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REVIEW

Lupus in Latin-American patients: lessons from the GLADEL cohort

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The need for comprehensive published epidemiologic and clinical data from Latin American systemic lupus erythematosus (SLE) patients motivated the late Dr Alarcón-Segovia and other Latin American professionals taking care of these patients to spearhead the creation of the **G**rupo **L**atino **A**mericano **D**e **E**studio del **L**upus (GLADEL) cohort in 1997. This inception cohort recruited a total of 1480 multiethnic (Mestizo, African-Latin American (ALA), Caucasian and other) SLE patients diagnosed within two years from the time of enrollment from 34 Latin American centers with expertise in the diagnosis and management of this disease. In addition to the initial 2004 description of the cohort, GLADEL has contributed to improving our knowledge about the course and outcome of lupus in patients from this part of the Americas. The major findings from this cohort are highlighted in this review. They have had important clinical implications for the adequate care of SLE patients both in Latin America and worldwide where these patients may have emigrated. These findings are highlighted in this review. *Lupus* (2015) **0,** 1–10.

Key words: Systemic lupus erythematosus; renal lupus; cardiovascular disease

Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by an array of laboratory abnormalities and clinical manifestations. Literature from the northern hemisphere has shown that socioeconomic factors and ethnicity have a major impact on the incidence, disease activity, damage and mortality of this disease.[1–11] One of the principal findings has been that non-Caucasian patients develop SLE more frequently and experience major organ involvement (renal, heart, lung and central nervous system) leading to diminished survival when compared to Caucasians.[7,12–14]

Excluding the United States (US) and Canada, the rest of the American continent is (by and large) Latin America. Several ethnic groups share this vast territory of 22 million square kilometers. These groups are: Caucasian, African-Latin American (ALA), Mestizo (mixed European and Amerindian ancestry) and pure Amerindian (individuals with purely local ancestors comprising an enormous variety of tribes and groups throughout

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the entire continent). However, the information from Latin America regarding SLE is scarce and, for the most part, from single centers.

From the outset **G**rupo **L**atino **A**mericano **D**e **E**studio del **L**upus or Latin American Group for the Study of Lupus (GLADEL) had two main objectives: 1) to establish an inception, multiethnic and multinational lupus cohort in order to obtain realistic data from SLE patients in Latin America, and 2) to enhance the understanding of lupus within the Latin American community.

The efforts of GLADEL were recognized by the international community, which chose it to host the 10th International Congress on SLE; it took place in Buenos Aires, Argentina, in April 2013 and allowed the close interaction of experts from around the globe and the showcasing of the GLADEL cohort.

General characteristics of the GLADEL cohort

This cohort started in 1997 and included patients diagnosed within the previous two years in Latin American centers with expertise in lupus. To date, GLADEL includes 1480 patients with more than 10 years of follow-up.

Database

Data were collected using the ARTHROS software,[15] a user-friendly, multilingual, rheumatology database developed by Argentine rheumatologists.

Centers and patients

Thirty-four centers from nine Latin American countries (Argentina, Brazil, Colombia, Cuba, Chile, Guatemala, México, Perú and Venezuela) took part in GLADEL. To have a balanced representation of centers, each center was asked to incorporate a minimum of 20 and a maximum of 30 randomly selected patients. Randomization was performed at each center using a random number table. Fulfillment of four American College of Rheumatology (ACR) 1982 SLE criteria at the time of diagnosis was not mandatory. Diagnosis relied on the qualified attending physicians' clinical impression. Nonetheless it is worth noting that 96.0% patients eventually met these criteria at enrollment or during their follow-up.

The majority of patients included 645 (43.6%) were Mestizo (individuals of European and Amerindian background) and 606 were Caucasian (40.9%); they were followed by ALA (174, 11.8%) and "other" (mainly pure Amerindians and Asian descendants) groups (55, 3.7%). Most patients were women 1330 (89.9%). The mean $\pm$ SD age at disease onset and at diagnosis was 28.0 ± 12.0 and 29.5 ± 12.3 years, respectively.

Six hundred and eighty (45.9%) patients had partial or no medical insurance, 1133 (76.6%) had 12 or fewer years of formal education and 901 (60.9%) were of middle-low/low socioeconomic status (SES). Finally, 134 (9.1%) of the patients were living in rural areas.

Publications

The key findings from the GLADEL cohort are depicted in Table 1 and summarized below.

Description of the GLADEL cohort[16]

In this publication the general characteristics of the cohort at disease onset were described. Mestizos predominated in Guatemala, México, and Perú; Caucasians in Argentina and Cuba and to a lesser degree in Brazil; and ALA patients were more prevalent in Venezuela, Brazil, and Colombia.

SES, medical care, and formal education were significantly higher among the Caucasian patients. Mestizos had significantly better SES but less adequate medical insurance coverage than ALAs; marital status was comparable for all groups. Mestizo and ALA patients were significantly younger at disease onset and at diagnosis than Caucasians. ALA patients experienced a shorter delay in diagnosis compared to Mestizos and Caucasians.

Regarding clinical features, Caucasians experienced significantly higher rates of fever while discoid lupus was more frequent in ALA patients. In addition, by multivariable logistic regression analysis, patients of Mestizo and ALA background were shown to have a higher frequency of lymphopenia whereas Mestizo patients had a higher frequency of renal damage when compared with Caucasians. It is worth mentioning that overall these findings were independent of the patients' country of origin.

In terms of laboratory features, anti-double-stranded DNA antibodies were significantly more frequent in Mestizos than in Caucasians, and immunoglobulin (Ig)M anticardiolipin (aCL) antibodies were more frequent in Caucasians and Mestizos than in ALAs. Low complement levels, including C3 and C4, were significantly more

Table 1 Relevant GLADEL cohort findings published over the past 10 years.

Year	*Authors*	*Key findings*
2004	Pons-Estel et al.[16]	-ALA and Mestizo patients in comparison with Caucasians, experienced: Early age at onset More severe disease Higher frequency of renal disease, pericarditis, polyadenopathy Higher maximum disease activity
2005	Alarcón-Segovia et al.[17]	-There is familial aggregation of SLE, RA, and autoimmune disease in general -Familial aggregation λs was 29. -The best fit model for genetic contribution is an additive polygenic model. -Familial autoimmunity was more likely in Mestizo SLE patients and those of higher socioeconomic level
2005	García et al.[18]	-Male patients: Represented 10% of GLADEL's cohort Experienced shorter delay in diagnosis Had a higher frequency of fever, weight loss, arterial hypertension, renal disease, hemolytic anemia, IgG anticardiolipin antibodies and low C3
2008	Ramírez Gómez et al.[19]	-Pediatric patients experienced: A more severe presentation Higher disease activity Major hematological, cutaneous and central nervous system involvement Were more frequently ALA and Mestizo Accrued SLE ACR criteria earlier and at greater number than adults
2010	Shinjo et al.[20]	-Antimalarials showed a protective effect on SLE survival -Effect was time dependent (at least six months needed to achieve this effect)
2012	Pons-Estel et al.[21]	-Mestizo patients are at increased risk of developing renal disease -Antimalarial use exerts a protective effect against renal disease in Latin-American SLE patients
2012	Pons-Estel et al.[22]	-Patients living in Rural areas were more likely to be: Mestizo To have a lower socioeconomic status, educational level and be less likely to have medical insurance coverage Experience more active disease at diagnosis and renal disease occurrence over time But not worse outcomes in terms of disease activity over time, renal damage, overall damage and mortality
2013	Pons-Estel et al.[23]	-Mestizo patients are at increased risk of developing renal disease early -Antimalarials seem to delay the appearance of renal disease
2014	Pons-Estel et al.[24]	-The SLICC criteria performed at least as well as the ACR criteria in the LUMINA and GLADEL cohorts -The SLICC criteria showed a more balanced and clinical representation of each of the organ systems -Comparable performance was achieved by the SLICC criteria when compared with the physicians' judgment
2014	Ugarte-Gil et al.[25]	-The number of flares patients experience, regardless of their severity, increases the risk of damage accrual
2014	García et al.[27]	-Primary cardiac disease occurred in 14% of GLADEL patients and pericarditis was the most frequent manifestation. -ALA ancestry, cardiac involvement at SLE diagnosis and damage (first recorded) were risk factors for primary cardiac disease occurrence -Antimalarials seems to minimize the occurrence of primary cardiac disease

GLADEL: Grupo Latino Americano De Estudio del Lupus; ALA: African-Latin Americans; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; Ig: immunoglobulin; ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; LUMINA: LUpus in MInorities: NAture versus Nurture.

frequently seen in ALAs and Caucasians than in Mestizos.

Disease activity was significantly higher in ALAs and lower in Caucasians when compared with Mestizos using either the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or the MEX-SLEDAI. Predictors of high disease activity were formal education <10 years, partial or no medical coverage, age > 27 years at diagnosis, follow-up time ≥ 20 months, delays in diagnosis ≥ 6 months and disease duration ≥ 32 months.

Regarding treatment, steroids were administered to most patients (91.8% of the patients) followed by antimalarials (chloroquine more than hydroxychloroquine) in 74.7% and intravenous cyclophosphamide in 29.2%. Overall, immunosuppressive drugs were more frequently used in non-Caucasians, particularly significant when Mestizo patients were compared with Caucasians.

Finally, at the time of publication, 34 (2.8%) patients had died with a 4.6-year survival rate of 95%. As expected, disease activity and infections were the most frequent causes of death followed by neoplasias. Predictors of mortality within the overall GLADEL cohort were <10 years of education, Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) score ≥ 1, ≥20 months of follow-up, "single" marital status, having partial or no medical coverage and being from Argentina as compared to other Latin American countries.

In conclusion, the study has shown, among other things, that GLADEL patients represent a very heterogeneous population although in North America they will all be considered Hispanics.

Familial aggregation[17]

A specific genetic background is crucial for the development of SLE but genes also contribute to the development of many other autoimmune diseases.[26] Genes seem to be implicated not only in the susceptibility to but also in the severity and outcome of SLE. Scarce information has been published on the frequency of familial aggregation of SLE and other entities, in part because large numbers of patients and families are needed.[28,29]

A total of 166 (14.1%) SLE patients had relatives with an autoimmune disease, whether systemic or organ specific; 42 of these 166 (25.3%) had at least two relatives with an autoimmune disease (the same or different), the most common also being SLE (9.9%); it was followed by rheumatoid arthritis (RA) (6.7%), and others to a lesser degree. The association between SLE and other autoimmune diseases was significantly higher in Mestizo (54.9%) than in non-Mestizo patients (41.1%).

The prevalence of SLE in first, second and third-degree relatives of SLE patients was 2.7%, 1.9% and 1.1%, respectively, while the corresponding figures for RA were 1.6%, 1.1% and 0.6%. Familial aggregation, calculated as the risk for siblings of patients to develop SLE (or λ_S) was then estimated using several figures of disease prevalence in the general population, and was as high as 29.

Because of the large number of patients involved, we were able to show not only that familial SLE occurred in our cohort but also that the association between SLE and RA was higher than had been reported in RA per se.[30]

Our work also concluded that a polygenic, additive model was the most appropriate behind the genetic contribution to SLE.

Male SLE[18]

SLE is more frequent in women than in men, but there is considerable regional variation in the female:male ratios, ranging from 5.3:1 in Curaçao to 23:1 both in Oman and the Philippines.[14] When lupus occurs in males, it tends to be quite serious.[5,31] We examined the influence of gender in the lupus phenotype in our patients.

The female:male ratio in our cohort was 9:1. GLADEL male patients had significantly higher frequency of fever, weight loss, arterial hypertension, IgG aCL positivity and low C3, and an earlier diagnosis than the female patients. They also had more severe organ involvement with higher frequencies of renal disease and hemolytic anemia. Finally, they experienced a higher (albeit not significant: 4.1% vs. 2.7%) mortality rate than women.

Childhood SLE[19]

Age at SLE onset varies as a function of race/ethnicity and geography.[32,33] In about 8%–20% of patients, the diagnosis is made for the first time in childhood; this wide range may relate to the different cutoff age used across studies.[34] Two hundred and thirty (18.9%) GLADEL patients whose disease onset occurred before age 18 were studied. The median age at SLE onset and diagnosis were 15.3 and 16.4 years, respectively. As compared to later disease onset patients, children significantly accrued four SLE criteria faster (median time of 2.04 vs. 4.4 months), had higher levels of disease activity and accrued less damage.

They also developed significantly more malar rash, fever, oral ulcers, thrombocytopenia and hemolytic anemia. Within each ethnic group, Caucasians were more likely to present with fever and malar rash, ALAs to develop fever, hemolytic anemia, thrombocytopenia and IgM aCL, and Mestizos to develop ischemic cerebrovascular accidents, cranial nerve involvement and malar rash.

In short, GLADEL pediatric age-onset lupus had a more severe presentation than the adult-onset patients with higher disease activity indices, with major hematological, cutaneous and central nervous system involvement. In spite of these findings, pediatric-age onset lupus was not an independent predictor of renal impairment or death.

Antimalarial treatment and lupus survival[20]

Standardized mortality ratios (SMRs) for SLE patients are two- to four-fold higher compared to the general population, even though survival rates in SLE have increased from under 50% to 95% in the last six decades.[14] This has been possible owing to an increase in early and mild disease diagnoses and to improved treatments for SLE and its complications, among other contributing factors. Although antimalarials have been used in SLE for decades, particularly for skin and joint disease, recently Ruiz-Irastorza et al. and Alarcón et al. proposed that antimalarial use could be associated with better survival in SLE.[35,36] However, in these studies neither the dose used nor treatment duration were examined. We assessed these possible effects on our patients.

Of the 1480 patients, 1141 (77%) were antimalarial users (chloroquine and/or hydroxychloroquine) and 81.1% had received it for >2 years. Using antimalarials was associated with a lower mortality rate when compared with not using them (4.4% vs. 11.5%; $p < 0.001$). In a Cox multivariable regression model adjusting for potential confounders, using antimalarial drugs was associated with a 38% delay in the occurrence of death. In conclusion, this study confirmed not only that antimalarials might prolong survival in SLE patients as others had shown, but it showed for the first time a time-dependent effect (>2 years) to attain this benefit.

Renal disease: Effect of ethnicity and of antimalarial use[21,23]

Renal disease in SLE can range from silent to severe renal failure and may occur in up to 70% of patients depending on the population studied.[16,37,38] Increased SLE prevalence and SLE-renal involvement, younger-onset disease and less favorable outcome are observed in some racial/ethnic groups including African Americans, "Hispanics" living in the continental US[37,38] and Asians compared with Caucasians.[39] Moreover, during the last few years, important insight has been gained in understanding the role of antimalarials on renal disease, but no information regarding this had emerged from Latin-American patients,[40–42] which we went on to examine.

We first performed a nested case-control (1:2 proportion; $n = 265{:}530$) study restricted to patients who developed renal disease (ACR criterion) after SLE diagnosis. In addition to some variables known to be associated with renal disease, Mestizo ethnicity was independently associated with a higher risk of developing renal disease, whereas antimalarial use was negatively associated with such occurrence in multivariable analyses. This protective effect persisted after adjusting for possible confounding variables associated with the intake of antimalarials.

Next we examined factors associated with the early occurrence of renal disease. To this end, 945 GLADEL patients free of renal disease at diagnosis were examined. Of them, 265 (28.0%) patients developed renal disease after entering the cohort. In multivariable time-dependent analyses, we showed that Mestizo patients were at increased risk of developing renal disease earlier than those from other ethnic groups. Additionally, we demonstrated for the first time that the use of antimalarials whether at diagnosis or over the course of the disease as a time-dependent variable retarded the development of renal disease in SLE regardless of the patients' ethnic background. The estimated cumulative probability of developing renal disease within five years of diagnosis was 37% for patients not taking antimalarials and 24% for those who received antimalarials on or before diagnosis (log-rank test $p < 0.0001$).

In summary, we demonstrated that antimalarial use not only is associated with decreased development of renal disease but also with a delay of its occurrence. Furthermore, we also showed that Mestizo patients are at an increased risk not only of developing renal involvement overall but of doing so earlier.

Impact of rural residency[22]

Because of the presence of large rural areas in the Latin American countries, we had been intrigued by the role the place of residency (urban vs rural) might have on the course and outcome in SLE.

One hundred and twenty-two (8.6%) out of 1426 GLADEL patients were identified as living in rural areas. These patients were significantly more frequently Mestizos and younger at diagnosis; they also had fewer years of formal education, lower SES and medical coverage than those living in urban areas. As to the clinical features, comorbid conditions such as hypertension and renal involvement were more frequent among these patients. Disease activity at diagnosis but not over time was significantly higher in rural patients. Renal damage and overall damage were comparable in both groups. As for the treatment variables, the use of methotrexate, cyclophosphamide pulses and the need for hemodialysis were found to be more common in the rural patients. A higher proportion of deaths occurred during follow-up among the rural patients but the difference was not statistically significant.

When multivariable logistic regression models were performed, we observed that rural residency was associated with high levels of disease activity at diagnosis and renal disease occurrence. However, no impact on the rates of hospitalization, disease activity over the disease course, renal damage, overall damage and mortality was found. This information may help physicians working in rural areas to identify these patients who can be promptly referred to specialists.

ACR and SLICC classification criteria for SLE[24]

Despite the worldwide use of the ACR classification criteria,[43,44] many concerns have been raised about them: the lack of inclusion of many cutaneous and neurological manifestations, the omission of low complement levels and the impossibility of classifying as SLE patients with a biopsy-confirmed nephritis compatible with SLE (in the presence of lupus autoantibodies) but who did not fulfill other criteria. The Systemic Lupus International Collaborating Clinics (SLICC) group decided to address these concerns and conducted a two-part study based on the evaluation of nearly 1400 patient scenarios or vignettes; these data were used for the derivation and validation of these newer classification criteria.[45]

In this report, three different questions were addressed: (1) How would the SLICC criteria work in different SLE cohorts? (2) Do they offer any advantage or disadvantage in relation to the ACR criteria? (3) How do the SLICC criteria perform in comparison to physicians' diagnosis?

To answer these questions we studied patients from the LUpus in MInorities: NAture versus Nurture (LUMINA) and GLADEL cohorts. First, we compared the ACR criteria and the SLICC criteria in both cohorts in order to determine which set of criteria would allow for an earlier patient classification, particularly for those patients with lupus nephritis. Second, we compared the physicians' clinical diagnosis and the SLICC criteria in the GLADEL cohort.

From these comparisons we concluded that: (1) The SLICC criteria worked at least as well as the ACR criteria in both cohorts. (2) The SLICC criteria have a more balanced and clinical representation of each of the organ systems. (3) At least a comparable performance was achieved by the SLICC criteria when they were compared with the physicians' judgment.

Number of flares and damage accrual[25]

Organ system damage in lupus is not only an important predictor of mortality, but it is associated with poor quality of life and increased cost of medical care.[46–48] Severe flares are a known risk factor for damage accrual but no studies have addressed the question: Does the number of flares a patient experiences over time affect damage accrual? To address this we performed an ambidirectional case-crossover design (a case interval was one in which there was an increase on the SDI of at least one point; in a control interval no such increase occurred; the case interval could have occurred before or after the control interval) to determine the association between the number of flares and damage accrual.

Of the 1480 patients, 901 were eligible for this study since they had both case and control intervals. Of them 500 (55.5%) presented with at least one flare. Of these 70.0% had mild to moderate flares (SLEDAI increase >3 and <12), 15.4% had severe flares (SLEDAI increase >12) and 14.6% had both. After performing a conditional logistic regression model to adjust for the length of the intervals and other known confounding factors, we found that the total number of flares, the number of severe and the number of mild to moderate flares a patient experiences increased the risk of damage accrual. These data support the notion that in patients with SLE a rapid and aggressive control of disease activity and measures to prevent flares might significantly reduce damage accrual.

Primary cardiac disease[26]

Primary cardiovascular involvement in lupus can range from pericarditis to pancarditis and is a

severe SLE manifestation. We examined the cumulative incidence of primary cardiac disease, the risk and protective factors associated with its presence as well as its potential role in mortality in our patients.

Primary cardiac disease occurred in 14.1% of the 1437 SLE patients studied over a median duration of follow-up of 57.2 months. The main manifestations were pericarditis (81.2%), valvular heart disease (17.3%), arrhythmias (11.4%), myocarditis (3.5%) and non-infectious endocarditis (0.5%).

The variables independently associated with increased risk of subsequent occurrence of primary cardiac disease were ALA ethnicity, primary cardiac disease at or before recruitment and damage (first recorded). On the other hand, central nervous system involvement and treatment with antimalarials at or before recruitment were negatively associated with its occurrence. Although the mortality rate was higher in primary cardiac disease patients (16.8%) than those without it (4.0%), no direct impact of primary cardiac disease on mortality was found. Finally, a protective effect of antimalarials over the later occurrence of primary cardiac disease was found. This is probably the most important finding of this paper, and extends the list of beneficial effects of antimalarials we have shown including disease activity, flares, overall damage, renal disease and mortality.

Conclusions and future directions

GLADEL is very active and planning for the future. The most important pending task is updating the cohort after more than 10 years of follow-up; this, by necessity, will be a concerted effort of all those involved that will allow us to better evaluate the long-term burden of this disease in terms of morbidity and mortality in Latin America.

GLADEL is also creating strategic partnerships with other lupus study groups around the world. In this sense, the close relationship with LUMINA is allowing us to compare Latin American Mestizos with their counterpart ''Hispanics'' in the US.

Similarly, GLADEL and new partner institutions, through a multicenter collaboration within Latin America (the Genome Network systemic lupus erythematosus (GLA-GENLES) consortium), are aiming to identify genome-wide associations and to examine the relationship between genetic ancestry, sociodemographic characteristics and clinical features in a large cohort of American Indian-European SLE patients.[49–54] The identification of new genes for lupus in individuals with Amerindian ancestry and the genetic structure contributed by the admixture will provide new information on the mechanisms behind the disease in these populations. Studies on genetics and clinical manifestations or serological markers will be produced.

As research and education go hand in hand, and considering GLADEL as an independent group of researchers associated with the Liga Panamericana de Asociaciones de Reumatología (PANLAR), a joint project has been proposed to develop ''Guidelines for the treatment of Latin American lupus patients.''

Finally, a very ambitious project of GLADEL is to nurture the next generation of Latin American researchers in lupus that we have named: ''GLADEL 2.0 generation.'' This may allow us to pass the baton to them for the development of new projects in the field of SLE in Latin America.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Author contributions

All authors were involved in drafting or revising this article critically for important intellectual

content, and all authors approved the final version to be published. Drs Guillermo J. Pons-Estel, Luis J. Catoggio and Bernardo A. Pons-Estel have full access to the data from the study and take responsibility for data integrity and accuracy of the analyses performed.

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References

1 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 2010; 39: 257–268.
2 Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. *Semin Arthritis Rheum* 1973; 3: 1–54.
3 Hochberg MC. The application of genetic epidemiology to systemic lupus erythematosus. *J Rheumatol* 1987; 14: 867–869.
4 Manzi S. Epidemiology of systemic lupus erythematosus. *Am J Manag Care* 2001; 7(16 Suppl): S474–S479.
5 Petri M. Epidemiology of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2002; 16: 847–858.
6 Calvo-Alén J, Reveille JD, Rodríguez-Valverde V, *et al*. Clinical, immunogenetic and outcome features of Hispanic systemic lupus erythematosus patients of different ethnic ancestry. *Lupus* 2003; 12: 377–385.
7 Uribe AG, McGwin G Jr, Reveille JD, Alarcón GS. What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs nurture) cohort? Where are we heading? *Autoimmun Rev* 2004; 3: 321–329.
8 Fernández M, Alarcón GS, Calvo-Alén J, *et al*. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum* 2007; 57: 576–584.
9 Cervera R, Khamashta MA, Hughes GR. The Euro-lupus project: Epidemiology of systemic lupus erythematosus in Europe. *Lupus* 2009; 18: 869–874.
10 Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. *Lupus* 2010; 19: 1365–1373.
11 Mok CC. Epidemiology and survival of systemic lupus erythematosus in Hong Kong Chinese. *Lupus* 2011; 20: 767–771.
12 Murali R, Jeyaseelan L, Rajaratnam S, John L, Ganesh A. Systemic lupus erythematosus in Indian patients: Prognosis, survival and life expectancy. *Natl Med J India* 1997; 10: 159–164.
13 Mok CC, Lee KW, Ho CT, Lau CS, Wong RW. A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. *Rheumatology (Oxford)* 2000; 39: 399–406.
14 Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. *Autoimmun Rev* 2010; 9: A277–A287.
15 Pons-Estel B, Villalba D, Alvarellos A, Caeiro F, Catoggio LJ, Soriano ER. ARTHROS 2.0: A rheumatology database [abstract]. *Ann Rheum Dis* 1999; 58: 153.
16 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.
17 Alarcón-Segovia D, Alarcón-Riquelme ME, Cardiel MH, *et al*. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum* 2005; 52: 1138–1147.
18 García MA, Marcos JC, Marcos AI, *et al*. Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients. *Lupus* 2005; 14: 938–946.
19 Ramírez Gómez LA, Uribe Uribe O, Osio Uribe O, *et al*. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. *Lupus* 2008; 17: 596–604.
20 Shinjo SK, Bonfá E, Wojdyla D, *et al*. Antimalarial treatment may have a time-dependent effect on lupus survival: Data from a multinational Latin American inception cohort. *Arthritis Rheum* 2010; 62: 855–862.
21 Pons-Estel GJ, Alarcón GS, Hachuel L, *et al*. Anti-malarials exert a protective effect while Mestizo patients are at increased risk of developing SLE renal disease: Data from a Latin-American cohort. *Rheumatology (Oxford)* 2012; 51: 1293–1298.
22 Pons-Estel GJ, Saurit V, Alarcón GS, *et al*. The impact of rural residency on the expression and outcome of systemic lupus erythematosus: Data from a multiethnic Latin American cohort. *Lupus* 2012; 21: 1397–1404.
23 Pons-Estel GJ, Alarcón GS, Burgos PI, *et al*. Mestizos with systemic lupus erythematosus develop renal disease early while antimalarials retard its appearance: Data from a Latin American cohort. *Lupus* 2013; 22: 899–907.
24 Pons-Estel GJ, Wojdyla D, McGwin G Jr, *et al*. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics Classification criteria for systemic lupus erythematosus in two multiethnic cohorts: A commentary. *Lupus* 2014; 23: 3–9.
25 Ugarte-Gil MF, Acevedo-Vásquez E, Alarcón GS, *et al*. The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: Data from a multiethnic Latin American cohort. *Ann Rheum Dis* annrheumdis-2013-204620 Published Online First: 13 February 2014.
26 Jawaheer D, Seldin MF, Amos CI, *et al*. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. *Am J Hum Genet* 2001; 68: 927–936.
27 García MA, Alarcón GS, Boggio G, *et al*. Primary cardiac disease in systemic lupus erythematosus patients: Protective and risk factors—data from a multi-ethnic Latin American cohort. *Rheumatology (Oxford)* 2014; 53: 1431–1438.
28 Guerra SG, Vyse TJ, Cunninghame Graham DS. The genetics of lupus: A functional perspective. *Arthritis Res Ther* 2012; 14: 211.
29 Alarcón-Riquelme ME. Family studies in systemic lupus erythematosus. *Rheumatology (Oxford)* 2002; 41: 364–366.
30 Vyse TJ, Todd JA. Genetic analysis of autoimmune disease. *Cell* 1996; 85: 311–318.
31 Andrade RM, Alarcón GS, Fernández M, *et al*. Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. *Arthritis Rheum* 2007; 56: 622–630.
32 Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann Rheum Dis* 1991; 50: 490–492.
33 Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. *Arthritis Rheum* 1995; 38: 551–558.
34 Font J, Cervera R, Espinosa G, *et al*. Systemic lupus erythematosus (SLE) in childhood: Analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis* 1998; 57: 456–459.
35 Ruiz-Irastorza G, Egurbide MV, Pijoan JI, *et al*. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus* 2006; 15: 577–583.
36 Alarcón GS, McGwin G, Bertoli AM, *et al*. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: Data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007; 66: 1168–1172.
37 Bastian HM, Roseman JM, McGwin G Jr, *et al*. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus* 2002; 11: 152–160.
38 Petri M, Perez-Gutthann S, Longenecker JC, Hochberg M. Morbidity of systemic lupus erythematosus: Role of race and socioeconomic status. *Am J Med* 1991; 91: 345–353.
39 Mok MY, Li WL. Do Asian patients have worse lupus? *Lupus* 2010; 19: 1384–1390.
40 Kasitanon N, Fine DM, Haas M, Magder LS, Petri M. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus* 2006; 15: 366–370.
41 Sisó A, Ramos-Casals M, Bové A, *et al*. Previous antimalarial therapy in patients diagnosed with lupus nephritis: Influence on outcomes and survival. *Lupus* 2008; 17: 281–288.
42 Pons-Estel GJ, Alarcón GS, McGwin G Jr, *et al*. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Rheum* 2009; 61: 830–839.

43 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271–1277.
44 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
45 Petri M, Orbai AM, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64: 2677–2686.
46 Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. *Clin Exp Rheumatol* 2008; 26(5 Suppl 51): S72–S79.
47 Mok CC, Ho LY, Cheung MY, Yu KL, To CH. Effect of disease activity and damage on quality of life in patients with systemic lupus erythematosus: A 2-year prospective study. *Scand J Rheumatol* 2009; 38: 121–127.
48 Meacock R, Dale N, Harrison MJ. The humanistic and economic burden of systemic lupus erythematosus: A systematic review. *Pharmacoeconomics* 2013; 31: 49–61.
49 Graham RR, Kozyrev SV, Baechler EC, *et al*. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat Genet* 2006; 38: 550–555.
50 Kozyrev SV, Abelson AK, Wojcik J, *et al*. Functional variants in the B-cell gene *BANK1* are associated with systemic lupus erythematosus. *Nat Genet* 2008; 40: 211–216.
51 Sánchez E, Rasmussen A, Riba L, *et al*. Impact of genetic ancestry and sociodemographic status on the clinical expression of systemic lupus erythematosus in American Indian-European populations. *Arthritis Rheum* 2012; 64: 3687–3694.
52 Sánchez E, Webb RD, Rasmussen A, *et al*. Genetically determined Amerindian ancestry correlates with increased frequency of risk alleles for systemic lupus erythematosus. *Arthritis Rheum* 2010; 62: 3722–3729.
53 Seldin MF, Qi L, Scherbarth HR, *et al*. Amerindian ancestry in Argentina is associated with increased risk for systemic lupus erythematosus. *Genes Immun* 2008; 9: 389–393.
54 Seldin MF, Tian C, Shigeta R, *et al*. Argentine population genetic structure: Large variance in Amerindian contribution. *Am J Phys Anthropol* 2007; 132: 455–462.