Early Renin-angiotensin System Blockade Improved Short-term and Longterm Renal Outcomes in Systemic Lupus Erythematous Patients with Antiphospholipid-associated Nephropathy

Cai Yue, Guanhong Li, Yubing Wen, Xuemei Li, and Ruitong Gao

ABSTRACT. Objective. To investigate the renal protective effects of early renin-angiotensin-aldosterone system (RAAS) blockade with renin-angiotensin system inhibitors (RASI) in systemic lupus erythematosus (SLE) patients with antiphospholipid-associated nephropathy (aPLN).

Methods. Medical data of 57 SLE patients with biopsy-proven aPLN were analyzed. Early RAAS blockade was defined as administration of RASI within 3 months after kidney biopsy and continued for ≥ 12 months.

Results. There was no significant difference in demographic data, laboratory findings, and renal histology by the time of kidney biopsy, except that the RASI group had higher proteinuria levels vs the non-RASI group [5.2 (2.8–8.8) vs 1.9 (0.6–2.8) g/d, p = 0.005, respectively] and higher prevalence of hypertension (75% vs 29%, p = 0.001, respectively). No significant difference between the 2 groups was observed in estimated glomerular filtration rate (eGFR), mean arterial pressure, and proteinuria level at 12 months after kidney biopsy. The improvement ratio of eGFR at 12 months was significantly higher in the RASI group versus the non-RASI group [26% (–5 to 86) vs –2% (–20 to 20), p = 0.028, respectively], and the rate of change in eGFR beyond 12 months was similar between the 2 groups. During a mean followup of 80 months, 4 (23%) patients in the non-RASI group and 3 (8%) patients in the RASI group developed kidney disease progression. Early RAAS blockade significantly decreased the risk of kidney disease progression [HR = 0.11 (0.02–0.59); p = 0.010]. Proteinuria and hypertension controls were similar between the 2 groups.

Conclusion. Early RAAS blockade improved the short-term and longterm renal outcomes in SLE patients with aPLN. The renal protective effect of RASI was independent of its antihypertensive and antiproteinuric effects. (J Rheumatol First Release February 15 2018; doi:10.3899/jrheum.170561)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
ANTIPHOSPHOLIPID SYNDROME
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

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Lupus nephritis (LN) develops in ≤ 60% of patients with systemic lupus erythematosus (SLE)1. Apart from the glomerular lesions seen in LN, patients with SLE may develop renal vasculopathies that may be identical to findings in patients with primary antiphospholipid syndrome (APS), and these lesions are correlated with antiphospholipid antibodies (aPL). In the most recent consensus criteria of APS, the term antiphospholipid-associated nephropathy (aPLN) was suggested to describe the entity of renal vasculopathies associated with aPL. Characteristic histopathologic changes of this disease entity include thrombotic microangiopathy (TMA), fibrous intimal hyperplasia (FIH) involving organized thrombi, fibrous and/or fibrocellular occlusions of arteries and arterioles, focal cortical atrophy (FCA), and tubular thyroidization2.

Coexisting aPLN is associated with more severe renal involvement and worsened renal outcome in patients with
SLE. In patients with SLE and renal involvement, it is crucial to distinguish between patients who have LN, which is immune-complex mediated, and those who have impaired kidney function related to aPL. However, the optimal treatment regimen for aPLN is not yet clear. Treatment modalities include immunosuppressive therapy, anticoagulants, or antithrombotic agents in selected patients, inhibitors of mammalian target of rapamycin complex (mTORC), and renin-angiotensin system inhibitors (RASI).

Renin-angiotensin-aldosterone system (RAAS) blockade with RASI has been shown to have a renal protective effect on renal vasculopathies other than aPLN, such as renal microangiopathies associated with scleroderma renal crisis, hemolytic uremic syndrome, and malignant hypertension (HTN). In these settings, RAAS blockade may induce beneficial vasodilatation, thus halting or even reversing the pathologic processes. However, except for anecdotal case reports, literature pertaining to RAAS blockade in aPLN is limited. Considering the features of vasculopathies and kidney ischemia in aPLN, there is a strong chance that patients with aPLN may benefit from RAAS blockade.

Our study aimed to investigate the renal protective effect of RASI in SLE patients with aPLN.

MATERIALS AND METHODS

Study cohort and data collection. Registered patients from the SLE-aPLN cohort at Peking Union Medical College Hospital were selected. Eligibility criteria for the cohort study included the following: (1) fulfilled the 1997 revised American College of Rheumatology classification criteria for the diagnosis of SLE; (2) positive for any serum aPL, including anticardiolipin antibody, anti-β₂-glycoprotein I antibody, or lupus anticoagulant, tested twice 12 weeks apart; and (3) positive for ≥1 histological features of aPLN by renal biopsy.

From January 2000 to December 2015, 1178 patients with SLE underwent kidney biopsy at the Division of Nephrology at Peking Union Medical College Hospital. Among them, 231 patients were positive for serum aPL, and their renal specimens were further analyzed, with a focus on pathological features of aPLN. Among them, 73 were eligible for the cohort, and 57 had a follow-up period of >12 months (Figure 1). Patients were followed up every 1–3 months during the first year, and 1–12 months during the following years as routine clinical practice. Baseline demographic, clinical, serologic, and medication data were collected by the time of kidney biopsy. Follow-up data were obtained at 3 months, 6 months, and yearly after kidney biopsy.

Our study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking Union Medical College Hospital in Beijing (approval number S-K261). All patients gave informed consent to participate in the study.

Histology of kidney biopsy samples. The methods of renal tissue preparation and staining have been reported previously. Briefly, the renal tissues obtained by biopsy were fixed in 10% neutral buffered formalin, dehydrated gradually, and embedded in paraffin. Paraffin-embedded tissue sections were stained with H&E, periodic acid-Schiff, Masson trichrome, and periodic acid–silver methenamine. Small portions of fresh renal tissue were snap frozen, and 4-mm cryostat-cut sections were incubated with fluorescein isothiocyanate–conjugated rabbit antisera against human immunoglobulin (Ig) G, IgA, IgM, complement factor C1q, C3, and C4 (Dako), and the direct immunofluorescence of these sections was examined. The biopsy specimens of the patients with SLE were classified using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN. The classification data are given in Table 1.

RESULTS

Clinical features. Baseline characteristics of the 57 patients are listed in Table 1. There was no significant difference in age, female percentage, and eGFR between the 2 groups. However, patients who received early RAAS blockade (RASI group) had more severe renal involvement compared to those who did not (non-RASI group), including higher prevalence of HTN (75% vs 29%, p = 0.001) and higher proteinuria level (5.2 (2.8–8.8) vs 1.9 (0.6–2.8) g/d, p = 0.005).

Kidney biopsy. All 57 patients underwent kidney biopsy (Table 1). There were 45 (79%) patients who had class III or IV LN according to the ISN/RPS classification. The percentages of class III or IV LN were similar between the RASI group and non-RASI group (respectively, 78% vs 82%, p = 0.955). Overall, 12/57 (21%) had acute aPLN, defined as observation of TMA in renal specimen. Percentages of acute aPLN were also similar between the 2 groups (25% vs 11%, p = 0.443). Among all patients (n = 57), FIH was the most common histological feature.
Figure 1. Flow chart of patient selection. aPL: antiphospholipid antibodies; aPLN: aPL-associated nephropathy; PUMCH: Peking Union Medical College Hospital; SLE: systemic lupus erythematosus.

Table 1. Demographic data, laboratory findings, renal histology, and initial treatment of SLE patients with aPLN by the time of renal biopsy. Values are mean ± SD, median (IQR), or n (%) unless otherwise specified.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-RASI, n = 17</th>
<th>RASI, n = 40</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>33.9 ± 12.4; 40 (22–48)</td>
<td>34.6 ± 9.9; 33 (28–43)</td>
<td>0.818</td>
</tr>
<tr>
<td>Female</td>
<td>13 (76)</td>
<td>30 (75)</td>
<td>0.827</td>
</tr>
<tr>
<td>APS</td>
<td>1 (6)</td>
<td>6 (15)</td>
<td>0.604</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>79.6 ± 43.7; 102 (55–125)</td>
<td>62.4 ± 28.8; 53 (35–85)</td>
<td>0.150</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>100 ± 19; 95 (85–98)</td>
<td>111 ± 21; 113 (90–128)</td>
<td>0.083</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (29)</td>
<td>30 (75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Proteinuria level, g/d</td>
<td>1.9 (0.6–2.8)</td>
<td>5.2 (2.8–8.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Proteinuria, ≥ 3.5 g/d</td>
<td>4 (24)</td>
<td>26 (65)</td>
<td>0.004</td>
</tr>
<tr>
<td>ISN/RPS class III or IVª</td>
<td>14 (82)</td>
<td>31 (78)</td>
<td>0.955</td>
</tr>
</tbody>
</table>

Pathological features of aPLN

| TMA                                            | 2 (11)           | 10 (25)      | 0.443 |
| FIH                                            | 16 (94)          | 30 (75)      | 0.191 |
| Fibrous/fibrocellular occlusions of arteries and arterioles | 5 (29) | 3 (8) | 0.078 |
| FCA                                            | 5 (29)           | 3 (8)        | 0.078 |
| Tubular thyroidization                          | 5 (29)           | 7 (18)       | 0.513 |

| Treatment                                       |                  |              |       |
| Mean prednisone dose, mg/d                      | 53.1 ± 12.3      | 49.8 ± 16.9  | 0.538 |
| CYC                                            | 14 (82)          | 34 (85)      | 0.883 |
| MMF                                            | 4 (24)           | 8 (20)       | 0.955 |
| Calcineurin                                     | 3 (18)           | 7 (18)       | 0.713 |
| Antiplatelet agents                             | 3 (18)           | 12 (30)      | 0.522 |
| Anticoagulants                                  | 4 (24)           | 6 (15)       | 0.694 |

ªISN/RPS class III + V and IV + V of LN are included. Data in bold face are statistically significant. SLE: systemic lupus erythematosus; aPLN: antiphospholipid-associated nephropathy; IQR: interquartile range; RASI: renin-angiotensin system inhibitor; APS: antiphospholipid syndrome; eGFR: estimated glomerular filtration rate; MAP: mean arterial blood pressure; ISN/RPS: International Society of Nephrology/Renal Pathology Society; TMA: thrombotic microangiopathy; FIH: fibrous intimal hyperplasia; FCA: focal cortical atrophy; CYC: cyclophosphamide; MMF: mycophenolate mofetil; LN: lupus nephritis.
common histological finding of aPLN [46 (81%)], followed by TMA [12 (21%)], and tubular thyroidization [12 (21%)].

Treatment. As the initial treatment, all patients received corticosteroids and ≥ 1 immunosuppressive agents (Table 1). Twenty-one patients (37%) received either antiplatelet agents or anticoagulants. Specifically, 10 received warfarin, with the INR titered to 2–3 (among whom 4 received concomitant aspirin) and 11 received aspirin alone. There were no significant differences of immunosuppressive therapy or antiplatelet/anticoagulation therapy between the 2 groups.

For the 40 patients who received early RAAS blockade, the equivalent dosages of ACE-I/ARB were fosinopril 10 mg/d in 20 (50%) patients, 20 mg/d in 14 (35%) patients, 30 mg/d in 4 (10%) patients, and 40 mg/d in 2 (5%) patients.

Responses to treatment at 12 months. Patient responses to treatment at 12 months after renal biopsy are summarized in Table 2. Despite the RASI group having more severe renal involvement at baseline, there was no significant difference in eGFR, MAP, and proteinuria level at 12 months after kidney biopsy. Notably, the improvement ratio of eGFR at 12 months was significantly higher in the RASI group [26% (–5 to 86) vs –2% (–20 to 20), p = 0.028], but the improvement ratios of proteinuria and MAP were similar between the 2 groups.

The RASI group was further divided into 2 subgroups according to the presence of TMA. Baseline and 12-month responses to treatment were evaluated in subgroups. Among the 40 patients receiving early RAAS blockade, 10 had TMA. Demographic data and baseline characteristics were similar, with acute and chronic aPLN, except that the acute aPLN group had lower eGFR at baseline [46 (20–60) vs 70 (46–92) ml/min/1.73m², p = 0.026], which continued to be lower at 12 months after kidney biopsy [65 (48–86) vs 94 (64–108) ml/min/1.73 m², p = 0.021] compared to the chronic aPLN group (data not shown). There was no significant difference in HTN and proteinuria levels at baseline and 12 months, nor in the improvement ratios of MAP, proteinuria, and eGFR.

Rate of change in eGFR beyond 12 months. There was no statistically significant difference in rates of change in eGFR from 12 months postbiopsy to the end of followup between the RASI and non-RASI groups [0.0 (–3.0 to 2.0) vs 1.0 (–0.5 to 9.5) ml/min/1.73 m² per year, p = 0.086]. The result was similar after adjustment for baseline eGFR and MAP with a mixed linear model (p = 0.162; data not shown).

Kidney disease progression. During a mean of 80 months’ followup (≥ 12 mos after kidney biopsy), kidney disease progression in each group was determined. Four (23%) patients in the non-RASI group and 3 (8%) patients in the RASI group developed kidney disease progression, defined as ESKD or a 30% decline in eGFR. The median (IQR) interval from kidney biopsy to kidney disease progression was 9 (6–36) months for non-RASI group, and 36 (36–40) months for RASI group. After adjustment for baseline MAP and its interaction with eGFR, early RAAS blockade significantly decreased the risk of kidney disease progression (HR 0.11, 95% CI 0.02–0.59, p = 0.010). The result was similar, with kidney disease progression defined as 15% decline of eGFR or progression to ESKD, and 50% decline of eGFR or progression to ESKD (Table 3, Figure 2).

Control of HTN and proteinuria. Cumulative incidence of proteinuria control and HTN control were compared using a Cox regression model adjusted for baseline proteinuria or MAP. There was no significant difference for proteinuria control for all levels, or blood pressure control between the RASI and non-RASI groups.

Risk factors for kidney disease progression. Risk factors for kidney disease progression in the RASI group (n = 40) were investigated with binary logistic regression and Cox regression (Table 4). Baseline proteinuria was correlated with kidney disease progression (HR 1.20, 95% CI 1.00–1.45, p = 0.046). A borderline correlation between baseline eGFR and poor kidney outcome (HR 0.95, 95% CI 0.90–1.00, p = 0.073) was also observed.

DISCUSSION

To our knowledge, this is the first study to investigate the short-term and longterm renal protective effects of early RAAS blockade in patients with aPLN associated with SLE. Results showed that although kidney involvement in patients with aPLN who received early RAAS blockade were more severe at baseline, there was better early improvement of kidney function at 12 months, and similar eGFR change during the following years, compared with patients who did not receive early RAAS blockade. Moreover, early RAAS blockade significantly reduced the risk of kidney disease progression by 90%.

Evidence has shown that RASI is effective in proteinuria control and blood pressure control, and is more effective than other antihypertensive agents in slowing the progression of chronic kidney disease13,22,23. However, in patients with aPLN, the renal protective effects of RASI seemed to be independent of its effects of proteinuria amelioration and
developed kidney disease progression. However, for patients who were normotensive at baseline, only 2/4 (50%) were normotensive at baseline (SBP = 110/80 and DBP = 75/40 mmHg). These patients might benefit from early RAAS blockade despite normal baseline blood pressure.

In renal vasculopathies associated with aPLN, TMA or FIH may cause narrowing and occlusions of interrenal arterioles and arterioles, subsequent ischemic change of glomeruli, and renal impairment. It was demonstrated that treatment inhibits intimal hyperplasia; specifically, mTORC inhibitors protected kidney transplant from loss of function in transplant recipients with aPLN. The effectiveness of RASI in halting, and even reversing, the pathologic processes of aPLN can be attributed to its 2 outcomes: interrupting the renin-angiotensin system, and hence attenuating angiotensin II-induced vasoconstriction, and interfering with the degradation of bradykinin, thus inducing a beneficial vasodilatation of the renal vessels.

Our findings provide some additional information for the use of RASI in the treatment of aPLN. First, it might be important to start RASI early. In the non-RASI group, 3/4 (75%) of kidney disease progression took place within the first year, at an average of 8 months after kidney biopsy. In comparison, there was no early kidney disease progression in the RASI group, and the average interval from biopsy to kidney disease progression was 37 months. Early RAAS blockade might effectively slow down the progression of aPLN.

Second, patients with aPLN who were normotensive at baseline may also experience rapid kidney disease progression and thus may benefit from RAAS blockade. It seemed that physicians tend to prescribe RASI in the setting of HTN or proteinuria. As we observed, patients with aPLN who received early RAAS blockade had more prevalent HTN and higher proteinuria level compared to those who did not. For patients with aPLN who received early RAAS blockade, only individuals with extreme HTN [MAP 130 (120–130) mmHg] developed kidney disease progression. However, for patients who had kidney disease progression in the non-RASI group, 2/4 (50%) were normotensive at baseline (SBP = 110/80 and DBP = 130/80 mmHg). These patients might benefit from early RAAS blockade despite normal baseline blood pressure.

Third, patients with high risk of kidney disease progression might benefit more from early RASI treatment. As our research demonstrated, baseline proteinuria was a risk factor for progression of kidney disease in aPLN associated with SLE. All patients who had kidney disease progression had baseline proteinuria > 10 g/d. However, 3 patients (75%) in the non-RASI group developed kidney disease progression despite a non-nephrotic proteinuria range [2.8 (2.6–3.0) g/d]. Considering the effect of proteinuria on kidney disease progression, it might be reasonable to suggest early RAAS blockade in patients with aPLN who have an albuminuria level of > 0.3 g/d, especially those who have a proteinuria level of > 1 g/d.

The optimal dose of RASI for treatment of aPLN is not yet clear. However, it seems that patients might benefit from even a small dose of RASI. In our cohort, the daily dose of RASI in a majority of patients was ≤ 20 mg fosinopril. It is worthwhile to further evaluate whether patients with aPLN who have a high risk of developing kidney disease progression may benefit from a higher dose of RASI.

The optimal duration of RASI therapy is another question to be answered. In our cohort, both acute and chronic aPLN benefited equally from RASI therapy, so it is reasonable to suggest that RASI therapy be continued as long as there are no adverse effects.

The most important concern of RAAS blockade is that it might decrease eGFR, causing acute kidney injury in certain patients, especially those with low baseline eGFR. However, none of the patients in our study experienced decline attributable to RAAS blockade. In patients who received early RAAS blockade, the baseline eGFR were...
Figure 2. Cumulative incidence of kidney disease progression in SLE patients with aPLN: (A) 15% decline of eGFR or ESKD; (B) 30% decline of eGFR or ESKD; and (C) 50% decline of eGFR or ESKD. SLE: systemic lupus erythematosus; aPLN: antiphospholipid-associated nephropathy; eGFR: estimated glomerular filtration rate; ESKD: endstage kidney disease; RASI: renin-angiotensin system inhibitor.
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18. Nochy D, Daugas E, Droz D, Beaumil F, Grunfeld JP, Piette JC, et al. Baseline proteinuria, for each 1.0-g/day increase 0.56 (0.29–1.09) 0.088 0.62 (0.36–1.05) 0.073
Baseline proteinuria, for each 1.0-g/day increase 1.28 (0.99–1.66) 0.057 1.20 (1.00–1.45) 0.046
Baseline MAP, for each 10-mmHg increase 1.53 (0.80–2.93) 0.198 1.43 (0.82–2.49) 0.210

Kidney disease progression is defined as 30% decline of eGFR or ESKD without remission until the end of followup. Data in bold face are statistically significant. RASI: renin-angiotensin system inhibitor; SLE: systemic lupus erythematosus; aPLN: antiphospholipid-associated nephropathy; ISN/RPS: International Society of Nephrology/Renal Pathology Society; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; MAP: mean arterial pressure; ESKD: endstage kidney disease.

< 30 ml/min/1.73 m² in 4 (10%) patients (15 ± 4 ml/min/1.73 m²). In these patients, RASI were titrated carefully from a very small dose. Hyperkalemia associated with RAAS blockade is another concern. In our observation, only 1 patient developed hyperkalemia associated with RASI; it was resolved after reducing RASI to a lower dose.

Our study has several limitations. First, the cohort was small, with limited patients. The number of patients who had kidney disease progression was small. Although we verified our conclusions by adopting different definitions of kidney disease progression, these conclusions still need to be confirmed in further studies. Second, the optimal dose and duration of RASI treatment remains unclear. We suggested that RASI should be continued as long as the patient has no adverse effects. However, the cutoff point needs to be verified in further studies. Whether patients may benefit from a maximal tolerable dose of RASI also needs verifying. Third, we believe aPLN is not well recognized by some clinicians, so a considerable portion of patients did not receive an anticoagulant or antiplatelet agent, which may have interfered with the results of our study. Well-designed prospective studies are needed to answer these questions.

Early RAAS blockade improved the short-term and longterm renal outcomes in SLE patients with aPLN, and the renal protective effect of RASI was independent of its anti-hypertensive and antiplatelet effects. Early RAAS blockade may be considered in SLE patients with aPLN.

Table 4. Risk factors for kidney disease progression in RASI group of SLE patients with aPLN.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.90–1.14)</td>
<td>0.845</td>
<td>1.01 (0.91–1.12)</td>
<td>0.878</td>
</tr>
<tr>
<td>ISN/RPS class III or IV, LN</td>
<td>0.55 (0.04–6.89)</td>
<td>0.644</td>
<td>0.32 (0.03–3.58)</td>
<td>0.358</td>
</tr>
<tr>
<td>Acute aPLN</td>
<td>7.2 (0.58–90.5)</td>
<td>0.124</td>
<td>6.71 (0.61–74.0)</td>
<td>0.120</td>
</tr>
<tr>
<td>Baseline eGFR, for each 10-ml/min/1.73m² increase</td>
<td>0.56 (0.29–1.09)</td>
<td>0.088</td>
<td>0.62 (0.36–1.05)</td>
<td>0.073</td>
</tr>
<tr>
<td>Baseline proteinuria, for each 1.0-g/day increase</td>
<td>1.28 (0.99–1.66)</td>
<td>0.057</td>
<td>1.20 (1.00–1.45)</td>
<td>0.046</td>
</tr>
<tr>
<td>Baseline MAP, for each 10-mmHg increase</td>
<td>1.53 (0.80–2.93)</td>
<td>0.198</td>
<td>1.43 (0.82–2.49)</td>
<td>0.210</td>
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