



## Editorial

### Multiethnic lupus cohorts: What have they taught us?

### Cohortes multiétnicas de Lupus: ¿qué nos han enseñado?

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Systemic lupus erythematosus (SLE) is a heterogeneous multisystemic autoimmune disease of unknown etiology of variable course and outcome. It affects predominantly women (9:1) on their reproductive age years but can occur at the extremes of life (from infants to nonagenarians). In older adults the disease is not very severe, yet because it occurs in persons who may already have other comorbidities it tends to have less than a favorable outcome. In children, adolescents and young adults the disease tends to be more serious than in middle age adults. It is more frequent and more serious among non-Caucasian population groups around the world.<sup>1,2</sup> Although it is not completely understood why there are differences in the incidence and prevalence of SLE in these populations and why its outcome is less than favorable, the fact of the matter is that differences do exist; it has become clear that biologic and non-biologic factors act in concert to predispose to this disease and to modulate its outcome. The study of multiethnic lupus cohorts may provide some insight on how these factors interplay. The concept of ethnicity (as opposed to race) encompasses not only the ancestral genes for the respective population group but also a number of socioeconomic, cultural and geographic features which characterize each one of them. In the USA, for example, Hispanics or those individuals originating from a Spanish-speaking country and African descendants (including Afro-Caribbean and African Americans) tend to be socially disadvantaged in comparison to the Caucasian majority. Moreover, even within these ethnic groups substantial biological and cultural differences do exist, as the proportion of ancestral genes (European, Amerindian and African within a three-hybrid model of inheritance) and the social context in which these groups have come about in the USA vary considerable; in the case of Hispanics, for example, older but also more educated immigrants may have a legally recognized status whereas a high proportion of the more recent immigrants, many of whom are poorly educated may be illegal, may differ considerably. Thus ascribing differences in disease expression between ethnic groups only to these groups' genetic

features, being those ancestral genes (also called ancestral informative markers) or not, is an oversimplification and it is indeed incorrect.

It will be close to impossible to refer to all the published work which has emanated from the LUMINA cohort. Thus for this article I will emphasize on six areas which we have studied in this cohort which our group constituted in the USA; they are **disease activity, damage accrual, renal involvement, pregnancy outcome, work disability** and **mortality/survival**. Before expanding on these teams, however, I should note first that LUMINA (for **Lupus in Minorities: Nature vs. Nurture**) is a multiethnic cohort (Hispanics from Texas and the Island of Puerto Rico, African Americans and Caucasians) of SLE patients, 16 years of age and older at entry into the cohort and meeting at least four of the American College of Rheumatology (ACR) classification criteria for SLE; these patients had to have less than five years of disease duration at enrollment into the cohort and to live in the catchment areas of the participating institutions, The University of Alabama at Birmingham (UAB, Birmingham, Alabama), The University of Texas Houston Health Sciences Center (Houston, Texas) and The University of Puerto Rico Medical Sciences Campus (San Juan, Puerto Rico). Hispanic patients were recruited in Texas and the Island of Puerto Rico whereas African Americans and Caucasians were recruited primarily in Birmingham but also in Texas (Houston and Galveston). The first patient was enrolled into the LUMINA cohort in the spring of 1994 with the exception of the patients from Puerto Rico where recruitment did not start until 2001<sup>3,4</sup>; the last patient was enrolled into LUMINA in the spring of 2008. The cohort is thus constituted by a total of 635 patients: 220 Hispanics (118 from Texas and 102 from Puerto Rico), 234 African Americans and 181 Caucasians. Patients had semiannual visits for the first year and yearly thereafter; these visits consisted of interviews and questionnaires, physical examination and laboratory evaluation. In addition sera and DNA were obtained and stored for future use. It should be said from the outset that what makes LUMINA such a distinct USA cohort, is the inclusion of Hispanic patients; prior to LUMINA, emphasis had been placed on the distinctive features and outcome of patients of African descent as opposed to those of the Caucasians. LUMINA placed into the map, so to speak, lupus among the Hispanic population of the USA, even before it was recognized as the largest minority group and the fastest growing.

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## Disease activity

We measured disease activity in LUMINA using the Systemic Lupus Activity Measure-Revised or SLAM-Revised or SLAM-R; we chose this instrument over the SLEDAI, the SELENA SLEDAI and the BILAG for its relative simplicity and ease of administration, the fact that it did not require expensive immunological tests, and our familiarity with it. Factors associated with disease activity at disease onset included the absence of *HLA-DRB1\*0301*, African American ethnicity, lack of health insurance, and the presence of inadequate coping styles.<sup>5</sup> Like others, we observed a decline in the level of disease activity as patients remained in the cohort for extended time periods; when searching for the factors predictive of the slope of change (decline in disease activity), we observed that the presence of *HLA-DRB1\*1503* was associated with the slowest decline of this slope.<sup>6</sup> In turn, when the factors associated with persistent disease activity over the course of disease were examined using generalized estimating equation, neither genetic marker identified in the analyses described was, however, statistically significant. Socioeconomic-demographic factors [lack of health insurance, inadequate coping styles and lack of social support along with African American and Hispanic (Texas) ethnicities] were instead independently associated with higher levels of disease activity over time<sup>7</sup>; moreover, even after removing baseline disease activity from the multivariable analyses (which encompassed the genetic marker identified early on), no genetic marker was retained in the multivariable model with the exception of African admixture. In contrast, high levels of social support were associated with a decline in disease activity levels.<sup>8</sup> These data clearly demonstrate the importance of genetic factors as contributing to the expression of the initial disease manifestations of SLE, disease activity a compendium of them; however as time elapses, socioeconomic factors seem to modulate disease activity in a significant and distinct manner with the role of genetic factors becoming much less prominent. Furthermore, it is not just one factor but several different ones, some of them like social support and inadequate coping styles, amenable to interventions, which influence disease activity over the course of the disease.

## Damage accrual

Damage in SLE, as defined by the SLICC (for Systemic Lupus International Collaborating Clinics) Damage Index or SDI has repeatedly been shown to be associated with disease activity, disease duration, age, and the use of glucocorticoids. These variables have been also associated with damage accrual in patients from the LUMINA cohort. In addition, we have also demonstrated that poverty (as defined by the US Federal government) and being of African descent or of Hispanic-Amerindian heritage are associated with damage accrual.<sup>9</sup> Moreover, the presence of damage is a predictor of further damage suggesting that every effort should be made to avoid this initial deleterious event.<sup>10</sup> Texan Hispanic patients also tend to accrue damage more rapidly than patients of the other ethnic groups.<sup>11</sup> Whether this represents patients from this ethnic group, many of them are considered illegal in the US, presenting later in the disease course to available health care providers, or true more rapid damage accrual cannot be stated for certain; however, it should be noted that within the LUMINA cohort, Texan Hispanic patients and patients of African descent were the ones more likely to experience an acute disease onset (symptoms that evolve over four weeks or less) which even in patients with an inadequate health coverage would prompt them to seek medical attention.<sup>12</sup> We have also assessed the role of gender and menopause in damage accrual; male gender was found to be a risk factor for the accumulation of damage particularly early in the course of the disease.<sup>13</sup>

Likewise, we have found menopause to be associated with damage accrual;<sup>14</sup> however, because half of the women studied had experienced premature menopause, we also examined whether premature menopause was also independently associated with the accumulation of damage. In this case, premature menopause was not found to be a risk factor; instead it was the use of cyclophosphamide with patients receiving between 1 and 6 pulses having a greater risk than those receiving none and those receiving more than 6 pulses having even a higher risk.<sup>15</sup> Finally, lupus that ensues at the extremes of life is also associated with increased risk of damage accrual.<sup>16,17</sup>

## Renal involvement

Lupus nephritis, perhaps the most typical and worrisome manifestation of lupus, occurs in about 20–65% of patients and may lead to end-stage renal disease in about 10% of those affected. In the LUMINA cohort the most constant feature associated with this occurrence has been ethnic affiliation. Hispanic (Amerindian, Mestizo) and patients of African descent tend to experience lupus nephritis more commonly. Renal involvement occurred in 62% of Texan Hispanic and African American patients and in 25% of Caucasian patients from LUMINA. Lupus nephritis also tended to occur earlier in the course of the disease in African Americans and in the Texan Hispanics who in contrast to the ones from the Island of Puerto Rico have a higher proportion of Amerindian ancestral genes.<sup>18</sup> Of interest, in the Puerto Rican Hispanics, lupus nephritis occurred with rates comparable to the Caucasians (26%). However, socioeconomic factors also contribute to the occurrence of lupus nephritis, being unmarried being one of the factors from this domain which we have identified.<sup>19</sup> The outcome of lupus nephritis tends also to be more severe among patients from these ethnic groups with a higher proportion of these patients developing renal damage, including end-stage renal disease.<sup>20</sup> Moreover, as shown in a parallel study conducted recently at UAB, patients of African descent also tend to have less favorable outcomes if they undergo a renal engraftment.<sup>21</sup> However, when, in an effort to sort out the contribution of socioeconomic-demographic factors and ancestral genes to the occurrence of lupus nephritis, both sets of factors were examined, they were found to independently explain some of the variance in the models examined whereas their combination also accounted for some of the variance.<sup>22</sup> Finally, we have also shown that angiotensin-converting enzyme inhibitors may protect patients with lupus from developing renal involvement while antimalarials may retard the occurrence of renal damage in those patients who already have lupus nephritis, and, that in those patients with proteinuria, *HLA-DRB1\*1503* is associated with its worsening.<sup>20,23,24</sup> These data, taken together with the data from the literature, suggest that although there seems to be a clear genetic predisposition to the occurrence of lupus nephritis, socioeconomic factors also influence not only its occurrence but also its course and ultimate outcome.

## Pregnancy outcome

Although pregnancy in the lupus patient does not portend any more a very ominous prognosis, adverse pregnancy outcomes do occur, particularly if patients become pregnant when they have lingering disease activity, renal involvement, hypertension or secondary antiphospholipid syndrome. Such adverse outcomes were relatively frequent in our cohort in which 65 of 102 pregnancies which occurred after SLE had been diagnosed culminated in an adverse outcome defined as either miscarriage, pregnancy termination, fetal death, premature delivery and/or intrauterine growth retardation. Although these adverse outcomes were more frequent

among the Texan Hispanics, 34% vs. 27%, and African Americans, 38% vs. 24%, in the multivariable analyses, it was education rather than ethnicity the variable significantly and independently associated with these adverse pregnancy outcomes.<sup>25</sup> In terms of damage accrual during pregnancy, we found that the presence of damage prior to pregnancy is a strong predictive factor of further damage accrual which is entirely consonant with the observations made in the entire cohort as already noted.<sup>26</sup>

### Work disability

This is another important outcome when dealing with adults during the years they are expected to be productive members of society whether working for pay or contributing to child-care and other unpaid (and oftentimes not properly valued) home-related activities. The Kaplan–Meier survival curves for this outcome clearly indicate an association between African American and Hispanic (Texas) ethnicities and becoming work disabled over the course of the disease. However, in multivariable analyses, poverty along with disease activity, damage at first study visit, age and disease duration but not ethnicity, independently contributed to the development of work disability<sup>27</sup> supporting again the role of socioeconomic factors in intermediate SLE outcomes; given that work disability contributes to the burden of disease, this is a very relevant finding.

### Mortality and survival

We have examined this outcome several times over the years having published our results when our cohort had only 288 patients and 34 of them had died<sup>28</sup> and subsequently with more than double the number of patients in the cohort and the number of deceased patients.<sup>29</sup> Although the Kaplan–Meier curves clearly show statistically significant differences in the mortality experience of the ethnic groups examined with Hispanics (Texas) and African Americans having the less favorable experience, when adjusting for socioeconomic features, it is poverty, as defined by the US Federal government, rather than ethnicity, which is independently associated with a shorter time to the event in multivariable Cox proportional hazard regression analyses. Our data are in consonance with the data from the Hopkins Lupus cohort in which ethnicity was not retained in the multivariable model examined but income was.<sup>30</sup> If the lupus mortality data from the Centers of Disease Control and Prevention (CDC)<sup>31</sup> demonstrating an increased in the mortality rates for middle age African American women had been adjusted for socioeconomic features, it is conceivable that the differences in the mortality rates between Caucasians and African Americans with lupus may have diminished considerably or perhaps disappeared altogether (of note similar data for Hispanics were not available at the time these analyses were performed at the CDC). Finally, to be able to examine the role of specific domains of the damage index (renal, cardiovascular and peripheral vascular) in mortality in lupus, we had to exclude poverty from the multivariable analyses so the influence of the SDI domains variables could be appreciated<sup>32</sup>; when left in, none of the specific domains of the SDI were retained in the multivariable models examined.

### Conclusions

The examples described above demonstrate the importance of including measures of socioeconomic status when examining intermediate and long-term outcomes in lupus. I leave to the sociologist to determine what is the best measure or proxy of socioeconomic status is (education, income, occupation, health insurance, marital status, neighborhood, other); at least in the US, there is a tendency

towards the use of geocoding or to match each patient to his/her zip code (neighborhood encompassing more than all other variables taken independently according with its proponents). It is of interest to note that in the different analyses performed and which I have succinctly summarized, we have included poverty, education, marital status, health insurance, social support and coping styles with one and sometimes more than one of these variables becoming significant in multivariable analyses. I also leave to the anthropologists to make a final decision about the use of the term race which, as erroneous as it seems to be according with them and as stated by the Institute of Medicine, has a social connotation which many investigators do not want to abandon; this is particularly the case for some special interest groups which draw some comfort in perpetuating the use of this term. Moreover, the US census, and the National Institute of Health still used both terms, race and ethnicity to report the distribution of the US population and of those to be studied utilizing federal funds.

In parallel to significant advances made over the last few years in understanding the biology of SLE at its onset and over time, the studies which have emanated from LUMINA and other multi-ethnic lupus cohorts point to the importance of the interplay between biology and environment when environment is defined broadly to encompass the social context in which the disease occurs and other culturally related patient characteristics. If the outcome of lupus is going to be significantly modified we need to make a concerted effort towards unraveling the biology of this fascinating disease but also towards intervening in those socioeconomic factors which are modifiable. Such interventions will certainly have a favorable impact in the health of the individual and will diminish the burden this disease posits over the society at large.

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