Reumatol Clin. (2021);**17(5)**:245–249

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

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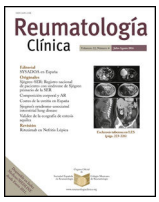

Special Article

Contributions of the lupus register of the Spanish Society of Rheumatology (RELESSER) to the knowledge of systemic lupus erythematosus in Spain☆

Iñigo Rúa-Figueroa Fernández de Larrinoa,[a,*] José María Pego-Reigosa,[b]

[a] *Servicio de Reumatología, Hospital Universitario de Gran Canaria Doctor Negrín, Gran Canaria, Spain*
[b] *Servicio de Reumatología, Complejo Hospitalario Universitario de Vigo, Vigo, Spain*

ARTICLE INFO

Article history:
Received 22 December 2019
Accepted 16 January 2020
Available online 14 June 2020

Keywords:
Systemic lupus erythematosus
Registers
Comorbidity

ABSTRACT

The lupus register of the Spanish Society of Rheumatology (RELESSER) is a multicentre register of patients with systemic lupus erythematosus (SLE) under follow-up by Spanish Rheumatology Services. It contains data on a total of 4024 patients with SLE. So far, 14 studies have been published from the transversal phase of RELESSER. Here we report the more relevant contributions of those studies, according to the authors' perspective, concerning cumulative clinical characteristics, level of activity, treatments, refractory disease, damage and mortality. We also review the main results of the analysis regarding incomplete SLE, lupus nephritis, respiratory manifestations, cardiovascular disease, serious infection, malignancies, fibromyalgia, SLE in males, SLE in Hispanics and juvenile-onset SLE, comparing the main characteristics of each subgroup to the global cohort. RELESSER has become one of the most important clinical SLE registers around the world, with a high yield in terms of knowledge generation about the disease in Spain, also useful for the entire scientific community.

Aportaciones del registro de lupus de la Sociedad Española de Reumatología (RELESSER) al conocimiento del lupus eritematoso sistémico en España

Palabras clave:
Lupus eritematoso sistémico
Registros
Comorbilidad

RESUMEN

El registro de lupus de la Sociedad Española de Reumatología (RELESSER) es un registro multicéntrico de pacientes con lupus eritematoso sistémico seguidos en servicios de reumatología españoles, que contiene cuantiosa información sobre 4.024 pacientes. Hasta la fecha han sido publicados 14 análisis sobre la fase transversal del registro. Se describen los resultados más relevantes, a criterio de los autores, concernientes a las características clínicas acumuladas, nivel de actividad, tratamientos, refractariedad, daño y mortalidad. Se revisan asimismo los resultados de análisis específicos sobre el lupus incompleto, la nefritis lúpica, las manifestaciones respiratorias, los eventos cardiovasculares, las infecciones graves, las neoplasias, la fibromialgia, el lupus en varones, el lupus en latinoamericanos y el lupus de inicio juvenil, comparando los diferentes subgrupos con el total de la cohorte. RELESSER se ha constituido como uno de los registros clínicos de lupus eritematoso sistémico más importantes del mundo, resultando altamente productivo en términos de generación de conocimiento de la enfermedad en pacientes españoles, útil también para toda la comunidad científica.

☆ Please cite this article as: Rúa-Figueroa Fernández de Larrinoa I, Pego-Reigosa JM, en representación de los investigadores del proyecto RELESSER y del grupo EASSER. Aportaciones del registro de lupus de la Sociedad Española de Reumatología (RELESSER) al conocimiento del lupus eritematoso sistémico en España. Reumatol Clin. 2021;17:245–249.

* Corresponding author.
E-mail address: iruafer@gobiernodecanarias.org (I. Rúa-Figueroa Fernández de Larrinoa).

◊ The names of the RELESSER project researchers are listed in Appendix A.

Introduction

RELESSER is a hospital-based multicentre clinical register of patients with systemic lupus erythematosus (SLE), promoted by the Group of Systemic Autoimmune Diseases of the Spanish Society of Rheumatology (EAS-SER), with support from the Research Unit of the SER (UI/SER). Its transversal phase (RELESSER-TRANS or RELESSER-T) has involved a retrospective collection of data from a broad representative sample of adults with SLE, coming from Spanish rheumatology services, spread over the different geographical areas of Spain. It includes sociodemographic data, frequent and infrequent accumulated clinical symptoms (<1%), activity variables, damage, severity, and comorbidity, together with treatments and mortality. During this phase, 359 variables per patient were registered, with standardised definitions. One article specifically dedicated to its methodology had been published previously, in this same journal.[1]

Justification: Why have a multicentre register in Spain?

Several international multicentre cohorts already exist, in active follow-up, which have been publishing their data for the last few years.[2–4] The relevance of this type of task is the infrequent nature of SLE and its heterogeneity and the registers have become essential tools for advancing in clinical and epidemiological awareness with regards to SLE. The few available data on SLE in Southern Europe in general, and in Spain in particular, for a disease which has proven to have major inter-ethnic and sociodemographic disparities,[5] justifies the creation of the RELESSER register. Furthermore, the standardised recording of clinical data in data bases promotes critical analysis of it, with the first step being to implement top quality optimisation programmes and to reduce the unjustified variability of disease management with possible contrasting of outcomes obtained in other population groups.[6]

The RELESSER register involved 2 phases: one transversal with data collection accumulated up until the first visit (RELESSER-T), and the other a prospective phase where several sub-cohorts, with their control groups, engaged in follow-up for at least 5 years (RELESSER-PROS). This second phase was still ongoing when this review was published.

Forty-five centres participated in RELESSER-T and this included 4024 patients with SLE or incomplete SLE (91% $\geq$ 4 ACR 1997 criteria). Ninety per cent of patients were women and 93% were Caucasian, with a median age of 33 years at diagnosis and median disease duration of 120 months. The mean follow-up by the rheumatology services was 104 months. At the time of study inclusion, 3222 patients (81%)[1] were in active follow-up.

Main contributions to knowledge on systemic lupus erythematosus

RELESSER-T is like a high resolution "snapshot" of the clinical characteristics and situation of patients with SLE in Spain, encompassing comorbidity, treatments, and outcomes. Median activity in the register visit was not high, specifically 2 (RI: 0–4), in compliance with the SELENA-SLEDAI (S-SLEDAI) and only 15% of patients had a S-SLEDAI above 6. Fifty three per cent of patients had been hospitalised on at least one occasion.[7] These figures indicate the major healthcare cost of SLE in Spain, since many of the direct costs associated with severe outbreaks of the disease are related to hospitalisation processes.[8] Eighty four point six per cent of patients had been treated with glucocorticoids at some point, and at the time of the study visit this figure was 52.4% (of the total). Regarding anti-malarial drugs, although 78.8% of patients had received them at some time, only 55.5% had been prescribed them at the time of the study. This figure is too low, under the terms of the current universal usage recommendation.[9] However, this result should be interpreted with caution, since the visit of patients included in the RELESSER-TRANS took place over a broad range of time.[1] Only 15% of patients received methotrexate on some occasion, and in 46% of cases it was withdrawn due to inefficacy or toxicity, which suggests this immunosuppressant has limited use in patients with SLE. Despite its greater popularity and usage frequency (31.2% in RELESSER), the percentage of azathioprine discontinuation (40.2%) did not greatly differ.[7] Another relevant aspect concerning therapies used was refractoriness, which was not widely explored as an outcome in SLE. Twenty four per cent of patients were refractory on occasion, which for this study was defined as any of the following: inefficacy of cyclophosphamide or of 2 or more immunosuppressants or resorting to the use of rituximab or splenectomy over the course of their disease. Refractoriness was associated with the male sex and a lower age on diagnosis, together with renal, neuropsychiatric, haematological or vasculitis activity.[7]

General characteristics: incomplete versus complete lupus erythematosus

The general characteristics of the patients, expressed in greater detail and comparing patients with 4 or more ACR 97 criteria with those who only had 3 ("incomplete" SLE) have been previously described in one of the first studies on the RELESSER-T[10] cohort. This is one of the best characterised incomplete SLE cohorts to date, in terms of variables included, and one of the largest, consisting of 345 patients (8.5% of the total). The patients with ACR97 criteria versus those with incomplete SLE were younger and with a longer duration of the disease. As a result of this last parameter, these patients suffered from oral ulcers (OR: 9; 95% CI: 6–14), malar rash (OR: 9; 95% CI: 6–13) and kidney disease (OR: 9; 95% CI: 5–16) more frequently. The subgroup of patients who met with the ACR97 criteria were a subgroup of more severe cases, with greater disease activity (median S-SLEDAI 2 [IQ: 0–4] versus 0 [0–2]) and greater accumulated damage (*Systemic Lupus International Collaborating Clinics* [SLICC]/ACR DI 1 [IQ: 0–2] median versus 0 [0–1]) at time of assessment of RELESSER-T.[10]

Lupus nephritis

RELESSER has been able to supply detailed information about the lupus nephritis cases being followed up by the Spanish rheumatology services, how they are treated and what their prognosis is.[11] A total of 1092 patients were shown to have nephritis through biopsy. As expected, 70% of cases had proliferative glomerulonephritis (WHO classes III or IV). Renal involvement was more common in women and in Latin American patients. Anti-malarial drugs were nephritis development protectors (OR .65 [95% CI: .52–.81]). Although these findings had already been previously reported in retrospective studies, a more robust adjustment for severity was added here using the Katz index.[12] This minimises the bias of confusion in the indication for patients with a less serious manifestation of the disease. Sixty eight per cent of patients responded completely to treatment, and this compared favourably with those of other European cohorts.[13,14] This is particularly outstanding, given the rigorous definition of remission used in the study (normal rates of creatinine and absence of proteinuria). Regarding associated factors, it was found that greater age was correlated with a higher possibility of complete response. Furthermore, it is notable that the use of anti-malarial drugs was also associated with a complete response (OR: 1.65 [95% CI: 1.18–2.32]), which was less common in patients who tested positive for anti-Sm (OR 1.69 [95% CI: 1.40–2.04]). The presence of thrombotic microangiopathy in renal biopsy was related to a higher risk of recurrence.

Eleven per cent of patients developed an advanced chronic kidney disease (ACKD), with figures comparable to those reported in other European cohorts.[11]

Respiratory involvement

It was confirmed that respiratory symptoms contributed to a decline in survival (HR: 3.13), basically dependent on parenchymatous involvement, with minimal impact on it from pleural involvement (the most common, in 21% of cases) or even, from thromboembolic disease. The presence of respiratory symptoms was associated with other major disease symptoms, including renal, neuropsychiatric, and cardiac symptoms.[15]

Accumulated damage

Data referring to accumulated damage were analysed in detail in RELESSER-T, in both adult onset SLE and juvenile onset SLE, with an original outlook using cluster analysis. In the total sample 3 clusters were identified which shared common characteristics in terms of damage. One of them, where the presence of CV events was constant, included 8% of cases and was associated with high mortality, with an over representation of males (19.2%).[16] In one differentiated study the same analysis was carried out in the subgroup of juvenile onset SLE patients, where 3 clusters of patients were also identified. One of these clusters which included 14.5% of patients, with kidney damage in 60% of cases, there was also a higher association with mortality. This cluster also had a concentration of cardiovascular, ocular, and gonadal damage.[17] One aspect which has hardly ever been studied in SLE is the chronology of accumulated damage. Analysis of this issue in RELESSER-T showed that possibly in contrast to the generally accepted idea, damage occurs in early phases of the disease, with a 2.9% annual rate of increase during the first 5 years, compared with a subsequent rate of 2.1% (in accordance with the SLICC/ACR index), reaching a maximum in the first year after SLE diagnosis. Thirty-four point four per cent of patients had at least one symptom of damage when the RELESSER-T[18] visit took place.

Analysis of demographic subgroups

The characteristics of the patient subgroups were studied in keeping with sex, ethnicity, and age on presentation. In this sense, it became obvious that SLE, at least in RELESSER, is more serious in males. This fact has been fairly controversial in the literature up until now. Male patients suffered more frequently from nephritis, with a higher percentage of ACKD (4.7% versus 2.6%), and a higher frequency of neuropsychiatric symptoms. Furthermore, they were hospitalised due to the disease and were refractory to treatments with greater frequency than females. With regard to mortality, it has only been possible to prove an increase in males over 50 years of age, probably due to the low number of deaths.[19] Bearing in mind the sample size of RELESSER and the consistency of results, it is difficult to question the difference between sexes in terms of prognosis.

Juvenile onset of SLE has also been the objective of specific analysis in RELESSER-T. Similarly to males, this subgroup of patients also had a worse prognosis. Disease severity according to the Katz severity index was greater, there was a higher prevalence of more symptoms and worse outcomes of nephritis. Nephritis was more relapsing and there was a higher risk of ACKD, dialysis and transplant. Here strength also lies in the number of patients. At 484 this was one of the largest SLE cohorts of juvenile onset and the most exhaustively characterised to date.[20]

Other differences between subgroups became clear by analysing the ethnic groups included in RELESSER. Due to numerical limitations, only potential differences between Latin American and Caucasian ethnic groups were able to be explored. Since follow-up included in RELESSER only refers to the follow-up conducted in Spanish hospitals, the possibility existed of providing new data on racial differences, with lower contamination of effects derived from healthcare conditions. Thus, the Latin American patients were also more seriously affected, again in accordance with the Katz index, with a different clinical profile when compared with the dominant ethnic group in the register which was obviously Caucasian. The main limitation of this analysis was not being able to consider the Latin American patients included in the study (5% of the total) as a heterogeneous ethnic group.[21]

Comorbidity in the lupus register of the Spanish Society of Rheumatology

RELESSER contains ample data on comorbidity with independent studies providing analysis on cardiovascular (CV) disease, serious infection, and the development of malignancies. Cardiovascular events were suffered after diagnosis of SLE by 7.4% of patients during the follow-up in RELESSER (compared with 10.9% at any time),[22] which is a lower prevalence compared with other European or American populations, but similar to that described in LUMINA.[23] Regarding vascular events, involved, stroke was more frequent (5.7%) than coronary events (3.8%), and this has been reported in other cohorts.[24] In keeping with the so-called "Spanish paradox", the prevalence of classical cardiovascular risk factors was high, similar to that occurring in the general population. For the first time a strong association between CV events and diabetes mellitus was reported (OR 22 [95% CI: 1.32–3.74]). Also, and among other associated factors, the OR were high for valvular dysfunction (according to the BILAG definition) (OR: 2.44 [95% CI: 1.34–4.26]) and hypocomplementemia (OR: 1.81 [95% CI: 1.12–2.93]), with both events standing out, tenuously outlined in the literature.[22]

Nineteen per cent of patients suffered from one or more serious infections during the RELESSER follow-up, which is lower than that referred to in the literature.[25] Data clearly show that patients with infection were in a more severe condition, regardless of the treatments received. Although as has been reported in other cohorts, the most common infection was respiratory, it was the bacteraemia which led to the most deaths by infection. Also here, in the multivariate analysis several factors were found to be associated with infection which had not been previously identified, such as Hispanic ethnicity (i.e. Latin American) (OR: 2.15 [95% CI: 1.54–3.00]) and tobacco consumption (OR: 1.33 [95% CI: 1.12–1.58]). One posterior analysis of the bacteraemias recorded in RELESSER revealed that the most common cause of this feared complication in our environment (rarely studied in SLE) were the gram-negative bacilli. Mortality was high, approximately 14%, and a high rate of recurrence was detected (27.2%). The factors associated with the risk of bacteraemia were comorbidity, elevated creatinine, and the presence of damage. Moreover, they were also shown to be associated with the use of immunosuppressants and glucocorticoids (dose-dependent in the latter). It was of interest that in 51% of cases empirical treatment was insufficient, either because the right empirical antibiotic had not been chosen or due to the tardiness of the blood culture results.[26] This outcome supports the need for establishment of a broad-spectrum empirical antibiotic administered as early as possible to all patients with febrile SLE, together with its continuity or withdrawal in keeping with microbiological test results.

Another study conducted on the RELESSER data base addresses malignancies. Again, an original outlook was undertaken, distinguishing between homonodependant (HD) cancers and non homonodependant ones. The cancer rate was higher than expected by age and sex, with a standardised incidence of 1.37 (95% CI: 1.15–1.59), with no differences when only HD cancers were

considered. The presence of damage (excluding the item "tumour" from the SLICC/ACR damage index) and the prescription of angiotensin converting enzyme inhibitors (OR: 2.87) were associated with non HD cancers.[27] The latter event, not previously described in SLE, is thought-provoking, and all the more so considering the current controversy regarding angiotensin converting enzyme inhibitors and tumours in the general population.[28]

Another aspect analysed in RELESSER-T was the prevalence of and associations with fibromyalgia syndrome. The conclusion reached was that the prevalence of fibromyalgia rises with the evolution of SLE, reaching up to 6.9% in patients who have suffered from the disease for over 5 years, and is associated with the development of mucocutaneous lesions (photosensitivity and oral ulcers) and secondary Sjögren's syndrome (OR: 2.44 [95% CI: 1.66–3.60].[29]

Collaborative studies

Different collaborative studies conducted with other cohorts are also delivering promising results in the RELESSER project. In a recently published article a severe infection risk calculation score was validated, developed from infection analysis of the RELESSER cohort, which was called *SLE Severe Infection Score* (SLESIS), in the SLE cohort of University College of London.[30] In the ROC statistics, the predictive value of SLESIS was higher when applied just before infection than when the disease was diagnosed (AUC .79 versus .63). Although it has yet to be validated prospectively, SLESIS may prove to be a useful tool in assessing the infection-associated risk of SLE.

In conjunction with the Portuguese register, Reumapt, external validation of the SLICC-2012 diagnostic criteria was performed on a total of 2055 patients. The criteria proposed by the SLICC group were more sensitive than the ACR 1997 criteria (93.2% versus 85.6%), with this difference being even greater in patients whose disease had evolved in under 5 years.[31]

A comparative comorbidity study was also conducted between the RELESSER and the SER register of patients with Sjögren's syndrome, on the initiative of the EAS-SER group. Advantage was taken of the circumstances of both registers, which share identical definitions of different comorbidities and which also share many researchers. It was confirmed that, with the exception of the risk of lymphoma which is notoriously higher in patients with primary Sjögren syndrome, the patients with primary Sjögren's syndrome in active follow-up accumulated fewer serious comorbidities than patients with SLE under the same circumstances, with OR adjusted to infection and CV events of .62 (.44–.86) and .57 (.35–.92), respectively.[32]

Limitations of the lupus register of the Spanish Society of Rheumatology in its transversal phase

Up until now the results of the transversal phase of the register (RELESSER-T) have been analysed, with cumulative variables and assessment of activity in the last visit of each patient, retrospectively. RELESSER-T therefore suffers from the limitations inherent in all retrospective studies, in terms of the possibility of lost information, etc.

In addition to this, with the exception of the variables referring to accumulated damage which were dated, the accumulated symptoms of SLE and their treatments were not time-measured and the associations described must therefore be treated with caution when establishing causality. The high patient number of the register does however suggest verisimilitude of the associations found in most cases.

Finally, we should indicate that patient inclusion was not random. Although participant centres were asked to include as many patients as possible, sample representativeness could not be completely guaranteed, because no data was available on patients who were not finally included. One reasonable possibility would be that there was a tendency to include more patients in follow-up at the expense of those who died, and this could have led to a bias towards cases of less severity.

The future of the lupus register of the Spanish Society of Rheumatology

Many other analytical studies on the transversal phase of the register (RELESSER-T) are ongoing, but the most promising and solid scientific future of the project whose idea is to minimise the limitations flagged up in the previous section, are currently in their prospective phase: the RELESSER-PROS. The design is that of a longitudinal study, with annual visits from a series of particularly interesting sub cohorts taken from the transversal phase (onset SLE, incomplete SLE and clinically quiescent-serologically active SLE), with their corresponding control groups, adjusted according to age and sex, with parallel follow-up. This latter aspect is novel compared with the normal design of prospective studies conducted in SLE to date, and may potentially obtain more robust outcomes when analysing subgroups of the disease in follow-up. The primary objective of RELESSER-PROS is to analyse predictive factors of unfavourable prognosis. The diagnostic techniques would be accumulated damage, quality of life related to health, impact of the disease on the life of the patients, hospitalisation, and mortality. The inclusion of many *Patient Reported Outcomes* in the follow-up would provide a particularly detailed patient perspective and support validation as another distinguishing trait of the RELESSER-PROS project.

Conclusions

RELESSER has been responsible for a relevant qualitative change in the cooperative research of Spanish rheumatologists in the SLE area, by enabling detailed information to exist on the clinical characteristics of the disease in Spain, its management, and its outcomes. Multiple analyses performed to date have also provided new information on the disease of use to the whole scientific community. All of this would not have been possible without such a multicentre, wide-ranging register, safeguarded by UI/SER methodologies.

Conflict of interests

The authors have no conflict of interests to declare with this narrative review.

Acknowledgements

To the members of the SER Unit of Research and all researchers who were involved in the transversal phase of RELESSER. Our thanks to the pharmaceutical industry (GSK, Roche, Novartis and UCB) who, through the SER Foundation, were responsible for financing a major part of the project.

Appendix A. RELESSER project researchers in its transversal phase

J. López-Longo, M. Galindo-Izquierdo, J. Calvo-Alén, V. del Campo, A. Olivé-Marqués, S. Pérez-Vicente, A. Fernández-Nebro, M. Andrés, C. Erausquin, E. Tomero, L. Horcada, E. Uriarte, M. Freire, C. Montilla, A. Sánchez-Atrio, G. Santos, A. Boteanu, E. Díez-Álvarez, J. Narváez, R. Blanco-Alonso, V. Martínez-Taboada, L.

Silva-Fernández, E. Ruiz-Lucea, J.L. Andreu, J.Á. Hernández-Beriain, M. Gantes, B. Hernández-Cruz, J. Pérez-Venegas, M. Rodríguez-Gómez, A. Zea, M. Fernández-Castro, Á. Pecondón-Español, C. Marras, M. Ibáñez-Barceló, G. Bonilla, V. Torrente-Segarra, I. Castellví, J.J. Alegre, J. Calvet, J.L. Marenco, E. Raya, T. Vázquez, V. Quevedo, S. Muñoz-Fernández, M. Rodríguez-Gómez, J. Ibáñez, O. Fernández-Berrizbeitia, J.Á. Hernández-Beriain, M. Gantes, L. Expósito, B. Hernández-Cruz, P. Carreira, G. Bonilla, M. Moreno, P.G. de la Peña, M.Á. Aguirre, T.C. Salman-Monte, A. Riveros Frutos, B. Tejera, T. Cobo-Ibañez, F. Sánchez-Alonso, R. Melero-González, T. Otón-Sánchez, M.J. García-Yebenes, R. Menor-Almagro, C. Mouriño, C. Fito-Manteca, C. Galisteo, J. Manero, A. Lois-Iglesias, E. Valls-Pascual, S. Manrique-Arija, E. Ucar, H. Borrell, E. Salgado

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