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PAPER

Predictive factors of flares in systemic lupus erythematosus patients: data from a multiethnic Latin American cohort

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Purpose: The purpose of this paper is to determine the factors predictive of flares in systemic lupus erythematosus (SLE) patients. **Methods:** A case-control study nested within the Grupo Latino Americano De Estudio de Lupus (GLADEL) cohort was conducted. Flare was defined as an increase ≥4 points in the SLEDAI. Cases were defined as patients with at least one flare. Controls were selected by matching cases by length of follow-up.

Demographic and clinical manifestations were systematically recorded by a common protocol. Glucocorticoid use was recorded as average daily dose of prednisone and antimalarial use as percentage of time on antimalarial and categorized as never (0%), rarely (>0–25%), occasionally (>25%–50%), commonly (>50%–75%) and frequently (>75%). Immunosuppressive drugs were recorded as used or not used.

The association between demographic, clinical manifestations, therapy and flares was examined using univariable and multivariable conditional logistic regression models. **Results:** A total of 465 cases and controls were included. Mean age at diagnosis among cases and controls was 27.5 vs 29.9 years, $p = 0.003$; gender and ethnic distributions were comparable among both groups and so was the baseline SLEDAI. Independent factors protective of flares identified by multivariable analysis were older age at diagnosis (OR = 0.929 per every five years, 95% CI 0.869–0.975; $p = 0.004$) and antimalarial use (frequently vs never, OR = 0.722, 95% CI 0.522–0.998; $p = 0.049$) whereas azathioprine use (OR = 1.820, 95% CI 1.309–2.531; $p < 0.001$) and SLEDAI post-baseline were predictive of them (OR = 1.034, 95% CI 1.005–1.064; $p = 0.022$). **Conclusions:** In this large, longitudinal Latin American cohort, older age at diagnosis and more frequent antimalarial use were protective whereas azathioprine use and higher disease activity were predictive of flares. *Lupus* (2017) **0,** 1–9.

Key words: Systemic lupus erythematosus; flares; risk factors; antimalarials

Introduction

The clinical course of systemic lupus erythematosus (SLE) is variable, with remissions and flares. Flare is defined as "a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or

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laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of change or an increase in treatment.''[1] However, the problem rests in the absence of a uniform definition of a measurable increase. There have been several definitions based on available disease activity indices including the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[2] and its variants (the Safety of Estrogen in Lupus Erythematosus National Assessment Trial-SLEDAI (SELENA-SLEDAI),[3] or SLEDAI-2K)[4] and the British Isles Lupus Assessment Group (BILAG).[5] However, only the SELENA-SLEDAI and the BILAG have a definition of flare that includes a change or an increase in treatment.

Flares have been associated with more hospitalizations,[6] damage accrual,[7,8] and a composite index of damage and death.[9] Furthermore, flares have been associated with higher costs[10,11] and a diminished health-related quality of life.[12,13] Predictive factors for flares have not been consistently reported; for example, the association between younger age and flares has been reported by some investigators,[11,14–17] but not by others.[18–20] Antimalarial withdrawal has been associated with flares,[21] but that has not been always the case.[14,18,22]

We conducted this study in order to determine which factors can predict flares in a large, well-characterized international Latin American lupus cohort.

Methods

Patients

Grupo Latino Americano De Estudio de Lupus (GLADEL) is an observational inception cohort study. It was started in 1997 by establishing a common protocol, consensus definitions, and outcome measures in 34 centers distributed among nine Latin American countries. Every group used ARTHROS as a common database to collect data. All GLADEL investigators were trained in data collection and entry prior to study initiation. The study was performed in accordance with the Declaration of Helsinki for the conduct of research in humans and following local institutional review boards' regulations.

The diagnosis of SLE was conducted 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[23] at the time of diagnosis was not mandatory. Also, disease diagnosis could occur subsequently to a patient accruing at least four ACR criteria. Data on socioeconomic, demographic and clinical characteristics, treatment features, and laboratory tests were included. The general characteristics and composition of the 1480 GLADEL cohort patients have been described in detail elsewhere.[24] For these analyses, only patients with at least one SLEDAI evaluation after baseline were included. In addition, only patients of Caucasian, Mestizo and African-Latin American ethnic background were included; thus, 55 patients from other ethnic groups were not included in these analyses.

Variables

Disease activity was ascertained using the SLEDAI,[25] and it was assessed, per protocol, twice a year. Flare was defined as an increase of at least four points in the SLEDAI between two consecutive study visits, regardless of its duration, but most visits occurred at six-month intervals.[2] For the purpose of these analyses, in addition to flare, SLEDAI was analyzed as SLEDAI at entry to the cohort and average SLEDAI post-baseline until the day before flare or last visit.

Demographic and clinical manifestations were systematically recorded by a common protocol. Clinical manifestations were grouped into 10 domains: muscular manifestations: myalgia and myositis; articular manifestations: arthralgia, arthritis, Jaccoud's arthropathy, overall musculoskeletal related to SLE, and osteonecrosis; cutaneous manifestations: alopecia, photosensitivity, malar rash, discoid rash, mucosal ulcers, panniculitis, livedo reticularis, subacute cutaneous lupus, bullous lupus, Raynaud's phenomenon, and overall cutaneous related to SLE; ocular manifestations: xerophthalmia, keratoconjunctivitis sicca, scleritis, episcleritis, uveitis, retinopathy, cytoid bodies, amaurosis, and overall ophthalmic related to SLE and cataracts; respiratory manifestations: lung serositis, interstitial lung disease, alveolar hemorrhage, pulmonary thromboembolism, pulmonary hypertension, shrinking lung, lung infarction and overall respiratory related to SLE; cardiovascular manifestations: pericarditis, myocarditis, endocarditis, rhythm disorders, hypertension, ischemic heart disease, coronary artery disease, atherosclerosis, thrombosis, peripheral artery disease and overall cardiovascular related to SLE; renal manifestations: proteinuria, cellular casts, glomerulonephritis, tubular interstitial alterations,

renovascular disease, renal failure (acute or chronic) and overall renal related to SLE; neurological manifestations: psychosis, seizures, neurologic syncope, vertigo, mood disorders, cognitive dysfunction, acute confusional state, dementia, motor/sensitive disorders, movement disorders, mononeuritis multiplex, polyneuropathy, cranial neuropathy, autonomic neuropathy, lupus headache and overall neurologic related to SLE; digestive manifestations: peritoneal serositis, xerostomy and overall digestive related to SLE; and hematologic manifestations: autoimmune hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia and overall hematologic related to SLE. For this study, clinical manifestations were recorded from the time prior to entry into the cohort to the day before the flare or the last follow-up visit.

Glucocorticoid use was recorded as average daily dose of prednisone. Parenteral glucocorticoids were not included. Antimalarial use was recorded as percentage of time with antimalarial (chloroquine or hydroxychloroquine) and categorized as never (0%), rarely (>0–25%), occasionally (>25%–50%), commonly (>50%–75%) and frequently (>75%). Immunosuppressive drugs were recorded as ever used or not used. Treatment was recorded from the time prior to entry into the cohort to the day before the flare or the last follow-up.

Disease damage was ascertained using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)[26] and it was measured, per protocol, once a year.

Design

A case-control study nested within the GLADEL cohort was used to determine factors predictive or protective of flare. Cases were defined as patients with at least one flare and controls were patients without flares during the follow-up. Difference between follow-up in cases and controls was less than two months. Cases were matched to controls on length of follow-up since baseline until flare (cases) or last visit (controls). Only cases that had a control were included. All variables included in the analysis were measured until the day before flare or last visit.

Statistical analyses

Categorical variables are summarized as frequencies and percentages while continuous variables are presented as means and standard deviations (SDs). The association between sociodemographic, clinical manifestations, treatment and flares was examined using univariable and multivariable conditional logistic regression models. Candidate variables for inclusion in the multivariable model were all variables with $p < 0.10$ in the univariable models. Model selection was based on backward elimination with alpha level to stay in the model set to 0.05. The results are presented as odds ratios (ORs) with their 95% confidence intervals (CIs). To avoid over-adjustment, when mean SLEDAI was included in the model, clinical manifestations were not included and vice versa. Immunosuppressive drugs were included individually in the multivariable model, but percentage of time with any immunosuppressive drugs was also included in univariable analyses. A subanalysis including patients with complement and anti-double-stranded DNA (anti-dsDNA) antibody data was performed in order to evaluate their impact on the probability of flares.

Statistical analyses were performed using SPSS v. 21.0 (IBM, Chicago, IL, USA).

Results

Of the 1021 patients with at least two SLEDAI assessments, 465 (45.5%) presented with at least one flare; patients of the three ethnic groups presented with flares. A total of 897 (96.5%) of the 930 patients included in this study accrued at least four ACR criteria, 456 (98.1%) of the cases and 441 (94.8%) of the controls, $p = 0.012$. Sociodemographic characteristics in patients with and without flares are depicted in Table 1. Mean age at diagnosis among patients with flares was 27.5 (SD 10.9) years and in those without flares 29.9 (12.5) years, $p = 0.003$; the gender distribution was comparable among patients with and without flares (417 (89.7) vs 419 (90.1); $p = 0.831$). Likewise was the ethnic distribution, Mestizo being the most frequent ethnic category (207 (44.5) vs 209 (44.9)) followed by Caucasian (196 (42.2) vs 199 (42.8)). Time until flare or last follow-up was 2.2 (1.5) vs 2.3 (1.5) years, respectively; $p = 0.168$.

The distribution of clinical variables in cases and controls is shown in Table 2. The average post-baseline SLEDAI was higher among patients with flares (6.0 vs 4.9, $p = 0.001$) as was the average last SDI (1.3 vs 1.0, $p = 0.007$). Renal, neurological and digestive involvement were more frequent among patients with flares than in those without them

Table 1 Sociodemographic characteristics of GLADEL patients included in a case-control study. Univariable analyses

Variable	*Case* (n = *465*)	*Control* (n = *465*)	*OR (CI 95%)*	p *value*
Age at diagnosis, years, mean (SD)	27.5 (10.9)	29.9 (12.5)	0.983 (0.973–0.994)	0.003
Age at diagnosis, every five years			0.917 (0.870–0.971)	0.003
Gender, female, *n* (%)	417 (89.7)	419 (90.1)	0.956 (0.629–1.451)	0.831
Socioeconomic status, *n* (%)				
High	39 (8.4)	43 (9.3)	Ref	
Medium	126 (27.1)	132 (28.6)	0.906 (0.678–1.211)	0.505
Low	300 (64.5)	287 (62.1)	0.870 (0.541–1.399)	0.564
Ethnic group, *n* (%)				
Caucasian	196 (42.2)	199 (42.8)	Ref	
Mestizo	207 (44.5)	209 (44.9)	1.007 (0.771–1.316)	0.959
African-Latin American	62 (13.3)	57 (12.3)	1.100 (0.735–1.648)	0.642
Medical coverage, *n* (%)	288 (62.1)	279 (60.7)	1.057 (0.810–1.378)	0.685
Years of education, mean (SD)	9.9 (4.2)	10.2 (4.2)	0.981 (0.950–1.013)	0.237

GLADEL: Grupo Latino Americano De Estudio de Lupus; OR: odds ratio; CI: confidence interval.

Table 2 Clinical characteristics of GLADEL patients included in a case-control study. Univariable analyses

Variable	*Case* (n = *465*)	*Control* (n = *465*)	*OR (CI 95%)*	p *value*
Baseline SLEDAI, mean (SD)	10.7 (8.5)	10.5 (8.2)	1.004 (0.988–1.021)	0.601
Average SLEDAI post-baseline, mean (SD)	6.0 (5.8)	4.9 (4.8)	1.047 (1.018–1.076)	0.001
Baseline SDI, mean (SD)	1.1 (1.3)	1.0 (1.2)	1.083 (0.965–1.214)	0.174
Last SDI, mean (SD)	1.3 (1.4)	1.0 (1.3)	1.149 (1.039–1.271)	0.007
Articular involvement, *n* (%)	433 (93.1)	423 (91.0)	1.333 (0.831–2.141)	0.234
Muscular involvement, *n* (%)	103 (22.2)	83 (17.8)	1.313 (0.948–1.817)	0.101
Cutaneous involvement, *n* (%)	433 (93.1)	427 (91.8)	1.207 (0.738–1.974)	0.454
Ocular involvement, *n* (%)	74 (15.9)	70 (15.1)	1.070 (0.746–1.536)	0.713
Respiratory involvement, *n* (%)	32 (6.9)	33 (7.1)	0.969 (0.591–1.588)	0.900
Cardiovascular involvement, *n* (%)	187 (40.2)	160 (34.4)	1.290 (0.984–1.692)	0.065
Renal involvement, *n* (%)	275 (59.1)	236 (50.8)	1.419 (1.089–1.851)	0.010
Neurological involvement, *n* (%)	161 (34.6)	102 (21.9)	1.868 (1.391–2.507)	<0.001
Digestive involvement, *n* (%)	220 (47.3)	173 (37.2)	1.522 (1.167–1.986)	0.002
Hematological involvement, *n* (%)	374 (80.4)	350 (75.3)	1.375 (0.996–1.897)	0.053

GLADEL: Grupo Latino Americano De Estudio de Lupus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; OR: odds ratio; CI: confidence interval.

(59.1% vs 50.8%, $p = 0.010$, 34.6% vs 21.9%, $p < 0.001$, 47.3% vs 37.2%, $p = 0.002$, respectively).

Treatment among cases and controls is depicted in Table 3. Patients without flares used antimalarials more frequently; 299 (64.3%) patients without flares received antimalarials frequently during their follow-up but only 259 (655.7%) of those with flares received them, $p = 0.012$. Patients with flares used immunosuppressive drugs more frequently (55.7% vs 41.3%, $p < 0.001$); among them, azathioprine was also more frequently used among patients with flares (30.5% vs 18.3%, $p < 0.001$); the same was the case for cyclophosphamide (37.6% vs 30.8%, $p = 0.035$) and cyclosporine (2.4% vs 0.6%, $p = 0.046$). In the multivariable analysis (depicted in Table 4) independent factors protective of flares were age at diagnosis (OR = 0.929 per every five years, 95% CI 0.869–0.975; $p = 0.004$), hence younger age was a risk factor, and antimalarial use (frequently vs never, OR = 0.722, 95% CI 0.522–0.998; $p = 0.049$) whereas azathioprine use (OR: 1.820, 95% CI 1.309–2.531; $p < 0.001$) and SLEDAI during the follow-up were predictive of them (OR = 1.034, 95% CI 1.005–1.064; $p = 0.022$). When we included clinical manifestations instead of SLEDAI, antimalarial use and age were protective of flares whereas azathioprine use and neurological involvement were predictive of them (Supplementary Table 1).

In a subanalysis of 249 pairs, including patients with complement and anti-dsDNA antibody

Table 3 Treatment of GLADEL patients included in a case-control study. Univariable analyses

Variable	*Case* (n = *465*)	*Control* (n = *465*)	*OR (CI 95%)*	p *value*
Prednisone average dose, mg/d, mean (SD)	19.9 (16.4)	17.1 (15.4)	1.002 (0.993–1.012)	0.630
Antimalarial use				
Never, *n* (%)	130 (28.0)	98 (21.1)	Ref	
Rarely, *n* (%)	16 (3.4)	14 (3.0)	0.827 (0.388–1.765)	0.623
Occasionally, *n* (%)	15 (3.2)	19 (4.1)	0.592 (0.283–1.238)	0.164
Commonly, *n* (%)	45 (9.7)	35 (7.1)	0.980 (0.579–1.659)	0.940
Frequently, *n* (%)	259 (55.7)	299 (64.3)	0.662 (0.486–0.902)	0.009
Any immunosuppressive drug, *n* (%)	259 (55.7)	192 (41.3)	1.788 (1.371–2.332)	<0.001
Immunosuppressive drug use				
Never, *n* (%)	209 (44.9)	282 (60.6)	Ref	
Rarely, *n* (%)	29 (6.2)	21 (4.5)	1.757 (0.973–3.171)	0.061
Occasionally, *n* (%)	39 (8.4)	21 (4.5)	2.529 (1.425–4.489)	0.002
Commonly, *n* (%)	39 (8.4)	22 (4.5)	2.319 (1.344–4.000)	0.003
Frequently, *n* (%)	119 (25.6)	149 (32.0)	1.707 (1.251–2.330)	0.001
Methotrexate, *n* (%)	45 (9.7)	37 (8.0)	2.018 (1.465–2.780)	0.340
Azathioprine, *n* (%)	142 (30.5)	85 (18.3)	1.327 (1.021–1.724)	<0.001
Cyclophosphamide, *n* (%)	175 (37.6)	143 (30.8)	3.667 (1.023–13.143)	0.035
Cyclosporine, *n* (%)	11 (2.4)	3 (0.6)	0.333 (0.067–1.652)	0.046
Mycophenolate, *n* (%)	2 (0.4)	6 (1.3)	1.000 (0.063–15.988)	0.178
Leflunomide, *n* (%)	1 (0.2)	1 (0.2)	1.00 (0.06–15.99)	1.000
Tacrolimus, *n* (%)	0 (0.0)	1 (0.2)	NA	NA

GLADEL: Grupo Latino Americano De Estudio de Lupus; OR: odds ratio; CI: confidence interval.

Table 4 Predictive factors of flares. Multivariable analysis

Variable	*OR (CI 95%)*	p *value*
Age at diagnosis, every five years	0.929 (0.877–0.984)	0.012
SLEDAI at follow-up	1.034 (1.005–1.064)	0.022
Antimalarial use		
Never	Ref.	
Rarely	1.004 (0.459–2.197)	0.992
Occasionally	0.674 (0.315–1.444)	0.310
Commonly	0.9192 (0.533–1.582)	0.759
Frequently	0.722 (0.522–0.998)	0.049
Azathioprine	1.820 (1.309–2.531)	<0.001

Only variables with a p value less than 0.05 are shown in the multivariable analyses.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; OR: odds ratio; CI: confidence interval.

measurements, low complement level and anti-dsDNA antibodies were associated with flares in the univariable model (OR = 1.67, 95% CI 1.14–2.44; $p = 0.009$ and OR = 1.62, 95% CI 1.08–2.44; $p = 0.021$; respectively); however, none of them were predictive of flares in multivariable models (data not shown).

Discussion

Utilizing the longitudinal data from GLADEL, a multiethnic, multinational inception cohort, we have now examined the factors predictive or protective of the occurrence of flares. During the follow-up, 45.5% of patients presented with at least one flare. We found SLEDAI post-baseline and azathioprine use as predictive factors and older age and antimalarial use as being protective. These data have substantial implications for the course and outcome of SLE, given that flares have proved to be associated with a worse prognosis in SLE patients, like damage accrual,[7,8] hospitalizations[6] and higher costs.[11]

We consider that the SLEDAI and its variants are reliable tools to measure disease activity in clinical practice, and, in the absence of a uniform definition of flares, we decided to use the one proposed by Gladman et al.[2] We have previously used this definition to report the association between flares, regardless of their severity, and damage accrual.[8] We have now used it to identify which patients are at higher risk of having flares.

Among the demographic factors, we found age at diagnosis as a protective factor of flares, hence younger age at diagnosis as a predictive factor of flares. Using several SLEDAI variants younger age has been found to be a risk factor in studies from Portugal,[14] Italy,[15] Europe (the Systemic Lupus Erythematosus Cost of Care in Europe (LUCIE) study),[16] Denmark[17] and Hong Kong[11] albeit the Danish study did not include the immunological

variables. That was not the case, however, for a study from Germany in which age was not associated with flares.[20] When flares have been defined instead by the BILAG instrument, no association between flares and age has been found in studies from the United States (the Hopkins lupus cohort)[18] and Great Britain.[19] In terms of gender, it has not been associated with the incidence of flares in studies from Europe (LUCIE study)[16] and Hong Kong;[11] in contrast, female gender was associated with flares in the Hopkins cohort, but this association was not retained in the multivariable model.[18] An association of male gender with renal flares but not with global flares was found in the Italian PADOVA study.[15] Finally, in terms of ethnicity, Caucasian ethnicity has been associated with a lower risk of flares[19] while African ancestry has been associated with a higher risk according to data from the Hopkins cohort[18] and the LUCIE study.[16]

In the Toronto Lupus Cohort, a higher disease activity (measured by adjusted mean SLEDAI) ascertained two or three years before flare was associated with a higher risk of its occurrence;[27] this is similar to our results. Additionally, in our alternative model, neurological involvement, like in the Italian Sapienza cohort, was predictive of flares.[28] In a post hoc analysis of patients included in the phase III belimumab trials, renal, neurological and vasculitis involvement were predictive of moderate or severe flares defined by BILAG, but only renal involvement was predictive when it was defined by the SLE flare index.[22] Anemia, lymphopenia and erythrocyte sedimentation rate had also been reported as predictive factors of flares in a German cohort.[20]

Immunological activity has not been reported to be a predictive factor of flares albeit not uniformly. Low complement was associated with flares in the Hopkins cohort but anti-dsDNA was not.[18] Anti-dsDNA was predictive of moderate or severe flares defined by SLE flare index and BILAG in a post hoc analysis of patients included in the phase III belimumab trials but low complement only when it was defined by SLE flare index.[22] Anti-dsDNA was predictive of reactivation in a study from the Netherlands.[29] In a study from Italy, anti-dsDNA was not predictive of reactivation, but there was an association trend.[30] In a German cohort neither complement levels nor anti-dsDNA titers were associated with flares.[20] Antinucleosome and anti-dsDNA antibodies were predictive of flares in serologically active but clinically quiescent SLE patients in a British cohort.[31] In a subanalysis of our cohort including patients in whom both complement levels and anti-dsDNA antibodies had been measured, neither one was associated with flares in the multivariable model likely because of the smaller sample size used in these analyses ($n = 249$ pairs).

Antimalarials have been associated with several benefits among SLE patients, like a better survival and longer time to damage accrual.[32–34] However, the association between flares and antimalarial use is still controversial; in this study we have found a protective effect of antimalarials when used frequently. In the landmark study from Canada, antimalarial withdrawal was reported to be associated with an exacerbation of the disease; however, this study preceded the availability of disease activity indices and disease exacerbation; a comparable concept was clinically defined.[21] In the Plaquenil Lupus Systemic (PLUS) study, a higher hydroxychloroquine concentration seemed to be associated with a lower risk of flare,[35] but in a cohort from Hong Kong hydroxychloroquine concentration was not associated with flares.[36] However, such a protective effect has not been corroborated in the Hopkins cohort,[18] in a study conducted in Portugal[14] or in the phase III belimumab trials.[22]

The association between glucocorticoid and immunosuppressive drug use and flares probably represent a surrogate marker of more severe disease as has been noted by others. Glucocorticoid use was associated with flares in the Hopkins[18] and Toronto[27] cohorts, but not in Portugal[14] or in the phase III belimumab trials.[22] Immunosuppressive drugs were associated with flares in the Hopkins[18] and Portugal[14] cohorts but not in the phase III belimumab trials.[22] The association between azathioprine and flares in our cohort could be reflective of a more severe disease that requires immunosuppressive drugs, but also could be related to a lower efficacy of azathioprine, as it has been reported to be less effective than mycophenolate mofetil in preventing relapses in lupus nephritis.[37]

Our study has some limitations. First, the interaction between variables has not been evaluated, which precludes us from clearly indicating whether azathioprine is predictive of flares because it is acting as a surrogate marker of severe disease or because it is truly associated with their occurrence given its relative low efficacy as an immunosuppressive drug. Second, as there is not a uniform definition of flare, it is possible that had we used different definitions our results could also have been different; however, a similar definition of flare has been used in other studies and it is considered to be reliable.[15,17,27,28] Third, there are some new medications for SLE treatment, and their

impact on flares could not be assessed in this cohort.

Despite these limitations, our data, from a very large, multiethnic, multinational lupus cohort, emphasize the importance of age at diagnosis and antimalarials as protective factors of the occurrence of flares and of higher disease activity and azathioprine use as predictive factors. These data give us another reason for using antimalarials in every SLE patient unless they are contraindicated, and have practical implications for individualized management of SLE patients.

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On behalf of GLADEL: In addition to the authors, the following participants are members of the GLADEL Study Group and have incorporated at least 20 patients into the database with adequate follow-up.

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