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Systemic lupus erythematosus in Latin America: Outcomes and therapeutic challenges

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ABSTRACT

Systemic lupus erythematosus (SLE) affects more severely non-White populations, which is also the case in Latin America; this is the result of a combination of genetic and non-genetic factors. Among the non-genetic factors, a limited income and a low educational level impact negatively on the course and outcome of the disease; in addition, lack of access to healthcare services deprives patients from the opportunity of being managed by specialists, making the availability of the newest drugs practically impossible. Taking together, these factors reduce the probability of patients achieving good outcomes, like remission, less damage accrual, a better survival and a better health-related quality of life, among others. Several strategies have been proposed to reduce these disparities, including peer education, educational activities for patients and primary care physicians, improving healthcare networks and generating cost-effectiveness analyses.

Introduction

Worldwide, systemic lupus erythematosus (SLE) affects more severely non-White populations, and this is also the case for Latin America; this is probably the result of a combination of genetic and non-genetic factors ([1,2]). In fact, Amerindian ancestry (genes native to the American continent) is associated with a higher probability of carrying risk alleles for SLE[3] and a higher risk of lupus nephritis occurrence[4]; Mestizo patients, who have an important Amerindian ancestry, as well as African American patients exhibit a high disease activity early in the course of the disease [5]. Mestizo patients also develop renal involvement more frequently than White patients [6]. Taken together, these data suggest that ancestry is associated with disease severity as its onset, but, over the years, socioeconomic status (SES) factors, like poverty [7] and/or lack of healthcare access [5] become more relevant and, in fact, they have been consistently associated with poorer lupus outcomes. Furthermore, mortality seems to be affected more by socioeconomic factors than by ethnicity per se, as shown in previous reports from the Hopkins and the LUMINA cohorts; in both, when socioeconomic factors were included in the models, ethnicity was no longer associated with survival ([8,9]). It should also be noted that the number of rheumatologists in many Latin American countries is suboptimal and poorly distributed in favor of the main cities [10] which results in their limited availability for those individuals living in small towns and rural areas.

There is also limited information about the prevalence of SLE in Latin America; figures ranging from 35 to 92 per 100 000 inhabitants have been reported ([11–16]); however, this information is based on single center or single system analyses, medical records review or using the COPCORD (Community Oriented Program for Control of Rheumatic Diseases) strategy. Unfortunately, the lack of reliable epidemiological information in the region reduces the probability of developing better management strategies for these patients.

In this review we will focus on the outcomes and therapeutic challenges experienced by Latin American SLE patients.

Outcomes

Should the target be the same in Latin America as in other parts of the world?

A Treat-to-Target (T2T) strategy has been proposed for SLE management. Remission has been defined by the DORIS group (Definition of Remission in SLE)[17]. Low disease activity (LDA), however, has several definitions, being the most widely used the one proposed by the Asia

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Pacific Lupus Collaboration (APLC) named lupus low disease activity state (LLDAS) [18]. Remission and LLDAS have been associated with a lower probability of damage accrual, lower mortality, lower flare rates and better health-related quality of life (HRQoL) suggesting that these parameters could be used as treatment targets in SLE patients [19]. It should be noted that, overall, White populations have a higher probability of achieving remission and LLDAS [20], even early in the course of the disease [21]. As mentioned before, these differences could be due to genetic factors, but also to sociodemographic factors and healthcare access. Regarding healthcare access, in addition to the limited number of specialists, new treatment modalities (i.g. biologic compounds) which are approved in high-income countries (HICs), have, by and large, not been approved in Latin America; even for those compounds that have been approved, they may not be covered by the healthcare system and are thus, unaffordable.

A real T2T strategy should include all treatments available as well as the possibility of having frequent visits with a multidisciplinary team, like those in established lupus clinics. Patients being cared for at dedicated lupus clinics would have a better quality of care [22], which, in turn, is associated with a lower probability of damage accrual [23]. This model is less commonly used in Latin America, due to its cost, administrative issues and limited resources; however, when it is used, it has been associated with a higher rate of remission and LDA [24]. Similar results have been found for rheumatoid arthritis (RA) patients in Colombia; patients who were taken care of in RA Centers of Excellence had a lower disease activity compared to those under regular care and the strategy was cost-effective, reducing cost by 36 % [25].

What are the probabilities of achieving good outcomes in Latin America?

There is scarce information about the probability of achieving remission and/or LDA in Latin America ([26–28]). In the *Grupo Latino-Americano de Estudio de Lupus* (GLADEL) cohort almost 66 % of the subjects never achieved remission or LDA, only 20 % achieved remission at least once during their follow-up and 14 % achieved LDA (not on remission) [27]. However, in the Almenara Lupus Cohort, a prevalent cohort in Lima-Peru, almost 55 % of the patients' visits met the definition of remission and 13 % of them of LDA (not on remission) [26]. Similarly, in a cohort from Mexico, 52.4 % of the patients achieved remission during their follow-up [29]. The differences between these cohorts could be related to the calendar year when patients' enrollment into them took place (late 1990′s for GLADEL, 2003 for Mexico and 2012 for Almenara); also, GLADEL is an inception cohort whereas the Almenara and the Mexican are prevalent cohorts, which could also affect the probability of achieving remission and LDA.

Additionally, it is important to point out that our flare rate is similar to that of other parts of the world (15.3 per 100 patient-year in the Almenara Lupus Cohort [30] and 17.0 per 100 patient-year in the GLADEL cohort [31] compared to between 7 and 24 per 100 patient-year in other parts of the world ([32,33]); additionally, the five-year survival in the GLADEL cohort is 94 % [34], is similar to that from other regions of the world [1]. However, the age-standardized mortality rate (ASMR) in Latin America is the highest in the world and it has increased significantly over the years while in Europe, North America, and Oceania it has decreased significantly. In 2014, the ASMR in Latin America was 5.53, in North America was 2.69, in Oceania was 1.33, in Africa was 1.27 and in Europe was 1.06 [35]. These ASMR differences probably reflect socioeconomic factors including limited access to healthcare and/or the impact of genetic and/or environmental factors.

Therapeutic challenges

Patient

A lower SES and/or lower educational level have been associated with higher mortality [9], damage accrual [36], lower treatment adherence ([37,38]) and higher occurrence of disability [39]. Additionally, patients living in rural areas have a higher disease activity and develop renal involvement more frequently than those living in urban areas [40]. Patients' associations or groups are relevant as they can positively impact at the local and country levels in terms of their access to the healthcare system and into health policies. Furthermore, peer education has shown to improve treatment adherence and the outcome of these patients [41]. The WELL (Women Empowered to Live with Lupus) study (Georgia, US) has shown that a self-management program improves patients' communications with their physicians as well as the management of their medications and of their possible side effects [42].

The association between ethnicity and outcomes is also influenced by the patient's genetic background. A study which included 804 Mestizo patients reported an association between Amerindian ancestry and the number of risk alleles for SLE; these authors reported an increase of 2.34 risk for SLE when comparing SLE patients with 100 % Amerindian ancestry with patients with 0 % Amerindian ancestry [3]. Furthermore, Amerindian ancestry was associated with an increased risk of renal involvement (OR 3.50) and a lower risk of discoid rash (OR 0.51), photosensitivity (OR: 0.58), oral ulcers (OR 0.55), arthritis (OR 0.59), serositis (OR 0.56), after adjustment by age at onset and gender. Additionally, Amerindian ancestry was associated with an earlier age of disease onset [4].

Provider

Those who manage SLE patients are very aware of the fact that their patients do not have enough information about this disease, and that many of them try to find it on the world wide web (www), specifically regarding its definition and the symptoms patients with this disease experience; in fact, these are the most searched www topics [43]. The downside of this searches is that not all the information in the www is reliable and patients do not have the means to discern that. Thus, a few years ago, GLADEL developed an educational program in Spanish and Portuguese (named "*Hablemos de Lupus*" and *Falando de Lupus* or "Let's Talk about Lupus"), which is aimed at improving the patients and their families' knowledge about the disease [44]. It is expected that these patients would have better self-management strategies and a better communication with their providers so they can embark in a shared decision-making model.

Additionally, during 2022, GLADEL launched the program "Is it lupus?" to allow primary care physicians (PCPs) to improve their knowledge about this condition, increasing the visibility of lupus and thus its early recognition followed by the proper referral of these patients.

Some complex laboratory tests are needed for the diagnosis and treatment of SLE patients, such as antinuclear antibodies (ANA), other specific antibodies (like anti-Sm, anti-dsDNA, antiphospholipid antibodies, among others), complement level as well as renal (or other) biopsies, and these tests are not available in all the regions of Latin American countries. In the largest hospitals, these tests are available, and they are used for diagnosis; that is not the case for smaller hospitals and in non-urban areas where the physician must count on his clinical skills to diagnose lupus. However, during these patients' follow-up, some indices that do not require immunological tests, such as the Mexican version of the SLEDAI (Mex-SLEDAI) (46)or the Lupus Foundation of America-Real Evaluation of Activity in Lupus Clinician Reported-Outcome (LFA-REAL ClinRO) [46] can be used. Both indices have been used in Latin American populations with a good correlation with the SLEDAI and with the physician global assessment ([45,47,48]).

Lack of effective drugs covered by the healthcare system, as well as their prohibitive cost, if a patient wanted to buy them out of pocket, may force the provider to use glucocorticoids at higher doses or for longer periods of time than in HICs. If there are no other options, the use of medium or high dose glucocorticoids could be an alternative but it

should be closely monitored to taper them as soon as possible; furthermore, preventive measures for glucocorticoid-related damage should be initiated. This will include osteoporosis and cardiovascular prevention, among others. In order to help Latin American rheumatologists to take care of their patients, GLADEL developed and published the first Latin American clinical practice guidelines for the management of SLE, taking into account regional information as well as patients access to the healthcare system [49].

The healthcare system

Healthcare has not been prioritized by Latin American governments, with only 7.96 % of its gross-domestic product (GDP) being invested on it, compared to 12.49 % in HICs [50]; this leads to a lower number of physicians per 1000 inhabitants as compared with HIC : 3.0 vs. 3.7 [51], Furthermore, the number of beds per 1000 inhabitants is 1.9 in Latin America vs. 5.3 in HIC [52]. The crucial role of healthcare access on patients' outcomes has been dramatically shown with the COVID-19 pandemic; a larger number of beds and a better human development index have been associated with lower mortality rates in the COVID-19 Global Rheumatology Alliance registry [53]. Furthermore, the inclusion of new drugs is not uniform in the region, and sometimes is not even predictable, increasing disparities.

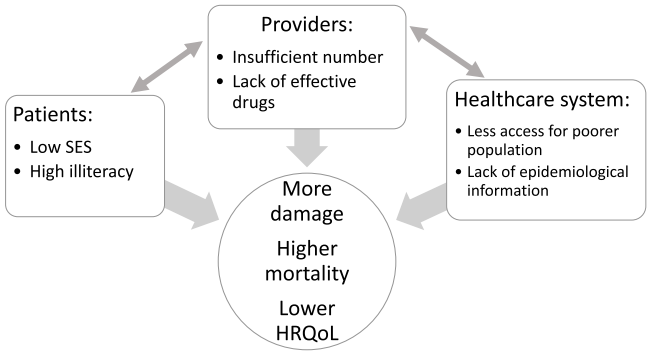
SLE diagnosis is difficult even in HICs. In these countries, the median (interquartile rank) diagnosis delay is 2 (0-[6]) years [54]. This delay is probably larger in Latin America, and it is important to note that such delay is associated with a higher disease activity, greater damage accrual and a lower HRQoL [55]. Additionally, poverty has been found to be negatively associated with access to healthcare, but even in those patients who had access to healthcare, they experienced poor access to specialty care, or it took them a long time to be referred to a specialist [56].

There are, however, several interventions that can be implemented to improve patients' access. For example, healthcare networks should allow rheumatologists to focus on those patients with active disease or with comorbidities who require a closer follow-up, while PCPs can take care of patients on remission, under the supervision of a rheumatologist. Also, collaborative efforts should be started or reinforced to constitute specialized lupus clinics which should include a multidisciplinary team. Additionally, we need more granular information about the characteristics of the disease among our patients to determine whether a patient may have a good or poor outcome; such recognition will allow us to determine who may require a closer follow-up in a more experienced medical setting. One of the currently ongoing projects, is the GLADEL 2.0 cohort, which is aimed at determining potential biomarkers in these SLE patients [57].

Additionally, cost-effectiveness studies, taking into account the prevention of flares and of damage, improvement in HRQoL and a delayed mortality may suggest the use of better drugs with the consequent improvement in the patients' probability of achieving remission and LDA. It is also important to point out that the cost-effectiveness thresholds for drugs should be lower in Low -Middle Income counties (LMIC) than in HIC; it has been suggested that this could be less than 0.5 GDP per capita on LMIC and between 1 and 2 GDP per capita in HIC [58].

Furthermore, the monies spent in SLE patients seems to be lower in Latin American than in HICs; for example, annual direct cost in Colombia in 2015 was $2355 [59], and for those with lupus nephritis, it raised to $12,624 [60]. These costs are lower than those reported in Europe, US & Canada (ranging between $4 271 to more than $30 000 in patients with SLE, in general, and between $10 000 and more than $70 000 for those with lupus nephritis) [61]; these differences could reflect the lack of access to some treatments and tests but also an increase on the indirect costs. Also, it is important to point out that damage accrual is the one of the main drivers of the increase in costs in SLE; for example, in the SLICC cohort, those patients with a SLICC/ACR damage index (SDI) $\geq$ 5 had a cost of 22 006 Canadian dollars while those with a SDI=0 had a cost of 1 833 Canadian dollars [62].

Based on this information, we should prioritize the drugs that reduced the probability of damage accrual. The new biologics (belimumab and anifrolumab) seem to reduce damage accrual and to increase the probability of achieving remission and/or low disease activity ([63–68]) which is a strong predictor of good outcomes such as less damage accrual, better health-related quality of life, lower mortality rates, among others [19]. Additionally, it is expected that these drugs would reduce the direct costs, by reducing damage. Furthermore, in a Chinese study, a higher prednisone daily dose was associated with



SES: Socioeconomic status. HRQoL: Health-related quality of life

Fig. 1. Impact of therapeutic challenges on SLE outcome.

Table 1
Factors associated with poorer outcome in SLE patient in Latin America and potential solutions.

Factors associated with poorer outcome		Potential solutions	
Genetic/ ancestry	Socioeconomic	Rheumatologists	Providers
Amerindian ancestry is associated with an increase number of risk alleles for SLE	Poverty and lower educational level are associated with poorer outcomes	To develop educational programs for patients and general practitioners	To develop networks between primary care and specialized centers
Amerindian ancestry is associated with an increased risk of renal involvement in SLE	Lack of/limited access to specialized tests delay the diagnosis of SLE	To be part of networks between primary care and specialized centers.	To constitute specialized lupus clinics
	Lack of/limited treatment reduce the probability of achieving remission and/or low disease activity; also, they could be associated with the use of higher doses of glucocorticoids	To develop evidence-based guidelines aimed at achieving remission and/or low disease activity early in the course of the disease	To increase the access to treatment, evaluating cost-effectiveness and encouraging the use of generics and biosimilars
	Lack of/limited access to rheumatologists would delay the diagnosis and adequate treatment of these SLE patients.	To initiate preventive measures for glucocorticoid-related damage	To participate in collective negotiations with the pharmaceutical industry

higher direct costs, reinforcing the impact of a better control of the disease on the costs [69]. Unfortunately, there is not enough evidence regarding the cost-effectiveness of these drugs. Other strategy to increase the access would be to encourage the use of generics and biosimilars through flexible patent laws as well as to participate in collective, multinational transactions that enhance negotiation power with drug companies [70].

Unfortunately, information regarding SLE patients is obtained mainly from the capitals or large cities of Latin American countries, so, research in small cities and rural areas should be strongly encouraged by the healthcare system which will allow to better impact on these patients' disease outcomes. The interaction between these challenges and SLE-related outcomes are shown in Fig. 1.

Factors associated with poorer outcomes in SLE patients in Latin America and potential solutions are shown in Table 1.

Conclusions

SLE is more severe in Latin American patients due to a combination of genetic and sociodemographic factors. Nevertheless, remission should be a reasonable target for these patients, being the alternative LDA for those who cannot achieve it. Working together patients, providers and the healthcare system can improve healthcare access including the development of specialized lupus clinics. Finally, we need more information about the characteristics of the disease and treatment options for patients living in small cities or rural areas.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Manuel F. Ugarte-Gil reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants. Manuel F. Ugarte-Gil reports a relationship with Pfizer that includes: funding grants. Manuel F. Ugarte-Gil reports a relationship with Tecnofarma that includes: travel reimbursement. Manuel F. Ugarte-Gil reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. Manuel F. Ugarte-Gil reports a relationship with GSK that includes: speaking and lecture fees.

Data availability

No data was used for the research described in the article.

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