Angiotensin-converting enzyme inhibitors delay the occurrence of renal involvement and are associated with a decreased risk of disease activity in patients with systemic lupus erythematosus—results from LUMINA (LIX): a multiethnic US cohort

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Objective. To examine if angiotensin-converting enzyme (ACE) inhibitor use delays the occurrence of renal involvement and decreases the risk of disease activity in SLE patients.

Methods. SLE patients (Hispanics, African Americans and Caucasians) from the lupus in minorities: nature vs nurture (LUMINA) cohort were studied. Renal involvement was defined as ACR criterion and/or biopsy-proven lupus nephritis. Time-to-renal involvement was examined by univariable and multivariable Cox proportional hazards regression analyses. Disease activity was examined with a case-crossover design and a conditional logistic regression model; in the case intervals, a decrease in the SLAM-R score ≥4 points occurred but not in the control intervals.

Results. Eighty of 378 patients (21%) were ACE inhibitor users; 298 (79%) were not. The probability of renal involvement free-survival at 10 yrs was 88.1% for users and 75.4% for non-users (P = 0.0099, log rank test). Users developed persistent proteinuria and/or biopsy-proven lupus nephritis (7.1%) less frequently than non-users (22.9%), P = 0.016. By multivariable Cox proportional hazards regression analyses, ACE inhibitors use [hazard ratio (HR) 0.27; 95% CI 0.09, 0.78] was associated with a longer time-to-renal involvement occurrence whereas African American ethnicity (HR 3.31; 95% CI 1.44, 7.61) was with a shorter time. ACE inhibitor use (54/288 case and 254/1148 control intervals) was also associated with a decreased risk of disease activity (HR 0.56; 95% CI 0.34, 0.94).

Conclusions. ACE inhibitor use delays the development of renal involvement and associates with a decreased risk of disease activity in SLE; corroboration of these findings in other lupus cohorts is desirable before practice recommendations are formulated.

Key words: Systemic lupus erythematosus, Lupus in minorities: nature vs nurture, ACE inhibitors, Renal, Disease activity.

Introduction

The renin–angiotensin system plays a crucial role in the regulation of cardiovascular and renal functions; the effects of angiotensin-converting enzyme (ACE) inhibitors in cardiovascular and renal outcomes have been extensively studied in several populations [1]. ACE inhibitors are currently used for the treatment of hypertension, heart failure, proteinuria of any cause and after myoccardial infarction. More recently they are being used to prevent microalbuminuria in patients with diabetes without clinical evidence of renal involvement [2].

It has been shown that angiotensin II has pro-inflammatory effects on cells from different organ systems; for example, angiotensin II promotes tubulointerstitial inflammation with monocytes and macrophages as well as kidney fibrosis by increasing the expression of cytokines and growth factors; it can also stimulate NADPH oxidase that is a key enzyme in the production of reactive oxygen species [3, 4]. Furthermore, elevated ACE activity has been found in the synovial membrane [5] and rheumatoid nodules [6] in patients with RA, suggesting that it plays a role in the pathogenesis of this inflammatory disease.

The beneficial effects of ACE inhibitors in patients with rheumatic diseases and in the corresponding animal models have been well demonstrated; for example, Martin et al. [7] have shown that RA patients treated with captopril exhibit a decrease in their joint symptoms, in the number of swollen joints and in the levels of CRP, whereas Godsel et al. [8] have demonstrated that captopril ameliorates experimental autoimmune myocarditis in mice.

ACE inhibitors are used for different purposes in patients with SLE; they are prescribed for hypertension and to reduce proteinuria in lupus nephritis or in diabetic nephropathy, if present. However, it is unclear whether or not ACE inhibitors, like in diabetes, may exert a beneficial effect delaying the occurrence of renal involvement; it is also unclear whether their use could be associated with a decreased risk of disease activity in SLE patients. We have now examined these possibilities utilizing data from the LUMINA (lupus in minorities: nature vs nurture) cohort.

Patients and methods

Patients

As has been previously described [9], LUMINA is a longitudinal study of outcome of SLE patients from three ethnic groups (Hispanics, African Americans and Caucasians) living in three distinct geographical areas of the United States (Texas, Alabama and the Island of Puerto Rico). Briefly, patients who meet the ACR criteria for the classification of SLE, have a disease duration ≤5 yrs, are ≥16 yrs of age at the time of enrolment into the cohort, are of defined ethnicity (all four grandparents of the same ethnicity as the patient) and live in the geographic catchment areas of the participating institutions, are eligible to participate. The institutional review board of each participating centre approved the LUMINA study; written informed consent was obtained from each patient according to the Declaration of Helsinki.

Prior to enrolment, all medical records are reviewed; this is done to confirm the patients’ eligibility and to gather information

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about their socioeconomic-demographic and clinical features before disease onset and the enrolment visit. Every patient has a baseline visit (T0); follow-up visits are conducted every 6 months for the first year (T0.5 and T1, respectively) and yearly thereafter until the last visit (Tn and TL, respectively). Each LUMINA study visit consists of an interview, a physical examination and laboratory tests. Data for missed study visits are obtained, whenever possible, by review of all available medical records.

Only those patients who were free of renal disease (as defined below) at T0 were included in the analyses of the effect of ACE inhibitors in the occurrence of renal involvement.

**Variables**

As previously reported [9], the LUMINA database includes variables from the following domains: socioeconomic-demographic, clinical, immunological, behavioural and psychological. These variables are ascertained at T0 and at every subsequent visit. The variables described subsequently are those included in the renal involvement analyses unless otherwise noted.

Variables from the socioeconomic-demographic domain are age, gender, ethnicity, years of education and smoking status. Clinical variables are disease duration defined as the interval between the time at which patients met the ACR criteria (TD) and T0, number of ACR criteria at T0 (renal criterion excluded) and hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on two or more occasions). Renal involvement was defined as ACR criteria (persistent proteinuria >0.5 g/day or >3+ by urinalysis) and/or biopsy-proven lupus nephritis occurring after patients met ACR criteria; patients with renal involvement, as defined, prior to criteria diagnosis were excluded from these analyses.

Disease activity was assessed using the SLAM-Revised (SLAM-R) [10] at all visits; a weighted average SLAM-R score was calculated from T0 to TL as a measure of disease activity over time by multiplying the SLAM-R score at each individual visit by the number of months in the preceding interval; these scores were then added up and averaged over the total disease duration. Damage was measured with the SLICC damage index (SDI) [11] at TL. Changes in the SLAM-R score were used for the disease activity analyses (see below).

Cumulative exposure to HCQ, glucocorticoids (as prednisone equivalent) and cyclophosphamide pulses were ascertained. The average dose of these medications were computed at each study visit taking into account the dose taken every month; a weighted average from T0 to TL was then calculated by multiplying the average dose for each individual visit by the number of months in the interval between visits and dividing it by the total follow-up time (T0–TL).

The primary independent variable of interest in this study was the use of ACE inhibitors. Given the observational nature of our cohort, ACE inhibitors are prescribed by the patients’ treating physicians (rheumatologists or primary care physicians, for the most part) but not by study physicians. ACE inhibitors use was defined as the intake of a compound from this family of drugs prior to the outcome of interest independent of dose, duration and possible indication (hypertension, chronic heart failure, diabetes mellitus, RP, myocardial infarction and pulmonary arterial hypertension); as per the LUMINA protocol, exposure was recorded as present if documented at the time of the study visit or at any time during the interval between visits. Patients who had not received ACE inhibitors at any time during or between visits were considered non-exposed. For the disease activity analyses, ACE inhibitor use was considered present if it had occurred at any time during the case or control interval being examined (see subsequently).

**Statistical analyses**

**Renal involvement.** The association between the use of ACE inhibitors (up to the time of renal involvement for those patients who developed it and up to TL for all other patients) and renal involvement was examined by univariable and multivariable Cox proportional hazards regression analyses. Variables previously known to affect renal involvement (education, smoking, ACR criteria number, total disease duration and hypertension) [12], those felt to be clinically relevant (age, gender and ethnicity) and the use of ACE inhibitors were entered into the multivariable analysis.

An alternative multivariable Cox proportional hazards regression model in which use of ACE inhibitors was excluded was also examined given the collinearity between their use and hypertension.

**Disease activity.** To examine if SLE patients using ACE inhibitors may experience a decreased risk of disease activity when compared with those patients not using them, a case-crossover study was designed [13]. Using this design, cases were matched with themselves thereby minimizing the role of confounding. An interval, or the period between two consecutive visits, was used as the unit of the analysis. A case interval was defined as one in which a decrease in the SLAM-R score >4 points occurred [14] whereas a control interval was one in which such a decline did not occur. Only patients in whom both intervals occurred were included. As many control intervals as were available were selected for each patient; exposure to ACE inhibitors at any time during the case and control intervals was recorded. The association between disease activity and the use of ACE inhibitors was examined with a conditional logistic regression model; given the case-crossover design, adjustment for possible confounding variables known to affect disease activity was not indicated and thus, not performed.

Statistical significance was defined as a P-value <0.05 for both sets of analyses. All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

**Ace inhibitor use and renal involvement**

Three hundred and seventy-eight patients without renal involvement at T0 were included in these analyses. Of them, 80 (21%) were ACE inhibitor users and 298 (79%) were not. The large majority of the 80 patients on ACE inhibitors were hypertensive (91%); however, more than one possible indication for their use was common (42 patients had two and nine had three). Forty-four (12%) of the patients had 1+ proteinuria at T0 but did not meet the definition of renal involvement and were, therefore, included in these analyses; a higher proportion of them were in the ACE inhibitor user group (18.6% vs 10.4%) but this difference did not reach statistical significance (P = 0.054).

The baseline characteristics of these patients are shown in Table 1. Ninety-one percent of the patients were women; their mean (s.d.) age, number of years of education and ACR

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of LUMINA patients free of renal disease*</th>
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<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
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<tr>
<td>Age, yrs, mean (s.d.)</td>
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<tr>
<td>Ethnicity, n (%)</td>
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<tr>
<td>Education, yrs, mean (s.d.)</td>
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<tr>
<td>ACR criteria number at diagnosis, mean (s.d.)</td>
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<tr>
<td>Smoking, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
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</tbody>
</table>

*As per American College of Rheumatology criterion and/or biopsy proven lupus nephritis.
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criteria number at TD were 38.6 (12.8) yrs, 13.2 (3.1) yrs and 4.9 (1.0), respectively. The ethnic groups were represented as follows: 57 (15%) Hispanic-Texans, 78 (21%) Hispanic-Puerto Ricans, 104 (27%) African Americans and 139 (37%) Caucasians. There were no differences in the prevalence of ACE inhibitor use between the ethnic groups (P = 0.234). Fifty-five (15%) of the patients were smokers, 98 (26%) had hypertension and 15 (4%) had diabetes mellitus at baseline.

The Kaplan–Meier survival curve for renal involvement is depicted in Fig. 1. The probability of renal involvement-free survival at 10 yrs was 88.1% for the ACE inhibitor users and 75% for the non-users; P = 0.0099 by the log rank test.

ACE inhibitor users developed persistent proteinuria and/or biopsy-proven lupus nephritis less frequently than non-users (7.1% vs 22.9%, P = 0.0016). Treatment for lupus including the average HCQ and glucocorticoid doses in milligrams per day and the mean number of cyclophosphamide pulses were comparable among ACE inhibitor users and non-users (data not shown).

The results of the univariable and multivariable Cox proportional hazards regression analyses are shown in Table 2. By univariable analyses, Hispanic-Texan [Hazard Ratio (HR) 3.94; 95% CI 1.58, 9.81] and African American (HR 4.73; 95% CI 2.13, 9.81) ethnicities were associated with a shorter time-to-renal involvement occurrence whereas older age (HR 0.96; 95% CI 0.94, 0.99), greater number of years of education (HR 0.90; 95% CI 0.83, 0.97) and the use of ACE inhibitors (HR 0.31; 95% CI 0.12, 0.79) were associated with a longer time-to-renal involvement occurrence.

In the multivariable analysis the use of ACE inhibitors (HR 0.27; 95% CI 0.09, 0.78) was associated with a longer time-to-renal involvement occurrence; in contrast, African American ethnicity (HR 3.31; 95% CI 1.44, 7.61) was independently associated with a shorter time. In the alternative model, excluding the ACE inhibitors variable, the results were overall consistent with those described earlier; hypertension was not significant (data not shown).

**ACE inhibitor use and disease activity**

Two hundred and eighty-eight patients provided 288 case intervals and 1148 control intervals for these analyses. Ninety percent of these 288 patients were women, 20% Hispanic-Texans, 16% Hispanic-Puerto Ricans, 38% African Americans and 26% Caucasians. Their mean (s.d.) age was 36.1 (12.0) yrs. The use of ACE inhibitors occurred in 54 of the case intervals (18.8%) and in 254 of the control intervals (22.2%).

Among the case intervals, the difference in the mean SLAM-R score between those exposed and unexposed to ACE inhibitors favoured the exposed with somewhat lower scores [4.2±(3.2) vs 4.8±(3.5); P = 0.23]. The use of ACE inhibitors (54/288 vs 254/1148) was associated with a decreased risk of disease activity (HR 0.56; 95% CI 0.34, 0.94; P = 0.026) by conditional logistic regression analysis.

**Discussion**

We are reporting for the first time the negative association between the use of ACE inhibitors and time-to-renal involvement occurrence as well as with a decreased risk of disease activity in patients with SLE. The case-crossover design to assess this effect on disease activity allows for the matching of potential confounding variables between users and non-users as each patient provides both, case and control intervals. We have also corroborated the association between African American ethnicity and a shorter time-to-renal involvement in these patients. As noted, the large majority of our patients were hypertensive but some of them also had one to three other possible indications for the use of ACE inhibitors. So despite these comorbidities, patients on ACE inhibitors did better than those not on them in terms of both, renal involvement development and disease activity; moreover, the effect of ACE inhibitors on renal involvement was independent of hypertension.

ACE inhibitors, used for the treatment of hypertension, are currently being used to treat cardiac (heart failure and post-myocardial infarction) and renal (proteinuria) events. Based on studies of patients with a number of different nephropathies, ACE inhibitors have been routinely used to reduce proteinuria in patients with lupus nephritis. Specific studies in lupus nephritis are, however, very few. Daza et al [15], for example, have reported that lupus nephritis patients treated with prednisone and cyclophosphamide plus captopril showed a decrease in the rate of proteinuria and in urine prostanglandin E2 at 6 months of treatment and Tse et al [16] have shown that lupus nephritis patients with persistent proteinuria (>1 g/day) treated with ACE inhibitors (n = 12) or angiotensin II receptor blockers (ARBs) (n = 2) diminished their proteinuria and improved their serum albumin from baseline. Furthermore, De Albuquerque et al. [17] have shown that captopril treatment delays the onset of proteinuria in lupus mice and this improvement correlates with reduced expression of TGF-β in the kidneys and of splenic levels of type 2 cytokines (IL-4 and IL-10).

ACE inhibitors are a group of compounds that inhibit the conversion of angiotensin II by removing the C-terminal His–Leu dipeptide of angiotensin I; they also prevent the inactivation of bradykinin and kallidin peptides. Mechanisms by which ACE inhibitors exert a protective effect against renal involvement are not well understood but the effect appears to be independent of

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**Table 2. Predictors of time-to-renal involvement occurrence in LUMINA patients by Cox proportional hazard regression analyses**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96 (0.94, 0.99)</td>
<td>0.97 (0.95, 1.00)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>0.62 (0.27, 1.38)</td>
<td>0.63 (0.27, 1.47)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>3.94 (1.58, 9.81)</td>
<td>2.70 (0.98, 7.45)</td>
</tr>
<tr>
<td>Hispanic-Texan</td>
<td>1.32 (0.45, 3.84)</td>
<td>1.63 (0.54, 4.87)</td>
</tr>
<tr>
<td>African American</td>
<td>4.73 (2.13, 10.50)</td>
<td>3.31 (1.44, 7.61)</td>
</tr>
<tr>
<td>Education</td>
<td>0.90 (0.83, 0.97)</td>
<td>0.91 (0.83, 1.01)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.22 (0.52, 2.86)</td>
<td>1.20 (0.49, 2.89)</td>
</tr>
<tr>
<td>ACR criteria number</td>
<td>0.90 (0.66, 1.21)</td>
<td>0.79 (0.59, 1.06)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.07 (0.99, 1.16)</td>
<td>1.08 (0.99, 1.17)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.78 (0.40, 1.53)</td>
<td>1.34 (0.62, 2.87)</td>
</tr>
<tr>
<td>Use of ACE inhibitors</td>
<td>0.31 (0.12, 0.79)</td>
<td>0.27 (0.09, 0.78)</td>
</tr>
</tbody>
</table>

*aCaucasian is the reference group.*
their anti-hypertensive effect. For example, ACE inhibitors can increase bradykinin half-life and its accumulation, resulting in the induction of endothelial nitric oxide (NO); they also reduce the post-glomerular capillary pressure by opening the efferent arterioles and can affect the hydraulic permeability of the glomerular capillaries [18]. Some other properties have been postulated because of its chemical structural similarities with D-penicillamine; in fact, captopril and D-penicillamine share a thiol or sulphydryl group that is thought to be responsible for the immunomodulatory effects of both components [19]. These immunomodulatory properties probably explain the favourable effect of the use of ACE inhibitors on disease activity that we have observed in our patients.

Our study is not without some limitations. First, we were unable to examine the type of ACE inhibitor used as this information is not part of the LUMINA database. Second, we could not examine the dosage or duration of ACE inhibitor treatment because the exposure was recorded only as present if they were taken during the interval between the visits. Finally, given the observational nature of our cohort, the decision to use or not to use ACE inhibitors did not follow a specific algorithm; rather, it was made by the treating physician.

SLE patients are at high risk for cardiovascular events and to accrue damage; therefore, they should be treated early to prevent serious complications. The literature supports the use of relatively safe medications such as HCQ [20], low-dose aspirin [21–23] and possibility of statins [24] to prevent damage accrual, prolong survival and diminish these patients’ cardiovascular risk. ACE inhibitors could now be added to this list regardless of blood pressure levels.

In summary, we are reporting for the first time that the use of ACE inhibitors is associated with a delay in the occurrence of renal involvement and a decreased risk of disease activity in lupus patients. Our data are relevant particularly to high-risk patients such as African Americans and some Hispanics subgroups who have not developed but who are known to develop renal involvement more frequently than patients from other ethnic groups and who tend to experience higher degrees of disease activity. Whether ACE inhibitors could be used in all lupus patients free of renal disease will depend on the independent confirmation of our findings.

Rheumatology key messages

- The use of ACE inhibitors in SLE patients is associated with a delay in the occurrence of renal involvement.
- Their use is also associated with a decreased risk of disease activity in these patients.
- Whether ACE inhibitors could be used in all lupus patients depends on corroborating studies.

Acknowledgements

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