosteroids were the most frequently used (90.9%). Seventy-five percent of patients were treated with antimalarials, and the immunosuppressive agent most often used was cyclophosphamide (26.8%).34 As RELESSER and GLADEL patients underwent similar regimens, it appears that the drug treatment did not change with the duration of disease. In other words, drug treatments for SLE patients were generally introduced during the early years of disease. There was a prominent difference in the EUROLUPUS data regarding antimalarial treatments. During the first 5 years of the EUROLUPUS study,39 only 40.2% of patients received them, in contrast with 75% of RELESSER subjects. This could be due to increased awareness about the benefits of antimalarial benefits or to differences in approach among specialists involved in caring for these patients.

The RELESSER registry has some limitations. The method by which hospitals are chosen to participate in the study, involving rheumatologist specially dedicated to SLE clinical investigation, could introduce some selection bias. Patients seen at these centers may have a more severe form of the disease or may be under stricter care. There may be differences between referral criteria, depending on the level of care or the involvement of certain systems that lead certain patient to particular specialists. In any case, the big sample size and the number and characteristics of the participating units across Spain helped minimize any such selection bias. Another limitation of the present study concerns the incomplete follow-up evident at the rheumatology units. Nonetheless, as the delay between first symptom and rheumatologic evaluation and diagnosis remained relatively short, the loss of information should not have significant ramifications.

However, the most important limitation of the RELESSER registry is its retrospective design, which supposes a higher
possibility of measurement mistakes and which lacks sufficient information regarding confounding variables.

However, some prospective studies are now being conducted, with a focus on specific patient groups from the RELESSER registry. The ongoing prospective phase of the registry also includes one study involving a cohort of iSLE patients. Such prospective studies will try to confirm any associations between the different variables and activity, damage, severity, mortality, and co-morbidities that become apparent during multivariate analysis of the study’s transversal phase.

CONCLUSIONS

1. RELESSER represents the largest European SLE registry compiled to date, on that provides comprehensive, updated and reliable information on SLE manifestations, disease status, and comorbidity conditions and treatments in daily clinical practice.

2. There are two well-differentiated groups of patients: SLE and iSLE. Although SLE patients typically present a stable, mild form of the disease with a low rate of major organ involvement and low refractoriness, lupus-caused mortality does not seem to differ between these two groups, with iSLE patients warranting adequate treatment and follow-up.

3. SLE in the southern European population does not seem to differ from other Caucasian populations, being similar in terms of low activity levels and severity grades.

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