EXTENDED REPORT

The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort

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ABSTRACT

Purpose To determine the association between the number of flares systemic lupus erythematosus (SLE) patients experience and damage accrual, independently of other known risk factors.

Methods SLE patients (34 centres, nine Latin American countries) with a recent diagnosis (≤2 years) and ≥3 evaluations were studied. Disease activity was ascertained with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and damage with the SLICC/ACR Damage Index (SDI). Flare was defined as an increase ≥4 points in the SLEDAI between two study visits. An ambidirectional case-crossover design was used to determine the association between the number of flares and damage accrual.

Results 901 patients were eligible for the study; 500 of them (55.5%) experienced at least one flare, being the mean number of flares 0.9 (SD: 1.0). 574 intervals from 251 patients were included in the case-crossover design since they have case and control intervals, whereas, the remaining patients did not. Their mean age at diagnosis was 27.9 years (SD: 11.1), 213 (84.9%) were women. The mean baseline SLEDAI and SDI were 13.6 (8.1), respectively. Other features were comparable to those of the entire sample. After adjusting for possible confounding variables, the number of flares, regardless of their severity, was associated with damage accrual (SDI) OR 2.05, 95% CI 1.43 to 2.94, p<0.001 (OR 2.62, 95% CI 1.31 to 5.24, p=0.006 for severe and OR 1.91, 95% CI 1.28 to 2.83, p=0.001 for moderate).

Conclusions The number of flares patients experience, regardless of their severity, increases the risk of damage accrual, independently of other known risk factors.

INTRODUCTION

Mortality in patients with systemic lupus erythematosus (SLE) has decreased during the past few decades, probably due to an early diagnosis, recognition of milder forms of the disease and improvements in treatment.1 2 As patients live longer, however, organ damage tends to increase due to sequelae of disease activity, side effects of treatment and/or comorbidities.3 Disease damage affects survival,1 health-related quality of life,4 psychosocial well being and vocational aptitudes5 and increases costs.6

There are several known risk factors for damage accrual, such as male gender,7 age at diagnosis,8–12 non-Caucasian race/ethnicity,13–15 poverty,14 15 lower educational level,16 disease duration,8 10 14 17 18 higher levels of disease activity,8 9 11 13 19 20 previous damage,9 14 21 the presence of antiphospholipid antibodies and of the antiphospholipid syndrome,22 23 higher doses of glucocorticoids (GC)24 25 and the use of immunosuppressive drugs.12 14 17 On the other hand, the use of antimalarials exerts a protective role on damage accrual.25 26

Severe flares have been associated with damage accrual,20 27 but the impact of the number of flares a patient experiences over time on damage accrual has not been evaluated. We have now conducted such assessment, taken into consideration other known risk factors, in a well-characterised international Latin American lupus cohort.

METHODS

Patients

GLADEL is an observational inception cohort study. It was started in 1997 by establishing a common protocol, consensus definitions, and outcome measures in 34 centres 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 according to the declaration of Helsinki for the conduct of research in humans, and following local institutional review boards regulations.

The diagnosis of systemic lupus erythematosus (SLE) was done based on clinical and laboratory data, and according to the expertise of the...
involvement in SLE). Fulfilment of four American College of Rheumatology (ACR) SLE criteria at the time of diagnosis was not mandatory. Also, disease diagnosis could occur subsequently to a patient accruing at least four ACR criteria. Data included socioeconomic, demographic and clinical characteristics, treatment features, and laboratory tests. The general characteristics and composition of the 1480 GLADEL cohort patients have been described in detail elsewhere. For these analyses, only patients with at least three evaluations were included.

Variables
Disease activity was ascertained using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and it was assessed, per protocol, twice a year. The adjusted mean SLEDAI was calculated according to the formula previously described. Briefly, the average between two consecutive SLEDAI scores was multiplied by the length of the interval between them and the procedure repeated for every interval; all values were added up and then divided by the length of the interval from the first SLEDAI to the last one. Flare was defined as an increase of at least four points in the SLEDAI between two study visits, regardless of its duration. Severe flare was defined as an increase of more than 12 points in the SLEDAI between two study visits, whereas, a mild-moderate flare was defined as an increase of more than three points but no more than 12. Disease damage was ascertained using the SLICC/ACR damage index (SDI), SDI was measured, per protocol, once a year. The use of immunosuppressive drugs, and antimalarials was defined as the use of any of these drugs during the follow-up period. The cumulative dose of prednisone was calculated during the follow-up period.

Design
A case-crossover design was used to examine the impact of the number of lupus flares on damage accrual. The unit of analysis in this design is the interval which is defined as the period between two consecutive SDI evaluations regardless of whether it occurred early or late during the follow-up. A case interval is one in which there has been an increase of at least one point in the SDI, and a control interval is one in which no changes in the SDI have occurred. The number of flares presented in each one of these intervals was recorded. The design is ambidirectional, meaning, that a case interval could have occurred before or after a control interval. Only patients who have both intervals were included in these analyses. In this design, there is self-matching for ethnicity, socioeconomic and demographic characteristics, as well as baseline SDI that can play a role as confounders; non-static variables, however, are not matched with this design and are adjusted by using standard techniques; these possible confounder variables were disease duration, adjusted mean SLEDAI, cumulative prednisone dose, antimalarials, and immunosuppressive drugs used and calendar time.

Statistical analyses
Categorical variables were summarised as frequencies and percentages while continuous variables are presented as means and SDs. Factors associated with damage accrual were examined using $\chi^2$ or Student t tests, as appropriate.

A conditional logistic regression model was then performed to evaluate the association between the number of flares and damage accrual adjusting for the non-static variables (length of the intervals, disease duration, adjusted mean SLEDAI, cumulative dose of prednisone, use of antimalarials and use of immunosuppressive drugs). Similar multivariable regression analyses were then performed taking into account the number of mild-moderate and severe flares. The results are presented as ORs with their 95% CIs.

### RESULTS
Nine hundred-and-one patients were eligible for this study; by and large, these patients were representative of the entire GLADEL cohort in terms of their socioeconomic, demographic and clinical characteristics. Of them, 874 (97.0%) fulfilled four ACR SLE criteria. Five hundred (55.5%) of these patients presented at least one flare; of them, 350 (70.0%) patients had mild-moderate flares, 77 (15.4%) had severe flares and 73 (14.6%) patients had both. There were 781 flares over 4587.1 patient/years of follow-up; of them, 660 (84.5%) were mild-moderate and 121 (15.5%) were severe. The incidence of overall flares was 17 per 100 patient/years, it was 14 for mild-moderate flares and three for severe flares per 100 patient/years.

#### Case-crossover design
In this set of analysis, 574 intervals from 251 patients were included; 216 patients had one case and one control interval, 34 had two case and two control intervals, and one patient had three case and three control intervals. Ninety-one (31.7%) of the control intervals occurred before the corresponding case interval, and 196 (68.3%) occurred after the case interval. The mean (SD) age at diagnosis of these 251 patients was 27.9 (11.1) years; the majority of them were Mestizo (patients of European and Amerindian ancestry) (118 (47.0%)) or Caucasian (96 (38.2%)); 30 (12.0%) were African–Latin American, and seven (2.8%) were from other racial/ethnic groups; other characteristics for these patients are shown in table 1. As compared with the patients whose intervals were not included in the analyses, these 251 patients were less frequently female, had a lower socioeconomic status, and higher disease activity and damage at baseline (see supplementary online only table S1).

#### Table 1
GLADEL patients included in the case-crossover design (n=251)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td>27.9 (11.1)</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>213 (84.9)</td>
</tr>
<tr>
<td>Socioeconomic status, n (%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19 (7.6)</td>
</tr>
<tr>
<td>Medium</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>Low</td>
<td>182 (72.5)</td>
</tr>
<tr>
<td>Racial/ethnic group, n (%)</td>
<td></td>
</tr>
<tr>
<td>Mestizo</td>
<td>118 (47.0)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>96 (38.2)</td>
</tr>
<tr>
<td>African–Latin American</td>
<td>30 (12.0)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>9.7 (4.2)</td>
</tr>
<tr>
<td>Baseline SLEDAI, mean (SD)</td>
<td>13.6 (8.1)</td>
</tr>
<tr>
<td>Baseline SDI, mean (SD)</td>
<td>1.3 (1.3)</td>
</tr>
<tr>
<td>Calendar time, n (%)</td>
<td></td>
</tr>
<tr>
<td>1994–1998</td>
<td>198 (21.1)</td>
</tr>
<tr>
<td>1999–2002</td>
<td>53 (78.9)</td>
</tr>
</tbody>
</table>

SDI, SLICC/ACR damage index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
Within these intervals, 319 flares were reported, of them 95 (29.8%) were severe and 224 (70.2%) were mild-moderate; overall they occurred more frequently in the case than in the control intervals (62.7% vs 33.8%, p<0.001). The characteristics of the case and control intervals are reported in table 2. After adjusting for the length of the intervals, disease duration, adjusted mean SLEDAI, cumulative dose of prednisone, use of antimalarials and immunsuppressive drugs and calendar time, for each flare, there was an overall increased risk of damage accrual (OR 2.05, 95% CI 1.43 to 2.94, p<0.001). That was also the case for severe flares ((23.7% vs 8.0%, p<0.001) (OR 2.62, 95% CI 1.31 to 5.24, p=0.006)) and for mild-moderate flares ((42.5% vs 27.2%, p<0.001) (OR 1.91, 95% CI 1.28 to 2.83, p=0.001)) (table 3). Of interest, if only one case and one control interval per patient were examined (251), the results are quite comparable with the ones presented (data not shown).

**DISCUSSION**

Using the longitudinal data from a multiethnic, multinational inception cohort, GLADEL, we have now examined the impact the number of flares has on damage accrual in these SLE patients. We found a significant impact with the total number of flares on damage accrual, but also with the number of severe flares, and with the number of mild-moderate flares in this case after adjusting for the number of severe flares. These data have substantial implications on the course and outcome of SLE patients, given that damage accrual is one of the most important explanatory factors of mortality in lupus as shown in a number of different studies conducted across the world.12 35–41

The case cross-over design allowed patients to be their own controls, and thus, only matching for non-static variables was necessary using this approach;42 furthermore, this approach allowed us to examine damage accrual over the patients’ follow-up time in the cohort. Our findings thus suggest that if disease activity increases over the background activity, that, on and by itself, increases the risk the patient will have of accruing more damage.

Of interest, the association between the occurrence of flares (not their number) and damage accrual has been reported in Italian patients with juvenile-onset SLE, but in that study, the association was with severe flares and not with those mild to moderate.43 The association between flares and damage accrual has also been reported in a group of 80 SLE patients from Iran, but this study lacks predictive value given its cross-sectional design.44 48

It can be speculated that damage accrual occurs in relation with the number of flares by one of two mechanisms. One, the inflammatory process associated with the lupus flare may lead to irreversible organ system involvement, and the other that the treatment adjustments required to control these flares result in damage accrual.

It is also worth pointing out that the rate of flares we have observed in our patients is consistent with the rates observed by investigators from Denmark (17 per 100 patient-years),45 Padova, Italy (19 per 100 patient-years)46 and Hong Kong (24 per 100 patient-years),48 but lower than the ones reported from Germany (124 per 100 patient-years),49 and higher than the rates reported in Rome, Italy (7 per 100 patient-years).49 Other definitions of flares have yielded higher rates of flares (65–194 per 100 patient-years) in patients with lupus. These include an increase in one point in the physician global assessment (range 0–3) in a study from the Johns Hopkins Lupus’ Cohort,50 or a new BILAG A or B in a British study51; however, the incidences reported using these definitions cannot be compared with the data we are reporting.

Despite a relatively high prednisone dose our patients used (probably as a function of their disease severity, with important organ system involvement, particularly renal), the cumulative dose of prednisone was not found to be associated with damage. This may be due to the fact that many of the intervals examined occurred very early in the course of the disease when the known time-dependent effect of steroids is not yet evident.

Our study has some limitations. First, as we only examined intervals, it is possible that the effect of flares would have a delayed impact on damage accrual and, thus, it will not be observed until a subsequent interval during which no flares have occurred; if that is the case, this would have minimised the effect not increased it; along these lines, since we included in the analyses the cumulative dose of prednisone, the interval occurring second in sequence, would have had a higher impact from this medication; however, since two-thirds of the control intervals occurred after the case intervals this may have acted in favour of showing a greater damage impact on the control intervals rather than the other way around; furthermore, in an alternative model including the 901 patients, the results were quite similar (see supplementary online only table S2). Second, because of the relatively long interval between study visits in

**Table 2** Comparison of case and control intervals characteristics from 251 GLADEL patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case (increased SDI) (n=287)</th>
<th>Control (no change in SDI) (n=287)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration, years, mean (SD)</td>
<td>2.78 (1.80)</td>
<td>3.20 (1.72)</td>
<td>0.005</td>
</tr>
<tr>
<td>Adjusted mean SLEDAI, mean (SD)</td>
<td>8.62 (6.55)</td>
<td>7.67 (5.48)</td>
<td>0.060</td>
</tr>
<tr>
<td>Length of the interval, years, mean (SD)</td>
<td>1.18 (0.72)</td>
<td>1.12 (0.54)</td>
<td>0.317</td>
</tr>
<tr>
<td>Number of flares, mean (SD)</td>
<td>0.75 (0.66)</td>
<td>0.37 (0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of mild-moderate flares, mean (SD)</td>
<td>0.49 (0.63)</td>
<td>0.29 (0.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of severe flares, mean (SD)</td>
<td>0.25 (0.47)</td>
<td>0.08 (0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative dose of prednisone, grams (SD)</td>
<td>27.3 (24.5)</td>
<td>29.2 (24.1)</td>
<td>0.348</td>
</tr>
<tr>
<td>Use of antimalarials (%)</td>
<td>203 (70.7)</td>
<td>16 (75.3)</td>
<td>0.222</td>
</tr>
<tr>
<td>Use of any immunosupressor (%)</td>
<td>214 (74.6)</td>
<td>222 (77.4)</td>
<td>0.435</td>
</tr>
<tr>
<td>Use of cyclophosphamide (%)</td>
<td>156 (54.4)</td>
<td>157 (54.7)</td>
<td>0.933</td>
</tr>
<tr>
<td>Use of azathioprine (%)</td>
<td>109 (38.0)</td>
<td>119 (41.5)</td>
<td>0.394</td>
</tr>
<tr>
<td>Use of methotrexate (%)</td>
<td>25 (8.7)</td>
<td>26 (9.1)</td>
<td>0.883</td>
</tr>
<tr>
<td>Use of mycophenolate mofetil (%)</td>
<td>5 (1.7)</td>
<td>7 (2.4)</td>
<td>0.560</td>
</tr>
<tr>
<td>Use of cyclosporine (%)</td>
<td>9 (3.1)</td>
<td>10 (3.5)</td>
<td>0.816</td>
</tr>
<tr>
<td>Use of leflunomide (%)</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

**Table 3** Multivariable analyses of the association between the number of flares and damage accrual in the case- crossover design*

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Number of flares</td>
<td>2.05 (1.43 to 2.94); p&lt;0.001</td>
</tr>
<tr>
<td>II. Number of mild-moderate flares</td>
<td>1.91 (1.28 to 2.83); p&lt;0.001</td>
</tr>
<tr>
<td>Number of severe flares</td>
<td>2.62 (1.31 to 5.24); p=0.006</td>
</tr>
</tbody>
</table>

*Adjustment variables: length of the intervals, disease duration, adjusted mean SLEDAI, cumulative dose of prednisone, use of antimalarials, use of immunsuppressive drugs and calendar time.
this cohort, some flares may have been missed; however, if that was the case, the association between the number of flares and damage accrual could be even stronger than what we are reporting. Third, because not all patients had case and control intervals, only about a third of them could be included in the case-crossover analyses; although there were some differences between those patients who could be included, and those who could not, the ones included were more likely to develop damage because of the higher proportion of males, their lower socioeconomic status and higher disease activity and damage at the baseline. Fourth, we were unable to adjust for observations that occurred in the same patient; however, since the large majority of the patients had only one case and one control interval, we do not think this is a major drawback. Fifth, because nearly 50% of our patients are Mestizo, it can be argued that our data may not be relevant to lupus patients overall; we do not think that is the case, but even if it was, there are nearly 600 million inhabitants in Latin America and 50 million Hispanics in the USA, at least one-half being Mestizo. Thus, we consider it important to describe what happens with patients from the GLADEL cohort, as their experience in this globalised world has relevance for Latin America, and also for North America and beyond. Finally, other components of the flare index as per the SELENA SLEDAI instrument could not be included given the lack of precise information between the flare and medications and hospitalisations; however, similar definitions of flares have been applied in other studies, and they are quite objective.

Despite these limitations, our data, from a very large multi-ethnic, multinational cohort of lupus patients emphasise for the first time the importance of the number of flares patients experience in the subsequent accrual of damage, even if those flares are mild to moderate in nature. This has practical implications for the appropriate and individualised management of patients with this potentially serious disorder; their treatment should include antimalarials, and the judicious use of prednisone, immunosuppressive drugs and biologics.

In conclusion, the number of flares patients experience, regardless of their severity, increased the risk of damage accrual in SLE patients, independently of other known risk factors.

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