Lupus (2019) 28, 1101–1110
journals.sagepub.com/home/lup

PAPER

Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multi-national, Latin American lupus cohort

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Aim: The aim of this study was to identify factors predictive of serious infections over time in patients with systemic lupus erythematosus (SLE). **Methods:** A multi-ethnic, multi-national Latin American SLE cohort was studied. Serious infection was defined as one that required hospitalization, occurred during a hospitalization or led to death. Potential predictors included were sociodemographic factors, clinical manifestations (per organ involved, lymphopenia and leukopenia, independently) and previous infections at baseline. Disease activity (SLEDAI), damage (SLICC/ACR Damage Index), non-serious infections, glucocorticoids, antimalarials (users and non-users), and immunosuppressive drugs use; the last six variables were examined as time-dependent covariates. Cox regression models were used to evaluate the predictors of serious infections using a backward elimination procedure. Univariable and multivariable analyses were performed. **Results:** Of the 1243 patients included, 1116 (89.8%) were female. The median (interquartile range) age at diagnosis and follow-up time were 27 (20–37) years and 47.8 (17.9–68.6) months, respectively. The incidence rate of serious infections was 3.8 cases per 100 person-years. Antimalarial use (hazard ratio: 0.69; 95% confidence interval (CI): 0.48–0.99; $p = 0.0440$) was protective, while doses of prednisone >15 and ≤60 mg/day (hazard ratio: 4.18; 95 %CI: 1.69–10.31; $p = 0.0019$) and >60 mg/day (hazard ratio: 4.71; 95% CI: 1.35–16.49; $p = 0.0153$), use of methylprednisolone pulses (hazard ratio: 1.53; 95% CI: 1.10–2.13; $p = 0.0124$), increase in disease activity (hazard ratio: 1.03; 95% CI: 1.01–1.04; $p = 0.0016$) and damage accrual (hazard ratio: 1.22; 95% CI: 1.11–1.34; $p < 0.0001$) were predictive factors of serious infections. **Conclusions:** Over time, prednisone doses higher than 15 mg/day, use of methylprednisolone pulses, increase in disease activity and damage accrual were predictive of infections, whereas antimalarial use was protective against them in SLE patients. *Lupus* (2019) **28,** 1101–1110.

Key words: Systemic lupus erythematosus; serious infections; antimalarial use; glucocorticoid use

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Received 26 February 2019; accepted 10 June 2019

10.1177/0961203319860579

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease of unknown etiology.[1] Treatment with glucocorticoids and immunosuppressive drugs has improved the survival rate in SLE, which is currently about 90% at 10 years;[2] however, treatment with these medications is associated with infections which usually correspond to the first peak in the bimodal pattern of SLE mortality.[3]

As noted above, infections are important causes of mortality in SLE patients; moreover, hospitalization rates due to serious infections have increased over the last few years, being about 12 times higher than in non-SLE patients.[4] In Latin America, infections have been described as a cause of mortality in 15% (infections only) and 44% (disease activity and infections) of SLE patients from the GLADEL (for *Grupo Latino Americano De Estudio del Lupus*) cohort.[5] On the other hand, in the same cohort, antimalarials have been shown to exert a protective effect, with mortality rates in antimalarial users and non-users of 4.4% and 11.5% ($p < 0.001$), respectively.[6]

There is no uniformity in the literature about the possible predictive factors of infections, with some studies clearly showing glucocorticoids and immunosuppressives to be risk factors but others not;[7–13] likewise, the possible protective effect of antimalarials has not been convincingly demonstrated. Furthermore, information on the time of antimalarial exposure required to exert a beneficial effect in terms of infections is lacking. We therefore aimed at resolving these inconsistencies by examining the factors predictive/protective of serious infections over time in SLE patients from GLADEL, a multi-national, multi-ethnic, Latin American cohort.

Patients and methods

As previously described, GLADEL is an observational inception cohort study of SLE patients whose recruitment started in 1997 and finished in 2004 by establishing a common protocol, consensus definitions and outcome measures in 34 centers distributed among nine Latin American countries.[5] Every group used ARTHROS software as a common database to collect data. All GLADEL investigators were trained in data collection prior to study initiation. The study was performed according with the Declaration of Helsinki for the conduct of research in humans and following local institutional review boards' regulations. The diagnosis of SLE was done based on clinical and laboratory data and according to the expertise of the investigator (rheumatologist or qualified internist with experience in SLE). Fulfillment of four American College of Rheumatology (ACR) SLE criteria[1] at the time of diagnosis was not mandatory. In addition, disease diagnosis could occur before a patient had accrued four ACR criteria. Data included socioeconomic–demographic and clinical characteristics, treatment features and laboratory tests. The general characteristics and composition of the entire GLADEL cohort have been described in detail elsewhere[5] and are now shown in Table 1.

Serious infection was defined as an infection that required hospitalization, occurred during a hospitalization or led to death.

Potential predictors included were sociodemographic factors (gender, age at diagnosis, ethnicity, marital status, socioeconomic status (as defined by Graffar's score[15]), educational level, medical coverage, place of residence), clinical manifestations (per organ involved, lymphopenia and leukopenia, independently) and previous infections (serious and non-serious) at baseline. Disease activity (by SLE Disease Activity Index (SLEDAI)[16]), damage (by Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[17]), non-serious infections, glucocorticoids (prednisone or equivalent) by categories (highest doses received), methylprednisolone pulses, antimalarials (chloroquine or hydroxychloroquine) and immunosuppressive drugs (global and per type

Table 1 Baseline features of lupus patients from the Grupo Latino Americano De Estudio del Lupus (GLADEL) cohort

Feature	*No.*[a]
Enrolled patients	1480 (100)
Race/ethnicity	
Mestizo	645 (43.6)
Caucasian	606 (40.9)
ALA	174 (11.8)
Others[b]	55 (3.7)
Female	1330 (89.9)
Age at disease onset[c]	26.0 (19.0–35.0)
Age at diagnosis[c]	27.0 (20.0–37.0)
Partial or no medical insurance	680 (45.9)
Twelve or fewer years of education	1133 (76.6)
Middle/low SES	901 (60.9)
Living in rural areas	134 (9.1)

[a]All data are shown in numbers and percentages, except where otherwise indicated.
[b]Values are median and interquartile range.
[c]Mainly pure Amerindians and Asian descendants.
ALA: African-Latin American; SES: socioeconomic status

of drug) use were included as time-dependent covariates. About antimalarials, patients were categorized according to exposure time as users (those that received them for at least six consecutive months) and non-users (those that never received them or who had received them for less than six consecutive months). Immunosuppressive drugs included were azathioprine (AZA), daily oral cyclophosphamide (Po-CYC) and pulsed intravenous cyclophosphamide (IV-CYC). We included all patients who had at least one SLEDAI score in the follow-up.

Statistical analyses

Categorical variables were summarized as frequencies and percentages while continuous variables were presented as medians and their interquartile ranges. Cox regression models were used to evaluate the predictors of serious infections using a backward elimination procedure. Univariable and multivariable analysis were performed. A $p \leq 0.05$ was considered the level of statistical significance. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 1243 patients included, 1116 (89.8%) of them were female. Their median age at diagnosis was 27 (20–37) years and the median follow-up time was 47.8 (17.9–68.6) months. Five hundred and thirty-one patients (42.7%) were Mestizo, 512 (41.2%) were Caucasian, 150 (12.1%) were African-Latin American, and 45 (3.6%) were of other ethnicities. Their median SLEDAI at baseline was 9 (4–15) and median SDI one year after the baseline visit was 1 (0–1). Eight hundred and ninety-seven patients (72.2%) were antimalarial users. The incidence rate of serious infections was 3.8 cases per 100 person-years. Two hundred and thirty-seven patients were excluded from these analyses because they did not have a SLEDAI score available. Excluded patients had comparable socioeconomic, demographic and clinical features to the ones included.

One hundred and sixty-nine (13.6%) patients had at least one serious infection during their follow-up and 28 of them (16.6%) died. Microbiological isolation and type of infection are depicted in Table 2.

Univariable analysis (depicted in Tables 3 and 4) showed that antimalarial use (hazard ratio: 0.54; 95% confidence interval (CI): 0.38–0.76; $p = 0.0004$) was protective of serious infections over time, while lower socioeconomic status (hazard ratio:

Table 2 Microbiological isolation and type of infection in patients who died due to serious infections

Variable	n *(%)*
Microbiological isolation, $n = 22$	
Positive	20 (90.9)
Negative	2 (9.1)
Type of infection, $n = 28$	
Lower respiratory tract	9 (32.1)
Urinary	2 (7.1)
Skin	6 (21.4)
Central nervous system	1 (3.6)
Other/not specified[a]	10 (35.8)
Etiological agent, $n = 20$	
Staphylococcus sp.	7 (35.0)
Candida sp.	2 (10.0)
Pseudomonas aeruginosa	2 (10.0)
Proteus mirabilis	2 (10.0)
Enterobacter sp.	2 (10.0)
Acinetobacter sp.	1 (5.0)
Klebsiella sp.	1 (5.0)
Escherichia coli	1 (5.0)
Listeria sp.	1 (5.0)
Other[b]	1 (5.0)

[a]Most of them were diagnosed as 'sepsis' with no specified site.
[b]Positive blood culture reported as 'gram positive cocci'.

Table 3 Sociodemographic variables predictive of serious infections. Univariable analyses

Variable[a]	*Univariable HR (95% CI)*	p *value*
Age at diagnosis, years	0.98 (0.91–1.04)	0.5282
Gender		
Male	Ref.	
Female	1.08 (0.64–1.81)	0.7744
Ethnicity		
Caucasians	Ref.	
Mestizo	1.20 (0.86–1.66)	0.2801
ALA	0.61 (0.33–1.23)	0.1146
Others	2.17 (1.08–4.35)	0.0299
Residence		
Urban	Ref.	
Rural	0.90 (0.52–1.56)	0.7141
Socioeconomic status		
High	Ref.	
Medium	1.86 (0.91–3.80)	0.0890
Low	2.20 (1.11–4.33)	0.0230
Marital status		
Single	Ref.	
Married/living together	0.87 (0.64–1.18)	0.3812
Medical insurance		
Partial or no coverage	Ref.	
Full coverage	0.96 (0.70–1.30)	0.7676
Educational level (years)		
0–7	Ref.	
8–12	1.30 (0.90–1.86)	0.1619
More than 12	0.82 (0.51–1.31)	0.4005

[a]None of these variables were retained in the multivariable analyses.
ALA: African-Latin American; HR: hazard ratio; CI: confidence interval; Ref.: reference

Table 4 Variables predictive of serious infections. Univariable and multivariable analysis

Variable	*Univariable HR (95% CI)*	p *value*	*Multivariable HR (95% CI)*	p *value*
Socioeconomic status				
High	Ref.			
Medium	1.86 (0.91–3.80)	0.0890		
Low	2.20 (1.11–4.33)	0.0230		
Previous serious infections	1.64 (0.99–2.70)	0.0542		
Previous non-serious infections	1.18 (0.65–2.14)	0.3066		
Manifestations at baseline, per group				
General	1.85 (1.26–2.70)	0.0016		
Renal	1.97 (1.45–2.67)	<0.0001		
Musculoskeletal	0.95 (0.57–1.58)	0.8324		
Cutaneous	0.89 (0.56–1.40)	0.6019		
Ocular	1.07 (0.65–1.76)	0.8009		
Respiratory	2.08 (1.20–3.59)	0.0088		
Cardiovascular	1.15 (0.77–1.71)	0.5012		
Neurologic	1.28 (0.89–1.83)	0.1835		
Digestive	2.19 (0.81–5.91)	0.1214		
Hematological	1.42 (1.01–1.99)	0.0411		
Individual manifestations				
Lymphopenia	1.31 (0.97–1.78)	0.0793		
Leukopenia	1.30 (0.96–1.77)	0.0892		
Increase on the SLEDAI, per one unit	1.24 (1.17–1.32)	<0.0001	1.03 (1.01–1.04)	0.0016
Increase on the SDI, per one unit	1.39 (1.28–1.51)	<0.0001	1.22 (1.11–1.34)	<0.0001
Prednisone (highest dose)[a]				
None	Ref.			
≤7.5 mg/day	0.85 (0.30–2.40)	0.7591	0.83 (0.29–2.34)	0.7190
>7.5; ≤15 mg/day	2.26 (0.87–5.84)	0.0939	1.93 (0.74–5.02)	0.1779
>15; ≤60 mg/day	6.09 (2.49–14.91)	<0.0001	4.18 (1.69–10.31)	0.0019
>60 mg/day	6.71 (1.94–23.21)	0.0026	4.71 (1.35–16.49)	0.0153
Methylprednisolone pulses				
Non-use	Ref.			
Use	1.31 (1.16–1.49)	<0.0001	1.53 (1.10–2.13)	0.0124
Antimalarials				
Non-users	Ref.			
Users	0.54 (0.38–0.76)	0.0004	0.69 (0.48–0.99)	0.0440
Immunosuppressive drugs				
Non-use	Ref.			
Use	1.43 (1.05–1.96)	0.0241		
Daily oral CYC				
Non-use	Ref.			
Use	3.05 (1.50–6.22)	0.0021		
Pulsed intravenous CYC				
Non-use	Ref.			
Use	2.22 (1.64–3.02)	0.0001		
Azathioprine				
Non-use	Ref.			
Use	1.00 (0.99–1.01)	0.3542		

[a]We performed an alternative multivariable analysis using 'prednisone >15 mg/day' as a combined category (>15 but ≤60 mg/day and >60 mg/day) and showed HR: 4.19; 95% CI: 1.70–10.35; $p = 0.0019$. Although minimal changes were observed in the other variables examined, the results remained essentially unchanged.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: SLICC/ACR Damage Index; CYC: cyclophosphamide; HR: hazard ratio; CI: confidence interval

2.20; 95% CI: 1.11–4.33; $p = 0.0230$), the presence of general manifestations (hazard ratio: 1.85; 95% CI: 1.26–2.70; $p = 0.0016$), of renal (hazard ratio: 1.97; 95% CI: 1.45–2.67; $p < 0.0001$), respiratory (hazard ratio: 2.08; 95% CI: 1.20–3.59; $p = 0.0088$) and hematological involvement (hazard ratio: 1.42; 95% CI: 1.01–1.99; $p = 0.0411$), dose of prednisone >15 and ≤60 mg/d (hazard ratio: 6.09; 95% CI: 2.49–14.91; $p < 0.0001$), dose of prednisone >60 mg/d (hazard ratio: 6.71; 95% CI: 1.94–23.21; $p = 0.0026$), use of methylprednisolone pulses (hazard ratio: 1.31; 95% CI: 1.16–1.49; $p < 0.0001$),

use of any immunosuppressive drug (hazard ratio: 1.43; 95% CI: 1.05–1.96; $p = 0.0241$), use of Po-CYC (hazard ratio: 3.05; 95% CI: 1.50–6.22; $p = 0.0021$), use of IV-CYC (hazard ratio: 2.22; 95% CI: 1.64–3.02; $p = 0.0001$), increase in disease activity per one unit (hazard ratio: 1.24; 95% CI: 1.17–1.32; $p < 0.0001$) and damage accrual per one unit (hazard ratio: 1.39; 95% CI: 1.28–1.51; $p < 0.0001$) were predictive factors.

Multivariable analysis (depicted in Table 4) showed that antimalarial use (hazard ratio: 0.69; 95% CI: 0.48–0.99; $p = 0.0440$) was protective of serious infections over time, while both prednisone doses > 15 but ≤60 mg/day and >60 mg/d (hazard ratio: 4.18; 95% CI: 1.69–10.31; $p = 0.0019$ and hazard ratio: 4.71; 95% CI: 1.35–16.49; $p = 0.0153$, respectively), use of methylprednisolone pulses (hazard ratio: 1.53; 95% CI: 1.10–2.13; $p = 0.0124$), increase in disease activity per one unit (hazard ratio: 1.03; 95% CI: 1.01–1.04; $p = 0.0016$) and in damage accrual per one unit (hazard ratio: 1.22; 95% CI: 1.11–1.34; $p < 0.0001$) were predictive factors of serious infections. We also performed an analysis in which both prednisone doses >15 but ≤60 mg/day and >60 mg/day were combined into a single category: 'prednisone >15 mg/day'; the resulting hazard ratio, 95% CI and p value for this combined dose were 4.19, 1.70–10.35 and $p = 0.0019$, respectively.

We also performed additional analyses considering two time-periods: 1996–1999 and 2000–2004. In the first period, there were 1031 (83%) patients and 142 (14%) of them had serious infections; in the second period, there were 212 patients (17%) and 27 (13%) of them had serious infections. In the first period, we obtained similar results to those of our original analysis, that is, the same predictors were identified. However, when we examined the data for the second period, none of the previously identified predictors was retained in the model (data not shown). These discrepant results may be due to the fact that fewer patients were included in the analysis of the second period.

Discussion

Infections are an important cause of mortality in patients with SLE. There are factors inherently associated with SLE that predispose these patients to experience them; they include impaired immune function (chemotaxis, phagocytosis), lymphopenia, complement dysfunction and, in some patients, hypogammaglobulinemia.[18] On the other hand, other factors such as treatment and disease activity, among others, may play a main role and could be potentially modifiable. In this multi-national, multi-ethnic cohort, we have found that prednisone doses higher than 15 mg/day, use of methylprednisolone pulses, increase in disease activity and damage accrual are predictive of serious infections over time, while antimalarial use is protective. Furthermore, when we performed additional analyses considering two time-periods (1996–1999 and 2000–2004), we obtained the same predictors in the first period; however, none of these predictors was identified in the second period, likely due to the lower number of patients included.

It is not surprising that increase in disease activity was associated with serious infections, because this leads to treatment initiation or increase (such as glucocorticoids and immunosuppressive drugs) and, in some cases, to the use of invasive therapies (i.e. mechanical ventilation). There are several studies supporting this premise. In the Toronto Lupus Cohort, there was higher disease activity in patients who developed infections (11.58 ± 3.14 *vs.* 7.06 ± 1.28; $p < 0.01$); infections were most likely to occur if SLEDAI > 8 (odds ratio (OR): 2.7; $p < 0.005$; sensitivity: 60.5%; specificity: 63.9%).[19] In the Hopkins Lupus Cohort, the highest disease activity (by SLEDAI) the previous year was a risk factor for hospitalization for infection (OR:1.12; 95% CI: 1.001–1.25; $p = 0.04$).[20] Jeong et al. found that SLEDAI >12 is a risk factor for infections (OR: 5.5; 95% CI: 1.5–20.0; $p = 0.01$).[21] At the same time, Zonana-Nacach et al., in a study from Mexico, found that SLEDAI ≥4 was associated with any infection (parameter estimate: 1.715; standard error: 0.771; $p = 0.026$)[22] and Teh et al. found that flares were predictive of infections-related mortality (hazard ratio: 3.98; 95% CI: 1.30–12.21).[10] Unlike these studies, we have examined whether any increase on the SLEDAI (i.e. new thrombocytopenia) was predictive of serious infections, which indeed was the case; even flares (defined as increase in SLEDAI > 4 units[23]) were predictive in our study (hazard ratio:1.11; 95% CI (1.04–1.19)) (data not shown). In addition to being harbingers of infections, flares have been also associated with damage accrual[24] and death;[25] thus, it is imperative to monitor for their occurrence with close clinical and serological surveillance. It should be noted that in our study, unlike others, we used disease activity as a time-dependent covariate.

The only previous study demonstrating that higher damage accrual is a predictor of serious infections was carried out by Rúa-Figueroa et al.

in Spain; this study included 3658 lupus patients.[13] We, on the other hand, found that any increase in the SDI was associated with the occurrence of serious infections, although which items or domains of the damage index account for this remains to be determined. It is possible that, for example, patients in whom a splenectomy is performed may be at risk of infections with encapsulated bacteria and that patients on hemodialysis will be predisposed to catheter-related infections, but these hypotheses will need to be explored. Infections may, in turn, be a potential risk factor of damage accrual as reported by Eudy et al.[26]

Glucocorticoids are a cornerstone in the treatment of SLE and their relationship with mild and severe infections is well-known. The mechanisms involved in such predisposition include a decrease in the function of monocytes, leucocytes, fibroblasts and endothelial cells.[27] Our study shows that prednisone at a dose >15 mg/day is predictive of serious infections (combined risk hazard ratio: 4.19; 95% CI: 1.70–10.35; $p = 0.0019$). This finding is similar to the data reported by Bosch et al.,[12] who found that a dose of prednisone >20 mg/day was predictive of infections. Other studies have shown an association with even lower glucocorticoid doses, as demonstrated by Ruiz-Irastorza et al.[9] (median of prednisone 7.5 mg/day), Merayo-Chalico et al.[28] (any dose, even prednisone ≤7.5 mg/day) and Rúa-Figueroa et al.[13] (prednisone ≥10 mg/day). It should be noted that this last study showed that infections were associated with an increased mortality risk. Lastly, in 2018, Gonzalez-Echevarri et al.[29] found, in an inception Spanish cohort, that a dose of prednisone > 30 mg/day (during the first year after diagnosis) and >7.5 mg/day (during the second year after diagnosis) was predictive of infections. Taking these data together, proper and conscientious glucocorticoid use, especially regarding dose and time of use, is mandatory. Currently, there are many studies that support this assertion; in fact, the same or better results are obtained with these 'low dose glucocorticoids', particularly in terms of complete response rates in lupus nephritis.[30–33] Moreover, nowadays there are new recommendations based on a treat-to-target approach[34] as to how to achieve remission with or without glucocorticoids (prednisone ≤5 mg/day),[35] or, at least, to achieve the lowest disease activity possible with glucocorticoids (prednisone ≤7.5 mg/day).[36] It is worth noting that the first Latin American clinical guidelines for treatment of SLE developed by GLADEL and PANLAR (for Pan-American League of Associations of Rheumatology) have as overarching principle the use of glucocorticoids at the lowest possible dose and for the shortest period of time.[37]

Our study showed that, like with oral glucocorticoids, the use of methylprednisolone pulses was associated with serious infections, but the risk was of lesser magnitude than with oral glucocorticoids. Some studies have shown this association[38,39] while others have not.[10,40] The studies mentioned above did not take into account methylprednisolone doses; however, Badsha et al.,[39] in a study from Singapore, compared a 'low dose' group (1–1.5 g) and a 'high dose' group (3–5 g) and showed that disease activity decreased at six months as per SLEDAI (2.0 (0–20) *vs.* 0.0 (0–10); $p = 0.19$); however, there was a lower number of infections in the first than in the second group (9 *vs.* 20; $p = 0.04$). It is worth noting that our study has shown that there is a higher risk of serious infections with oral glucocorticoids than with methylprednisolone pulses; regarding this, Ruiz-Irastorza et al.[33] compared two groups of lupus nephritis patients with two types of treatments: 'The Lupus Cruces' protocol (use of 125 mg of methylprednisolone pulses with each fortnightly pulse of IV-CYC and prednisone ≤30 mg/day with tapering over 12–14 weeks until 2.5–5 mg/day) versus international lupus nephritis guidelines (high glucocorticoids doses and IV-CYC or mycophenolate). They found that 'The Lupus Cruces' protocol decreased glucocorticoid doses at the sixth month (8.3 *vs.* 21.0 mg/day; $p < 0.001$), improved rates of complete response at the 12th month (86% *vs.* 42%; $p < 0.001$) and had a lower risk of glucocorticoid side effects (hazard ratio: 0.19; 95% CI: 0.04–0.89); furthermore, the number of methylprednisolone pulses was associated with complete response (hazard ratio: 3.8; 95% CI: 2.05–7.09). Therefore, the use of lower doses of methylprednisolone followed by low doses of glucocorticoids could be effective and safe and may be preferable to the use of high doses of them.

As to the immunosuppressive drugs, the literature reviewed supports their predictive role.[11–13] However, we have not been able to corroborate this assertion perhaps due to the fact that we excluded from our analysis patients with non-serious infections (i.e. herpes zoster, upper respiratory tract infections). Based on the type of drug (AZA, Po-CYC or IV-CYC) used, we performed two analyses considering the highest dose received (data not shown) and their use or non-use; however, we still found no association. It also should be noted that in the study by Feldman et al.[11] and in our study immunosuppressive use was included as a time-dependent variable.

Several benefits of antimalarial use are already well-known: improvement in survival, flare prevention and a longer time to damage accrual.[6,41–43] Currently, many studies have attributed a new benefit to them: protective against the occurrence of any type of infection.[7–11,13,40] This finding is not surprising due to the broad antimicrobial properties of antimalarials. These compounds have activity against bacteria (*Escherichia coli, Mycobacterium tuberculosis*), viruses (*Herpes virus,* HIV*, influenza*) and fungi (*Histoplasma, Aspergillus*).[44] The antibacterial and antifungal effects are exerted by pH-dependent iron deprivation and by increasing lysosomal pH, leading to growth inhibition of intracellular organisms.[44] In turn, their antiviral effect is mediated by the inhibition of pH-dependent steps of viral replication and by the alteration of posttranslational modifications of newly synthesized proteins.[45] Despite this knowledge, the minimal time of antimalarial exposure necessary for the prevention of infections has not been examined in the previously reported studies. From the data we are reporting, we can state that six months appears beneficial (compared with 'non-users'); however, whether a shorter time of exposure or what dose of antimalarials will have the same effects remains to be determined.

Lymphopenia was not found to be predictive of infections in our study, which is consistent with what has been reported by others.[10,21,46] There are only two studies which show lymphopenia to be predictive of infections, but both have limitations, due to their retrospective nature and their small sample size.[28,47] However, in a recent systematic review, no evidence of a significant association between overall reduction of white blood cells and infection occurrence was found.[48] Nevertheless, close follow-up is recommended in these patients, particularly due to the association of leukopenia with lupus nephritis, disease activity and damage accrual.[49]

Neither ethnicity nor other demographic factors were associated with serious infections in our study. However, it is worth commenting on some other studies. In the aforementioned study by Rúa-Figueroa et al.,[13] patients of Latin American (Amerindian/Mestizo) ethnic background were found to be at a higher risk of developing infections (hazard ratio: 1.01; 95% CI: 1.009–1.023); of note, however, Latin Americans were only a very small proportion (5%) of the total population studied. On the other hand, Feldman et al.[11] studied a large US Medicaid database with similar percentages of African-American and Caucasian patients, finding that being African-American was predictive of the occurrence of infections (37.5% and 37.9%, respectively) (hazard ratio: 1.14; 95% CI: 1.06–1.21). This could be explained by a higher disease activity[50] and damage accrual in patients from this ethnic group.[43]

Our study has some limitations. First, although GLADEL is a longitudinal cohort, the database does not include information on opportunistic infections or on most of the etiological agents as these analyses were not conceived at the planning stages of this inception cohort. Second, the relatively short time of follow-up may have tended towards finding a larger number of infections. Notable strengths, however, include the multi-ethnic nature of the population studied, with similar numbers of Caucasian and Mestizo patients, and the large number of patients studied. Moreover, unlike other studies, exposure time to antimalarials has been clearly defined and this is another important strength.

In conclusion, prednisone doses higher than 15 mg/day, use of methylprednisolone pulses, and mild increases in disease activity and damage accrual were predictive of the occurrence of serious infections in lupus patients whereas use of antimalarials for more than six months was protective against their occurrence.

Acknowledgements

We are grateful to Daniel Villalba and Leonardo Grasso for providing expert assistance with the ARTHROS (version 6.0) software. Author contribution: 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. VRP-Q, MFU-G, GBH, DW, GSA and BAP-E have full access to all data from the study and take responsibility for their integrity and the accuracy of the analyses performed.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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