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Challenges for lupus management in emerging countries

Zoubida Tazi Mezalek[1,2], Wafaa Bono[3]

1. Université Mohamed V Souissi, Faculté de médecine et de pharmacie, 10000 Rabat, Morocco
2. Ibn Sina University Hospital, internal medicine department, 10000 Rabat, Morocco
3. Hassan II University Hospital, internal medicine and immunology Clinic, Fès, Morocco

Correspondence:
Zoubida Tazi Mezalek, Ibn Sina University Hospital, internal medicine department, 10000 Rabat, Morocco.
z.tazimezalek@gmail.com

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In this issue

Summary

In emerging countries, systemic lupus erythematosus (SLE) has been associated with several unfavorable outcomes including disease activity, damage accrual, work disability and mortality. Poor socioeconomic status (SES) and lack of access to healthcare, especially in medically underserved communities, may be responsible for many of the observed disparities. Diagnostic delay of SLE or for severe organ damages (renal involvement) have a negative impact on those adverse outcomes in lupus patients who either belong to minority groups or live in emerging countries. Longitudinal and observational prospective studies and registries may help to identify the factors that influence poor SLE outcomes in emerging countries. Infection is an important cause of mortality and morbidity in SLE, particularly in low SES patients and tuberculosis appears to be frequent in SLE patients living in endemic areas (mainly emerging countries). Thus, tuberculosis screening should be systematically performed and prophylaxis discussed for patients from these areas. SLE treatment in the developing world is restricted by the availability and cost of some immunosuppressive drugs. Moreover, poor adherence has been associated to bad outcomes in lupus patients with a higher risk of flares, morbidity, hospitalization, and poor renal prognosis. Low education and the lack of money are identified as the main barrier to improve lupus prognosis. Newer therapeutic agents and new protocols had contributed to improve survival in SLE. The use of corticoid-sparing agents (hydroxychloroquine, methotrexate, azathioprine and mycophenolate mofetil) is one of the most useful strategy; availability of inexpensive generics may help to optimize access to these medications.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by wide-ranging symptoms and multiple organ system impairments, predominantly affecting young women during the childbearing years. It is a chronic relapsing inflammatory illness causing accrual of organ damage over time as well as increased morbidity and mortality.

Advances in therapy and management in recent decades have dramatically improved patient survival in SLE, from 50% in the 1950s to over 90% currently. As a consequence, disease- and

treatment-related (particularly glucocorticoid) complications are expected to rise. Increased understanding of the molecular mechanisms underlying the pathogenesis of autoimmune rheumatic diseases has led to the development of new drugs that improve disease control and quality of life and reduce both accrued damage and glucocorticoid usage. But many other aspects of SLE remain challenging, including prompt diagnosis, disease monitoring, management of refractory disease, quality of life (QoL), and, in patients with long-standing disease, accelerated complications of atherosclerosis [1].

How do emerging countries deal with these difficulties? Few data are available from those areas, but worse outcomes are generally associated with ethnic minorities, low socioeconomic status (SES), and low educational levels. In SLE, poor SES has been associated with several unfavorable outcomes including disease activity and severity, damage accrual, work disability, and mortality [2–4].

Emerging countries are currently facing a dichotomy in healthcare demand: they must attempt to provide adequate care to cure and prevent communicable diseases at the same time as they must deal with the growing prevalence of chronic illnesses (such as diabetes, hypertension, cardiovascular diseases, cancer, and rheumatic diseases). Growing disparities in healthcare access and delivery characterize these nations. Many factors besides the very low percentage of people covered by health insurance may explain these disparities; some are individual factors (poverty, malnutrition, unhealthy behaviors, lack of adherence to medical advice), while others concern the healthcare system (lack of access to specialized facilities, geographic isolation, and barriers) and the society (poor gross-domestic product, inadequate health policies, lack of social support) [5]. The SLE challenges discussed above are still more difficult in emerging countries, especially because they must also deal with other crucial needs, including long delays in access to diagnosis, especially immunological diagnostic services, more severe presentation, end-stage organ damage, infectious complications, healthcare access, and the cost of treatment.

Our goals in this review are two-fold. First, we will report the differences and specificities of lupus patients and management in emerging countries. We will then discuss the perspectives for improving SLE outcomes there.

Methods

Published studies were searched by querying PubMed, Medline, Embase, and Cochrane. The search process used the following keywords: systemic lupus erythematous, epidemiology, registry, diagnosis, treatment, prognosis, trials, emerging countries, and developing countries, challenges, with a specific look at publications from Africa, Asia, and Latin America. The search was performed with no date limit, and then focused on the last 20 years. The populations of the emerging countries were likened to minorities living in developed countries because they often share socioeconomic characteristics.

Results

Epidemiology

SLE has been reported all over the world. Many epidemiological studies have detailed its incidence, prevalence, and mortality rates and their distribution according to gender, age, race, and disease presentation.

However, the epidemiology of SLE in developing countries remains largely unknown and probably underestimated, while that in developed countries is known through registries and cohorts. Some of these have contributed substantially to lupus research, especially on the differences in presentations and outcome according to ethnicity. Thus, the LUMINA cohort (Lupus in Minorities: Nature versus nurture) compared SLE in three different ethnic groups in the United States: Hispanics, African-American, and whites [3]. The GLADEL registry (Grupo LatinoAmerican De Estudio del Lupus) includes patients from different Latin American countries [6]. The Euro-Lupus project [7], the Johns Hopkins cohort [8], the Canadian multiethnic cohort [9], and data from the UK [10] have also helped to highlight the epidemiological differences among lupus patients. Analysis of racial origins suggests a higher prevalence of SLE among black Americans, Afro-Caribbeans, and Asian groups than among whites [2,4,9,11,12]. A similar pattern has been reported in the aboriginal populations of Australia, whose SLE prevalence is higher among whites [13]. In contrast to the high prevalence of SLE in those of African ancestry reported in USA registries [11], the incidence of SLE on the African continent itself seems low. This is likely largely due to the paucity of published data and underdiagnosis [14]. The mean age of disease onset seems low, and the female preponderance appears to be higher in several developing countries than in developed countries [15–25] (*table I*).

Clinical features and outcomes

The clinical manifestations of SLE show substantial geographical and ethnic variation between populations. In emerging countries and in minorities, SLE tends to be more severe, have more clinical manifestations, entail more prevalent and more severe nephritis, have higher rates of disease activity, and finally lead to more rapid accumulation of organ damage and higher mortality [3,26–28]. These points have been well described in different cohorts [15–25] and are illustrated in *tables II and III*.

Different cohorts have found lupus nephritis to be two to three times more prevalent among African-Americans and Hispanics (62%) than whites (26%) [3,10,15,28–30]. Afro-Caribbeans have high lupus nephritis rates and higher damage scores than other Canadian ethnic groups [9], and in the GLADEL cohort African-Latin Americans and mestizos both have higher

TABLE I

Epidemiology of systemic lupus erythematosus in developing countries compared to known registries

Countries	Years of publication	Sample size	Incidence/ prevalence	Mean age of onset	Female/ male ratio	Observations
MENA						
Tunisia (TuLuP) [25]	2013	749	–	30.66	9.26	Bias of frequency Incidence and prevalence cannot be clarified
Saudia [24]	2007	86	–	24	10.1	–
Turkey [16]	2013	428	–	40.3	13.75	–
Africa						
Barbados Registry [17]	2012	183	12.21/100,000 person-year	–	15.6	High mortality
RSA [18]	2007	226	–	34	18.1	High mortality
Asia						
Hong Kong [19]	2003	709	–	30	–	–
Pakistan [21]	2004	196	–	31	7.2	–
Philippines [22]	2008	115	–	31	28.1	–
China [20]	2013	2104	–	29.2	10.1	No prevalence
Latin America						
Brazil [23]	2013	888	–	29.9	11,3	–
GLADEL cohort [6]	2004	1214	–	30	9	34 centers
Known registries						
LUMINA study [3,15]	2006	554	–	36.8	12.1	Discrepancies between ethnicities
Euro-Lupus Project (European cohort) [7]	2009	1000	–	29	–	Increasing frequency
Hopkins cohort [8]	2013	2054	–	33	–	–

GLADEL: Grupo LatinoAmerican De Estudio del Lupus; LUMINA: Lupus in Minorities: Nature versus nurture; MENA: Middle East and North Africa; RSA: Republic of South Africa; TULUP: TUnisian LUPus.

rates of renal involvement than whites (44% vs. 55–60%), of progression to end-stage renal disease (ESRD), and of renal disease on SLE diagnosis [6]. In Asian lupus patients (both in Asia and in the US), the rate of nephritis was high: it ranged from 45 to 70% with mortality three times higher than among whites [11,19,31].

Compared with North America and Western Europe, lower survival rates are also reported in Middle East countries [32] (excluding Saudi Arabia [24]), Eastern Europe [33], and South Asia [22,34]. Those rates are the same as those reported among ethnic minorities from the LUMINA and the GLADEL cohorts and from the UK, with African-Americans two to three times more likely to die than whites [3,6,10,35]. The few published studies from Africa report, despite the apparent rarity of SLE, a high prevalence of lupus nephritis and a very high rate of SLE mortality (29% at 1 year in Zimbabwe [36]), except in Tunisia, where the 5-year survival rate is 86% [28]. In South Africa, black SLE patients have a poor prognosis, with survival rates ranging from 57 to 72% [12,18].

Except for lupus nephritis, lupus presentations differ very little between developed and developing countries. Discoid lupus is seen more frequently in black patients, and photosensitivity appears less frequent in mestizos [2,6]. Venous thromboembolic complications and neuropsychiatric disease are reported to be less frequent among Chinese populations [19,31,37], while lymphopenia is been more commonly observed in African and Arab populations [6,24–28]. Autoantibody profiles do not appear to vary with ethnicity and geographic location, except that the frequency of antiphospholipid antibodies is lower among Asian and African groups [25,38].

These findings raise a question about these disparate severity and mortality rates: do they reflect real genetic and biological differences with more aggressive disease and poorer response to therapy or do they express socioeconomic discrepancies

TABLE II

Clinical characteristics and complications of systemic lupus erythematosus in developing countries compared to known registries

Characteristics	Clinical features (rates in %)						Complications
Countries	Skin	Nephritis	Hematological	Neuropsychiatric	Arthralgia Arthritis	Cardiac	
MENA							
Tunisia (TuLup) [25]	81.7	49.5	81	37	71	31.9	–
Saudia [24]	Malar rash 37% Photosensitivity 22%	61	–	19	68	–	–
Turkey [16]	Photosensitivity 70.1%	32.9	Thrombocytopenia 18% Hemolytic anemia 6.5%	12.9	76.9	–	–
Africa							
RSA [18]	Less photosensitivity	43.8	52.2	15.9	70.4	–	Infections: 32.7 Renal failure: 16.4
Barbados Registry [17]	36.4	47	74.1	17.2	84	–	Sepsis: 59% of death Renal failure: 65% of death
Asia							
Hong Kong [19]	Malar rash 56% Photosensitivity 35%	50	Thrombocytopenia 25% Hemolytic anemia 20%	6	84	–	–
Pakistan [21]	Malar rash 29% Photosensitivity 26%	33	Thrombocytopenia 26%	26	38	–	–
Philippines [22]	Malar rash 70% Photosensitivity 45%	80	Thrombocytopenia 10% Hemolytic anemia 3%	24	64	–	Great rate of skin lesions and severe involvements as nephritis and neurological
China (CSTAR cohort) [20]	Malar Rash 47.9% Photosensitivity 25%	47.4	56.1	4.8	54.5	3.5	Several differences between ethnicities
Latin America							
Brazil [23]	90.7	36.9	44	9.7	87.4	Pericarditis 10.9	–
GLADEL cohort [6]	Malar Rash 61.3% Photosensitivity 56.1%	51.7	72.5	26.4	–	–	–
Known registries							
LUMINA study [3,15]	–	H 59% AA 62% Caucasian 32%	H 86%, AA 90% Caucasian (77%)	–	–	H 47%, AA, 54% Caucasian 32%	Severe disease between Hispanics and African-American than Caucasian
Euro-lupus Project [7]	Malar rash 31.3% Photosensitivity 22.9%	27.9	18.2	19.4	48.1	–	–
Hopkins cohort [8]	Malar rash 57.7% Photosensitivity 58.4%	55.6	–	–	–	–	–

AA: African-American; H: Hispanics, MENA: Middle East and North Africa; RSA: Republic of South Africa; LUMINA: Lupus in Minorities: Nature versus nurture; GLADEL: Grupo LatinoAmerican De Estudio del Lupus; CSTAR: Chinese SLE Treatment and Research group; TULUP: TUnisian LUPus.

TABLE III

Survival rates and main causes of death in systemic lupus erythematosus in developing countries compared to known registries

Countries	Survival rates (SR)	Mortalities/causes of death	Observations
MENA			
Tunisia [25]	85.3% at 5 years	7.5% SLE activity 38.2% Infections 26.5%	–
Saudia [24]	92% at 5 years	Infections 63% vascular 25%	–
Turkey [16]	96% at 5 years	4.43% at 5 years Chronic renal failure Ischemic heart disease Sepsis	Probability of survival is similar to Western data
Africa			
Barbados registry [17]	79.9% at 5 years	13.11% (complications of nephritis and comorbidities)	SR decrease to 68% in nephritis
RSA [18]	57% at 5 years	24.3% (16.4% renal failure and 32.7% infections)	SR worse in nephritis at presentation
Asia			
Hong Kong [19]	–	–	–
Pakistan [21]	–	–	–
Philippines [22]	75% at 5 years	Infections 80%	–
China (CSTAR cohort) [20]	–	–	18.7% of severe disease (SLEDAI > 14)
Latin America			
Brazil [23]	–	–	–
GLADEL cohort [6]	95% at 4 years	2.8% SLE activity 35% Infections 15%	–
Known registries			
LUMINA study [3,15]	–	–	–
Euro-Lupus Project [7]	92% at 10 years	6.8% SLE activity 26.5% Infections 25% Thrombosis 26.5%	–
Hopkins cohort [8]	50% at 5 years > 90% at 10 years	Not SLE activity	–

MENA: Middle East and North Africa; RSA: Republic of South Africa; SLE: systemic lupus erythematosus; LUMINA: lupus in minorities: nature versus nurture; CSTAR: Chinese SLE Treatment and Research group; GLADEL: Grupo LatinoAmerican De Estudio del Lupus; SLEDAI: SLE Disease Activity Index.

between minority groups and whites and between emerging and developed countries? Almost all studies have highlighted the common principal explanations for most of these adverse outcomes: ''minorities'' are more likely to be living below the poverty line and to have less education and inadequate access to health care. In the Hopkins cohort, adjustment for SES and education mitigated the effect of ethnicity in adverse outcomes among African-Americans [39]. Similarly, according to Ward and the LUMINA analyses, it is poverty rather than ethnicity that is an independent contributor to mortality [3,40,41].

Diagnostic delay

SLE is also characterized by late or even sometimes absent diagnosis. Its heterogeneous nature can delay diagnosis and

thus make treatment very difficult. There is no diagnostic test specific for SLE. Accordingly, the diagnosis remains a clinical one, relying on a combination of clinical and laboratory features. The 1992 Revised American College of Rheumatology (ACR) classification criteria, although developed to aid trial design, offer a useful reminder of some of the more common features of SLE [42]. Newer criteria have only recently been published but are likely to be more widely used in the future and should be validated in different areas [43]. Few studies have assessed the impact of this delay on the adverse outcomes in lupus patients who either belong to minority groups or live in emerging countries. In a survey in Africa, 77% of participants agree that SLE diagnosis is delayed most of time [14]. Moreover, routine performance and analysis of renal biopsies is impossible for many healthcare facilities. Delay between the detection of the onset of renal disease and renal biopsy is a significant predictor of subsequent kidney failure (RR 4.9; 95% CI [1.7 to 14.5]; $P < 0.001$) and death due to lupus renal involvement (RR 6.7; 95% CI [2.1 to 21.2]; $P < 0.001$) [44,45].

Infections

Infection remains an important cause of mortality and morbidity in patients with SLE. Despite the great improvement in lupus management, these figures have not changed substantially in the past three decades.

In the Euro-Lupus cohort, 36% of patients had infections during follow-up, and almost 30% of deaths during the first 5 years were related to infections [46]. Infections were also one of the leading causes of hospitalization in the Hopkins Lupus cohort and in the British UCLH cohort [47,48]. This rate is much higher in emerging counties. Infections are responsible for 52% of SLE deaths in Thailand [34], 58% in Brazil [49], 55% in China [31], and up to 80% in the Philippines [25,50]. Risk factors for infection in patients with SLE are mainly disease activity and nephritis, both of which are more prevalent in lupus patients from emerging countries [51]. High doses of methylprednisolone or cyclophosphamide (CYP) are also well-recognized risk factors for infection; these medications are usually necessary because of the greater severity of disease in emerging countries and the high costs of other drugs.

The rate of tuberculosis (TB) appears to be higher in patients with SLE than in the general population, but the actual incidence varies depending on the specific area. A prevalence of TB around 5–15% has been estimated in SLE patients living in endemic areas, six to seven times higher than expected [52]. A recent retrospective study in South Africa reported that 20% of SLE patients developed TB [53]. Series from endemic areas showed that although the lungs remain the most common TB site, the frequency of extrapulmonary TB and severity of infection are both higher in SLE patients, as is mortality (10–30%) [54–56].

The human immunodeficiency virus (HIV) is epidemic in Africa. Because the two diseases have many overlapping features, it is likely that some patients with SLE cases may be assumed to be HIV-positive and misdiagnosed [57]. Indeed, in a recent survey 52.4% of respondents agreed that distinguishing SLE from HIV infection can be difficult [14].

SLE management

Although guidelines for SLE management have been proposed by various professional societies in developed countries, these do not provide comprehensive recommendations for low-income countries. Moreover, SLE treatment in the developing world is restricted by the availability and cost of some immunosuppressive drugs and by the lack of facilities for laboratory monitoring. Although hydroxychloroquine (HCQ), corticosteroids, CYP, vitamin D, non-steroidal anti-inflammatory drugs (NSAIDs), and ACE-inhibitors are relatively inexpensive and widely available, the cost of immunosuppressants such as azathioprine and especially mycophenolate mofetil (MMF) is very high and clearly out of reach for most individual patients or even state healthcare budgets. Moreover, dialysis support is extremely expensive in many countries, and opportunities for kidney transplants are very limited, mainly due to cost and lack of infrastructure. These points again underscore the importance of early and adequate nephritis treatment, before the onset of ESRD.

Antimalarial drugs have been shown to have a protective effect, particularly when administered early enough, on lupus flares, damage, thrombotic complications, and survival. A recent report by the GLADEL group indicates that mestizo SLE patients are at increased risk of developing renal disease early but that antimalarial treatment seems to delay the appearance of this manifestation: (HR 0.70, 95% CI [0.50–0.99]) [58]. Antimalarial drugs were shown to have a protective effect on SLE survival in this cohort as well, with a 38% reduction in the mortality rate (HR 0.62, 95% CI [0.39–0.99]) [59]. These data have important implications for the treatment of these patients regardless of their geographic location.

Randomized controlled trials suggest that the efficacy of MMF is similar to that of CYP for the induction of a response in lupus nephritis [60], while MMF appears to be a safer immunosuppressive agent, does not cause gonadal failure, and might be cost-effective [61]. MMF was not found to be superior to CYP as induction treatment, although more black and Hispanic patients responded to MMF than CYP; however, this trial was not designed to be powered to detect an effect of a specific race or ethnicity [62]. Moreover, in a post hoc subgroup analysis of patients with significant reduction in kidney function in the Aspreva Lupus Management Study, CYP did not appear superior to MMF induction, and eGFR of MMF-treated patients improved at a substantially faster rate than in patients treated with CYP over 24 weeks [63]. In Hong Kong, a retrospective single-center

study demonstrated that the rate of treatment-related hospitalization and infection was 82.5% lower in patients who used MMF compared with those who were given CYC [64]. Wilson et al. demonstrated that MMF was more cost-effective than intravenous CYP as induction therapy for lupus nephritis in terms of quality-adjusted life years (QALY) gained [65]. Although more costly, MMF may ultimately be more cost-effective in the long run for lupus patients, even with low SES [61].

Poor adherence to therapeutic regimens is a common problem in patients with SLE and is associated with a higher risk of flares, morbidity, hospitalization, and poor renal outcome. Few studies have evaluated treatment adherence in SLE and they were conducted mainly in developed countries, where the cultural, social, and economic reality differs from that of developing countries. Non-adherence to treatment is multifactorial for most patients, and non-adherence rates in SLE patients range from 3% to 76%. Chambers et al. pointed out the role of low SES in Jamaica, which they considered an important factor affecting adherence [66]. Low-income is considered a barrier to adherence among patients in North America [67]. Petri et al. [68] assessed patient compliance with treatment and found that black patients, although twice as likely as white patients to have serious renal disease, were also more often classified as non-compliant (56%) than white patients (34%). Poor compliance was one of the most important variables associated with hospitalization in lupus patients in an emergency unit in Mexico [69]. The association between education level and adherence in lupus patients has also been studied, and two studies showed that low education is related to poor adherence [70,71]. In Brazil, an assessment of adherence to drugs found that only 31% of patients adhered thoroughly to their drug treatment and that 51% of the interviewees related this lack of compliance to financial factors. Lack of money to purchase medicine was identified as the main difficulty [72].

Economic burden of SLE

The literature evaluating disease costs in SLE remains limited and has included only developed countries in Europe and North America. Data from Asia and South American countries are very sparse. A study describing data from 4 published analyses of costs in patients with newly diagnosed or newly active lupus in the US found that the average direct medical cost per patient ranged from $13,735 to $27,531 a year compared to $7794 to $9788 in people without lupus. Healthcare costs were significantly higher in patients with lupus nephritis, ranging from $29,034 to $62,651 [73]. These findings are consistent with the range of $3735 to $14,410 for the average annual direct costs of SLE, as estimated in 11 studies covering the US, Canada, Germany, the UK, and Hong Kong [74–76]. Drivers of higher direct costs of SLE were similar among these countries and included shorter disease duration, more active disease, and higher disease damage scores [75–77]. Inpatient hospital stays were the primary medical cost drivers, followed by physician office visits and outpatient hospital visits, which accounted for 40 to 55% of total direct costs for patients who did not have flares and 70% for those who did. Severe flares had the highest attributable cost, 20 times higher than that of moderate flare [78]. Healthcare costs doubled in patients with lupus nephritis compared with patients without nephritis and were 8 to 10 times higher in patients with renal damage and ESRD [79,80]. It is important to add that many SLE patients had multiple comorbid conditions. Three in 10 SLE patients had hypertension, one in four cardiac disease, and more than one in 10 pulmonary disease, diabetes, or depression. Medications are usually needed in the treatment of those comorbidities and increased the direct cost of the disease.

Unfortunately, patients with low SES and low-income have poor outcomes with more severe and flaring SLE, more prevalent and severe nephritis and thus a higher direct disease cost.

Besides the direct cost, these studies highlighted the importance of indirect costs, pointing out that they account for most of the total healthcare cost and range from 1.5 to 3.5 times higher than the corresponding direct costs [76,77,81,82]. Poor QoL and work disability result in high indirect costs [83], with an important loss in salary that in emerging countries leads to huge social consequences. More, than half of SLE, patients cannot work. Partridge et al. [84] found that up to 40% of patients lost their jobs, at a mean of 3.4 years after their SLE diagnosis. In Hong Kong and China, 56% of patients lost their jobs within 2 years after SLE diagnosis [85]. This work disability was associated with older age, disease activity, high disease damage scores, nephritis, neurological impairment, lower education level, and poverty [84–86]. Indirect costs include also the lost work productivity (or household activity) from a societal perspective, which affects not only patients and their families, but also society [87]. These costs should be explored in more detail and should take into consideration factors such as marital status and deterioration in social support for young women without incomes [88]. These items cannot necessarily be evaluated in monetary terms but can definitely be devastating.

Research

Data from a bibliometric study of literature on SLE research between 2002 and 2011 showed that SLE has become a field of interest, but that publications about lupus research in developing countries have lagged behind [89]. The contribution of the developing world needs to be improved: less than 1/5 of the publications come from those countries, 12% if we exclude China, even though SLE prevalence and incidence in these areas were high. Moreover, most clinical research in lupus is

conducted in developed countries, and the transposition of the results is not always possible and meaningful.

Discussion

Both ethnicity and SES are independently associated with disease activity and overall organ damage. However, the components of poor SES, including less optimal medical care and insurance coverage, higher level of poverty, and lack of formal education, act synergistically with SLE, contributing to greater overall organ damage and lower survival rates among minority population groups and lupus patients from emerging countries, while ethnicity appears to play a minor role. This interaction with diagnostic delay, infection, poor treatment adherence, and more severe flares aggravates the deleterious effects of disease in SLE patients in those populations and finally leads to more costly management. These outcomes are a major problem in emerging countries, as they are associated with work disability that leads to loss of earning and increased social disparity producing a vicious circle. Meaningful management must focus on modifiable factors and target accessible objectives that can break this circle and optimize management of SLE in emerging countries.

First, epidemiological studies are needed to determine the true incidence of SLE in developing countries. Research is needed to identify the clinical risk factors for severe disease and severe complications, such as infections. As the economy and budgets of these regions can allocate relatively little funding to research, the developed countries should provide support to and conduct more cooperation projects with developing countries. There is clearly a need for longitudinal observational prospective studies and registries to identify the factors, especially the modifiable factors that influence SLE outcomes in emerging countries. Registries are highly helpful because they can provide meaningful real-world information that promotes best practices in health care. The GLADEL study and the China registry are good examples [6,20], and the data they have obtained has been useful in planning, designing, and conducting clinical studies in lupus [90]. They also improve communication between different groups supporting lupus patients (physician, epidemiologists, and other healthcare providers). The ALUGEN project, which will set up an informal network of researchers and physicians caring for lupus patients, may be the first step for lupus research in Africa [14].

The long delay in diagnosis results in longer untreated disease duration before diagnosis, and thus more severe disease and greater organ damage. Given the overlapping nature of lupus symptoms, its ability to affect multiple organs and systems within the body simultaneously, and the periodicity of symptoms, patients face significant challenges in search of diagnosis and care. Low disease recognition, related to low awareness of SLE at primary points of care and an inadequate number of specialists, contributes substantially to the diagnostic delay. One study suggests that placing medical specialists in community health centers improves general care [91]; this step might also speed up recognition of lupus symptoms. Moreover, patients cannot always afford immunological tests, which are expensive and in some countries need to be sent for analysis to developed countries. Increasing the limited availability of biological diagnostic tests is essential for improving clinical diagnosis performance. Furthermore, the assessment of disease activity at the time of diagnosis is far from optimal. Insufficient follow-up is standard in low-income countries, due to lack of both awareness and point-of-care accessibility. For example, lupus nephritis is usually asymptomatic in the early stages and it can and must be diagnosed by simple and inexpensive urinalyses. A delay in testing for lupus nephritis is often associated with increased glomerular injury and poorer response to immunosuppressive drugs; it is a strong independent predictor of poor outcome [44,45].

If we are to lower infection-related mortality, particularly in emerging countries, it is critical to adopt several preventive measures. Vaccination is one of the most important. Despite some controversy regarding the efficacy (slightly weaker immunological responses) and safety (low risk for triggering SLE exacerbations) of vaccines for SLE patients, European consensus recommendations have recently been published [92]. Vaccination status should be assessed early in the course of SLE, and a vaccination history against *Haemophilus influenzae* b, hepatitis A, hepatitis B, human papillomavirus, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and tetanus should be recorded at that point.

TB is frequently encountered in SLE patients, particularly in endemic zones. Thereby, screening according to local guidelines should be performed before glucocorticoid and immunosuppressive agents are used in patients from those areas. Prophylaxis with isoniazid (INH) is controversial, even for patients from these areas, because the effectiveness of INH in preventing TB development is not well established in lupus patients; nonetheless, prolonged glucocorticoid therapy in patients who screen positive for latent TB should be combined with INH [93]. Because of the potential liver toxicity (especially if combined with other hepatotoxic drugs such as azathioprine or methotrexate), hepatic function must be closely monitored in these patients. In some countries, 3-month regimens of INH and rifampicin may be proposed as an equal option, according to local guidelines [94]. Finally, it should be noted that most TB cases are reactivations of latent infections and therefore not preventable by vaccination.

Handling infectious complications in SLE is very challenging, and the frequency and clinical relevance of infections requires that the therapy prescribed for SLE bear this risk of infection in mind, prescribing the minimal possible dosage of corticosteroids. Moreover, clinicians and patients must remain vigilant for

early signs of infection and ensure rapid access to health care and admission as necessary.

Over the past decade many medical advances and a number of newer therapeutic agents have contributed to improved survival in SLE in industrialized countries. Unfortunately, they are generally costly and not available in poorer countries. Thus, clinicians treating patients have limited choices for therapy: corticosteroids, antimalarials, and CYP are the mainstays of SLE treatment, but often come with numerous unwanted (sometimes life-threatening) side effects. There is an urgent need for adequate therapy in lupus patients of low SES. Moreover, access to treatment can be difficult when renal transplant or dialysis is necessary. Thus, optimal treatment of SLE before nephropathy and for nephropathy is of overriding importance. There are now a number of quality guidelines to help healthcare workers in their day-to-day management of lupus patients to achieve the best possible control of the disease and avoid preventable comorbid conditions; their implementation, however, is still suboptimal [95–97].

Even optimizing ''basic'' treatment may be challenging, because these medications are not always obtainable in emerging countries. For example, compared with chloroquine, HCQ has been shown to be protective against damage, flares, and thrombotic complications and to decrease mortality [58,59] as well as ophthalmological complications while requiring less testing [98]. HCQ, while inexpensive, is unavailable in many emerging countries. Of the few patients who can afford to pay for treatment, many will rely on friends and family living in Europe, for example, to send these medications to them. The overuse of steroids or insufficient use of corticoid-sparing agents such as antimalarials, methotrexate, or azathioprine can increase treatment-related comorbidities, such as cardiovascular disease, osteoporosis, or infections. MMF may be cost-effective as induction treatment of lupus nephritis against CYP and a good option for maintaining remission. Wider availability of inexpensive generics may help to optimize access to this medication.

Lack of adherence to medical recommendations has been proposed as an important predictor of poor outcomes in patients with SLE [70–72]. The paradox is that effectively managing the multiple health problems present in diseases such as SLE often requires self-management skills that are related to higher SES and education [99]. Optimizing adherence to treatment and providing local education materials and specialist care may be challenging. Programs can be designed to provide continuous effective patient education at low cost and easy accessibility to patients with SLE. It has been proven that this can modify self-management behaviors, improve health status, decrease health service utilization among SLE patients, decrease costs, and ultimately contribute to reducing health disparities in SLE. The research on interventions to promote adherence has mainly focused on modifying patient behavior using combined strategies (patient education and social support). In the USA, during the 6 months after an educational program (the Chronic Disease Self-Management Program [CDSMP]) for low-income African-Americans with SLE, researchers observed a significant improvement in cognitive symptoms, communication with physicians, and treatment adherence [100]. Future research should focus on implementing inexpensive specific programs targeting medically isolated and underserved lupus populations, to optimize health care access and promote personal responsibility.

Assaying HCQ concentrations may be also a novel way to evaluate treatment adherence. Two studies have shown that undetectable blood HCQ concentration may be a simple and reliable marker of non-adherence in SLE patients and may then avoid unnecessary treatment escalation [101,102].

Reliable data from properly conducted SLE cost studies around the world are imperative, especially in countries where limited resources are unable to cope with the population. The management of SLE is costly, and SLE patients have significantly higher healthcare utilization and higher overall expenditures than patients with no SLE. The treatment arsenal against SLE is adding new biologic agents. Although these drugs are much more expensive than older therapies, their overall costs may be lower if they improve disease severity and reduce hospitalization and other direct or indirect medical costs. An interesting approach in these new economic evaluations in SLE will be the future treat to target strategies that will include cost-effectiveness and cost-utility analyses [103].

Finally, we discuss an interesting new option proposed to optimize SLE management in minorities and low-income countries. Interventions including peer support programs, educational initiatives, patient navigators, and health passports have been designed to improve the health of individuals with chronic diseases [104] and shown to reduce obstacles to diagnosis and treatment [105]. Dr. Paul Fortin and his group have recently developed a personalized ''Lupus Health Passport'', a pocket-sized booklet containing educational and personal health information, such as emergency contacts, general information on lupus, comorbidities prevention, diet and exercise advise, the patient's medication list, and medical history, blood test results, past hospitalization record, and upcoming visits [104].

Conclusion

The prevalence, morbidity, and mortality associated with lupus are highest among racial and ethnic minorities, the poor, and those lacking medical insurance and education. Lack of access to healthcare, especially in medically underserved communities, may be responsible for many of the observed disparities. Multinational collaboration can help SLE research to improve the medical technology and research methods in

developing countries. Appropriate educational programs for healthcare providers and patients, sponsored by health authorities, could facilitate early recognition, diagnosis, and treatment of SLE and therefore prevent long-term damage, reduce disability and dependence, have a positive impact on lupus care, thereby substantially reducing the costs of this disease to society.

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