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ORIGINAL ARTICLE

Prolonged remission is associated with a reduced risk of cardiovascular disease in patients with systemic lupus erythematosus: a GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) study

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Abstract

Prolonged remission (PR), defined as a 5-year consecutive period of no disease activity based on SLEDAI-2K, has been reported to be associated with a lower damage accrual over time in patients with systemic lupus erythematosus (SLE), as the consequence of a lower activity burden. Since disease activity is considered to play a role in the incidence of cardiovascular disease (CVD), we investigated the relationship, if any, between PR and the occurrence of a subsequent first CV event in patients with SLE. Out of 488 patients consecutively admitted to two tertiary Italian centers from November 1, 2000, to December 31, 2016, the 294 patients, who had been followed at least for 5 years, had not experienced any CV event at admission, and had been visited biannually during follow-up, were considered for the present study. The incidence of a first CV in patients who had achieved PR was compared with that registered in those who had not. Moreover, it was compared among PR patients subdivided into three groups: complete remission, clinical off-corticosteroids (offCR), and clinical on-corticosteroids remission (onCR). Kaplan–Meier curves and the log-rank test were used to analyze differences in event-free survival among groups. Cox regression was used to investigate disease and therapeutic features associated with the development of a first CV event. During 9 years median follow-up time, 24 (8.1%) CV events occurred. Out of the 294 patients, 126 (42.8%) had achieved PR. Kaplan–Meier analysis revealed a greater overall CV event-free rate in these patients as compared to both those with a shorter lasting remission and those who had never remitted (log-rank test $\chi^2 = 14.43$; $p = 0.0001$). In addition, CV outcome did not differ among PR patients, irrespectively the type of remission achieved ($p > 0.05$). At multivariate analysis, hydroxychloroquine therapy and PR resulted to be protective (HR 0.19; HR 0.18), while arterial hypertension and antiphospholipid positivity increased the risk of a first CV event (HR 2.61; HR 2.47). The PR, whichever the subtype, is associated with a better CV outcome and should be considered as a treat-to-target goal in the CV risk management of the lupus patient.

Keywords Cardiovascular disease · Remission · Systemic lupus erythematosus

Introduction

Despite the improvement in survival over the past decades, the overall mortality in patients with systemic lupus erythematosus (SLE) is still higher compared to that of the general population. In particular, cardiovascular disease (CVD) is the leading cause of death among SLE patients [1].

The high risk of CVD in SLE is only partially explained by an increased prevalence of traditional CV risk factors; SLE related factors also contributing to the risk.

As in other autoimmune systemic rheumatic diseases, the chronic inflammatory state has been suggested to be linked to

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acceleration of the atherosclerotic process in SLE. Nevertheless, distinct disease features underlying the association between disease activity and atherosclerosis in SLE has been poorly understood to date [2–4].

Disease activity as assessed by SLEDAI [5] either at admission or at the last visit did not result to be associated with the subsequent occurrence of CV events in our previous studies [6–8]. However, as SLE can be remitting-relapsing, an isolated activity assessment at a single point in time may be misleading in identifying the activity burden affecting the SLE patient. On the other hand, the arithmetic mean of SLEDAI values may not consider the fluctuation from visit to visit. The disease course may include periods of different levels of activity (mild, moderate, severe, or remission) for variable lengths of time, and many patterns of disease activity can be seen when looking at SLEDAI over time [8]. Zen et al. [9] have recently demonstrated that prolonged remission (PR), based on the SLEDAI-2K with three levels and lasting at least five consecutive years, is associated with lower damage progression. In the present study, we analyzed our SLE inception cohort to investigate the role, if any, of achieving a PR remission on CV outcome.

Methods

Patients

From our database, which includes two inception cohorts of SLE patients attending two tertiary GIRRCS Units (Naples and Rome) since November 1, 2000, we selected those who:

- at the first visit fulfilled the updated American College of Rheumatology (ACR) [10] classification criteria for SLE
- at the first visit had not experienced any prior CV event
- were subsequently assessed biannually during follow-up

The duration of follow-up was defined as the time from the first visit (baseline visit) to the first CV event or to the last observation in patients without thrombosis. Patients with a duration of follow-up less than 5 years were excluded from the analysis. Written informed consent had been obtained by each patient at admission. The study was approved by local Ethics Committees (CE 278/17).

Clinical and laboratory data

Our database contains information about each patient from admission to throughout follow-up and includes demographics, clinical features, exposure to drugs, and laboratory investigations. The following traditional CV risk factors were registered: smoking status, dyslipidemia (low-density lipoprotein > 120 mg/dL and/or triglycerides > 150 mg/dL and/or intake of lipid-lowering drugs), diabetes (two fasting serum glucose levels > 126 mg/dL and/or antidiabetic drugs), arterial hypertension (blood pressure ≥ 130 e/o 85 mmHg on two occasions and/or intake of antihypertensive drugs) and obesity (BMI > 30) and were considered to be present if they were observed at any time during the follow-up period [10]. Disease activity as assessed by SLEDAI-2K [11], and hypocomplementemia and anti-dsDNA positivity measured by an enzyme-linked immunosorbent assay ELISA [12] were recorded at each visit. Organ damage using the SLICC/ACR damage Index (SDI) [13] and antiphospholipid antibody (aPL) positivity, as defined when at least one of the following was detected at medium-high titers on two or more occasions at least 12 weeks apart: Lupus anticoagulant, anticardiolipin, and anti-b2 glycoprotein I antibodies (IgG and IgM) were assessed once a year [14, 15]. Moreover, treatments with aspirin (ASA) and hydroxychloroquine (HCQ) were recorded if they were prescribed at any time during the follow-up period. Dosages and duration of corticosteroids use were also recorded at each visit. Therefore, the cumulative steroid dose (prednisone equivalent for all oral, IV, SC, or IM administrations) was calculated at the end of follow-up.

Definition of prolonged remission

Criteria for PR as previously described by Zen et al. [9] were applied. PR was defined as a 5-year consecutive period of no clinical activity. To define the overall remission duration, we considered only the longest period of continuative remission before the event or before the last patient observation.

According to Zen et al. [9], patients with PR were further subdivided into three groups based on serological activity, use of immunosuppressive agents, and prednisone dose:

- Complete remission: no clinical and serological activity (SLEDAI-2K = 0) and no treatment other than antimalarials.
- Clinical off-corticosteroids remission (offCR): serological activity is allowed as well as stable immunosuppressive therapy.
- Clinical on-corticosteroids remission (onCR): serological activity is allowed as well as a daily dose of prednisone or equivalent up to 5 mg, immunosuppressants, and antimalarials.

We categorized patients as being in prolonged remission if fulfilling any of the three definitions of remission for five consecutive cohort years.

Other disease status parameters

The arithmetic mean of each patient SLEDAI values, the occurrence of flares, and disease damage were also assessed. The SLEDAI arithmetic mean, as the sum of disease activity scores divided by the numbers of all observations, was

chosen, instead of the adjusted mean, because the time interval between all visits was the same (6 months) according to the study protocol. Flares were defined by SELENA-SLEDAI [16] and disease damage by SDI [14].

Outcome variables

At each visit, any new-onset CVD was recorded. A CVD was defined as the presence of at least one of the following:

1. Ischemic heart disease (IHD), including angina pectoris (confirmed by exercise stress test) or MI (confirmed by electrocardiography and cardiac enzymes)
2. Ischemic cerebrovascular disease (ICVD), including transient ischemic attack (TIA) or stroke supported by an imaging procedure (i.e., computed tomography angiography or magnetic resonance angiography)
3. Ischemic peripheral vascular disease (IPVD): intermitted claudication or peripheral arterial thrombosis, confirmed by an imaging procedure (angiography or Doppler flow studies)

We did not exclude patients with venous thrombosis and/or with obstetric antiphospholipid syndrome (APS), who were not treated with oral anticoagulants.

Statistical analysis

Continuous variables are presented as the mean ± SD if normally distributed or as median and quartiles if distribution was skewed. Kaplan–Meier curves and the log-rank test were used to analyze differences in event-free survival. Comparisons were performed using the chi-square or Fisher's test for categorical variables and using the Wilcoxon–Mann–Whitney test or Student's unpaired test for continuous variables, as appropriate. Univariate Cox regression analysis served to identify factors associated with the occurrence of a CVD in the overall cohort. The factors found to be significant in univariate analysis were entered in the multivariate model. A p value < 0.05 was considered significant. Analyses were performed with Medcalc software, version 15.4.

Results

Baseline data

A total of 488 consecutive SLE patients were admitted to our Units from the 1st of November 2000 to 31st of December 2016. Of these, 74 had a history of CVD and were therefore excluded; 120 patients had a duration of follow-up less than 5 years, and thus, 294 SLE patients (277 women and 17 men) were included in the analysis (Fig. 1).

The main epidemiological, serological, and clinical features of the cohort at baseline are listed in Table 1. Mean age at the first visit was 37 ± 12.2. Regarding traditional thrombosis risk factors at baseline, 91 (30.9%) patients had hypercholesterolemia, 80 (27.2%) patients were smokers, 81 (27.5%) had hypertension, 11 (3.7%) were diabetics, and 15 (7.9%) patients had a body mass index (BMI) > 30 kg/m^2. The median baseline disease activity as measured by SLEDAI-2K score was 3.5 (interquartile range [IQR] = 2–8), and the median baseline SDI was 0 (IQR = 0–1).

Follow-up data

At December 31, 2017, the median duration of follow-up was 9 years (IQR 6–13 years). The median disease duration was 13 years (IQR 7–22). Out of the 294 patients, 131 (44.5%) had achieved a remission state for five consecutive cohort years. In particular, 43 (32.8%) patients achieved an immunosuppressive-free remission at all visits; 30 (22.9%) patients achieved an offCR at all visits, while an onCR was registered in 58 patients (44.2%) (Fig. 1).

A first CV event occurred in 24 (8.1%) patients. In particular, ICVD occurred in 11 patients, IHD in 10 patients, and IPVD in 3 patients. Only two events occurred in patients who had undergone PR. A stroke occurred in one male patient (smoker, with hypertension and hypercholesterolemia, and with kidney cancer) at age of 58 years, while a peripheral gangrene developed in a 66-year-old woman with aPL positivity after 12 years of follow-up.

Regarding medications, 131 (44.5%) patients had been treated with high-dose steroids (cumulative dose prednisone equivalent ≥ 40 g, which is reported to be associated with atherosclerosis in SLE) [17]. A total of 258 (87.7%) patients were prescribed HCQ at a dose of 6 mg/kg of the current body weight per day (maximum daily dose prescribed 400 mg). The

Table 1 Demographic, serological, clinical, and clinimetric characteristics of SLE patients at baseline

Patient number	294
Gender (*n*; %)	F (277; 94.2%) M (17; 5.7%)
Age, years (mean, SD)	37 ± 12.2
Active nephritis (*n*; %)	44; 14.9%
Ever smokers (*n*; %)	80; 27.2%
Obesity (*n*; %)	15; 7.9%
Hypertension (*n*; %)	81; 27.5%
Dyslipidemia (*n*; %)	91; 30.9%
Diabetes (*n*; %)	11; 3.7%
SLEDAI-2K, median (IQR)	3.5 (2–8)
SDI, median (IQR)	0 (0–1)

IQR interquartile range, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SDI* SLICC/ACR damage Index

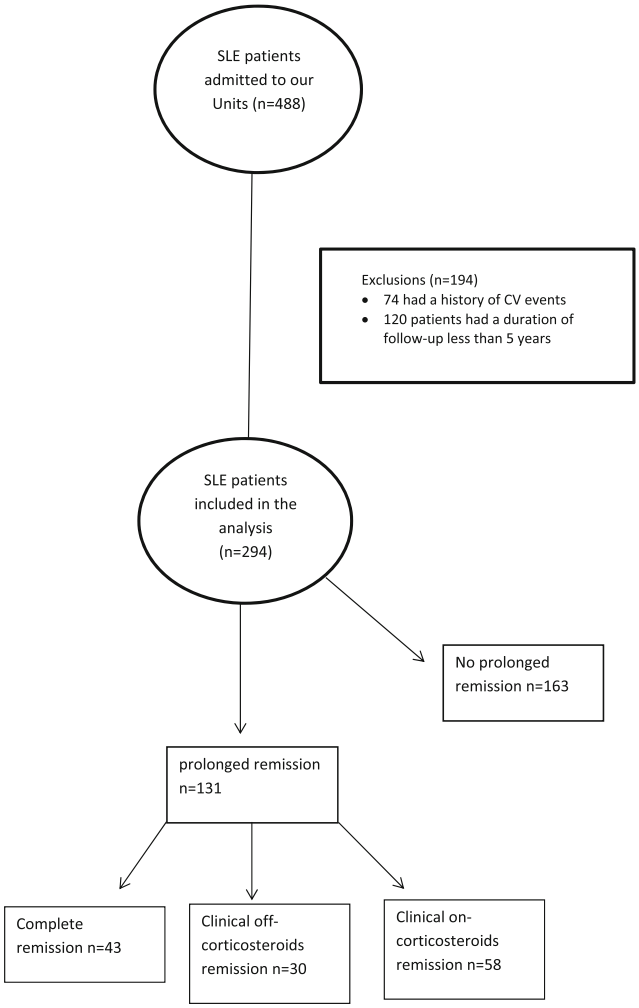

Fig. 1 Flow chart of patient selection

median treatment duration was 5 years (IQR 3–8 years). A total of 199 (67.6%) patients were treated with ASA.

Of the 488 patients, eight (1.6%) died during the study. Heart failure was the main cause of death (three patients, 37.5% of deaths). Another patient died of hepatic cirrhosis at the age of 61 years after 9 years of follow-up. In two patients, the final event was caused by active disease manifestations. Cancer was the cause of death in the remaining two cases.

Predictors of CVD

Kaplan–Meier analysis (Fig. 2) revealed a greater overall CV event-free rate in patients achieving a PR compared to both those in shorter lasting remission and those who had never achieved a remission (log-rank test $\chi^2 = 14.43$; $p = 0.0001$). No difference was detected in CV outcome among the three subgroups of PR patients ($p > 0.05$). Nevertheless, the low number of events prevents any conclusion on this topic.

Table 2 lists the features predictive of CVD at univariate analysis. With respect to those without any thrombotic event,

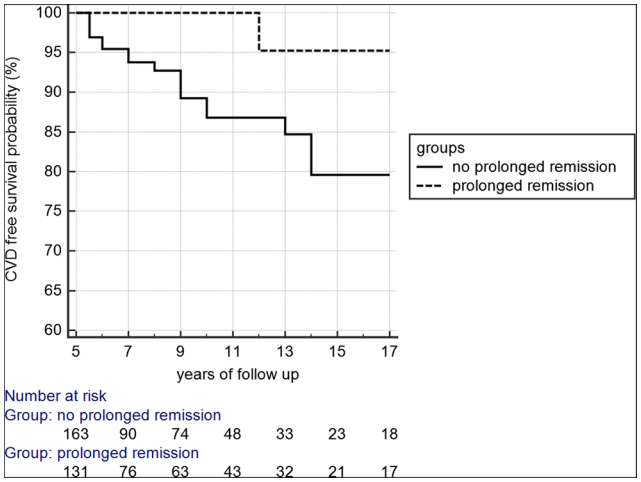

Fig. 2 Kaplan–Meier analysis

patients with a CV event had significantly higher prevalences of arterial hypertension (HR 3.05; 95%CI 1.37–6.80; $p = 0.006$) and aPL positivity (HR 2.74; 95%CI 1.22–6.14; $p = 0.013$). On the contrary, PR (HR 0.11; 95%CI 0.02–0.47; $p = 0.003$), HCQ treatment (HR 0.13; 95%CI 0.05–0.9; $p < 0.0001$) and female sex (HR 0.13; 95%CI 0.05–0.9; $p < 0.0001$) were found to be protective against CVD. No other variable, including traditional CV risk factors (smoking, obesity, hypercholesterolemia, diabetes mellitus), mean SLEDAI, disease damage, age at diagnosis, active nephritis, and high

Table 2 Factors predicting the occurrence of a first cardiovascular event during follow-up in univariate analysis (values in italics are statistically significant at an alpha of 0.05)

Features	*p* value	Hazard ratio	95% CI
aPL positivity (ever)	*0.013*	*2.74*	*1.22–6.14*
Anti-dsDNA positivity (ever)	0.781	0.88	0.37–2.08
Nephritis at baseline	0.173	1.99	0.73–5.40
Cumulative damage at baseline	0.362	1.26	0.76–2.09
Smoke (ever)	0.359	1.47	0.64–3.36
Hypertension (ever)	*0.006*	*3.05*	*1.37–6.80*
Hypercholesterolemia (ever)	0.438	1.40	0.59–3.29
Obesity (ever)	0.907	0.94	0.35–2.53
Diabetes mellitus (ever)	0.740	1.27	0.29–5.49
High cumulative steroids dose	0.146	1.89	0.80–4.47
Aspirin	0.264	0.62	0.27–1.42
Hydroxychloroquine	*< 0.0001*	*0.13*	*0.05–0.29*
Prolonged remission	*0.003*	*0.11*	*0.02–0.47*
mean SLEDAI	0.057	1.08	0.99–1.18
Age at diagnosis	0.737	1.00	0.97–1.04
Sex F	*0.006*	*0.24*	*0.09–0.67*

aPL antiphospholipid antibodies, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index

steroids dose, was found to be associated, either positively or negatively, with the occurrence of CVD. Analysis for neurological involvement was not performed to avoid the risk of incorporation bias (it is usually related to thrombotic events). ASA therapy was not associated with the development of CVD in the whole cohort, while resulted to be protective in Naples cohort (HR 0.29; 95%CI 0.08–0.95; $p = 0.04$) where it is administered to all patients (except for those in whom it is contraindicated or has to be stopped because of side effects) and not only in those with a high CV risk as assessed by traditional risk factors, as it is currently done in Rome. At multivariate analysis (Table 3), all the variables remained significantly associated with CVD, except for female sex.

Discussion

The heterogeneity of SLE has greatly delayed agreement on methods for quantification of disease activity over time. Currently, many efforts have been spent to test a definition of remission or low disease activity as a target against long-term outcome [9, 17–20], but no consensus has been achieved yet. Actually, distinct definitions of remission have been so far proposed [9, 19, 20] that present differences in four critical domains: definition of disease activity, presence of serological activity, minimal duration required, and treatment allowed.

In the present study, we considered PR as defined by Zen et al. [9] for two main reasons. First, it was achieved by approximately a third of lupus patients in two studies [9, 21], suggesting that the target would have been reached in a sizeable percentage of our cohort, making feasible a comparison among subgroups with different disease course. This would have not been the case if we would have used DORIS definition [18], which was found to be both rare and short lasting by Wilhelm et al. [22]. Secondly, PR as defined by Zen et al. [9] had been already demonstrated to be associated with an improvement in a gold standard outcome measure such as damage accrual. Our data confirm this finding, and remission in our cohort was not rare. However, in this study, we have considered patients with a follow-up of at least 5 years, to provide a considerable window to evaluate the CV disease, which is a long-term complication of SLE, as acute and chronic CV deaths are more common in those dying more than 5 years after diagnosis [23].

On the other hand, it is known that there is a continuous increase in the probability of achieving remission from the diagnosis up to 70% after 30 years of the disease duration [24] and, in part, the lengthy SLE duration of our cohort could explain the high percentage of our patients in remission.

This is the first study devoted to investigate if achieving PR is associated with a lower risk of CVD. We were able to accomplish this task because of the characteristics of our inception cohort study on SLE patients. Actually, it is a long-lasting project, characterized by visit intervals ≤ 6 months whichever the disease activity. We demonstrated that PR, as defined by clinical, serological, and therapeutic criteria, is associated with a lower risk of new occurrence of a CVD. We could not detect any difference in CV outcome among the three subgroups of PR patients, namely complete remission, offCR, and on CR. Since corticosteroids have long been implicated in increasing the CV risk in treated patients whatever the underlying disease [22], our results might suggest that at least in SLE patients, glucocorticoids do not increase CV risk if a PR is achieved. Nevertheless, the low number of events that occurred in the whole PR group prevents any conclusion on this aspect. Moreover, in our cohort, a high percentage (44.5%) of patients has been on high cumulative steroids dose, probably due to the long disease duration at admission. For these reasons, our data on the effect of steroids on CVD could be not conclusive. In that regard, in a recent report by Zen et al. [25], there was no difference between the three types of remission on damage progression in the short term, meaning that the absence of disease activity is more significant than the low daily dose of prednisone allowed in the definition of on CR. However, corticosteroids can contribute to organ damage in the long term.

Interestingly, we failed to find any predictive role of the mean SLEDAI, as already reported [4], and even a low disease activity or a short-lasting remission are not associated with any significant reduction in CV risk. Our data may indicate that a continuous period of remission is more favorable on CV outcome than the sum of short periods combined with flares.

As far as other CV predictive factors, we confirmed the negative prognostic role of arterial hypertension and aPL positivity and the protective role of HCQ, but failed to confirm in the whole cohort the protective role of ASA, previously reported in the Naples cohort [5, 6]. The absence of any ASA protective role in the Rome cohort is likely to depend on a confounding for indication bias (ASA being only prescribed in this Unit to patients with a high CV risk as assessed by traditional risk factors). These evidence might suggest to administer ASA to SLE patients, particularly to those taking glucocorticoids in whom the drug might counteract the effects of steroids on PGI2/Tx2 balance [26].

Table 3 Factors predicting the occurrence of a first cardiovascular event during follow-up in multivariate analysis (values in italics are statistically significant at an alpha of 0.05)

Features	*p* value	Hazard ratio	95% CI
aPL positivity (ever)	*0.032*	*2.48*	*1.08–5.62*
Hypertension (ever)	*0.022*	*2.61*	*1.15–5.92*
Hydroxychloroquine	*0.001*	*0.21*	*0.08–0.45*
Prolonged remission	*0.023*	*0.18*	*0.04–0.79*
Sex F	0.707	0.80	0.25–2.50

aPL antiphospholipid antibodies

Our study has some limitations. It is retrospective and includes only patients from a Mediterranean Country, who have been found to present a lower incidence of CV events [27, 28]. Therefore, our results may not be relevant for patients seen in other centers, with different ethnicity, disease characteristics, and duration. Moreover, our patients had a long disease duration at the time of inclusion in the study, and this fact could explain the high percentage of our patients in remission or with a mild disease. On the other hand, this design of the study was indispensable, because the definition of PR requires a minimum of 5-year remission.

Nevertheless, we provided a strong support to the identification of PR as surrogate outcome measure in SLE patients. In our cohort, PR was not rare, suggesting that remission using this definition could be a suitable target for SLE treatment. Actually, this condition, which had already been found to be associated with a lower damage accrual, has also resulted to imply a lower CV risk.

Compliance with ethical standards

Disclosures None.

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