CASE REPORT

Remission inductive efficacy of the combination of ARB, MRA, and saireito for nephrotic syndrome of membranous nephropathy

Takahiko Ono1,2 | Hiroyuki Nagai1 | Noriyuki Suzuki3 | Fumiaki Nogaki3

1Department of Nephrology, Amagasaki Eijinkai Clinic, Amagasaki City, Japan
2Division of Kampo Medicine, Department of Internal Medicine, Shimada General Medical Center, Shimada City, Japan
3Division of Nephrology, Department of Internal Medicine, Shimada General Medical Center, Shimada City, Japan

Correspondence
Takahiko Ono
Tel: +81-6-6413-3515
Fax: +81-6-6411-0104
Email: takaono@clear.ocn.ne.jp

Abstract
Case: Angiotensin II receptor blockers (ARBs) effectively reduce urinary protein. An increase in aldosterone after ARB is termed aldosterone breakthrough and mineralocorticoid receptor antagonists (MRAs) are useful against this phenotype. The Japanese traditional medicine saireito has the potential to reduce proteinuria. MRAs may suppress licorice-induced pseudoaldosteronism.

Outcome: A 25-year-old Japanese female with idiopathic membranous nephropathy developed anasarca and a urinary protein/urinary creatinine ratio of 6.07. Her serum albumin level was 1.0 g/dL. Prednisolone, ciclosporin, and the ARB losartan were prescribed. After four months, prednisolone was tapered from 50 to 20 mg, and urinary protein/creatinine mildly decreased to 2.2. Although proteinuria was not reduced after the addition of the MRA eplerenone, further addition of saireito markedly reduced her proteinuria to 0.31. The serum albumin increased to over 3.0 g/dL.

Conclusion: The combination of ARB, MRA, and saireito may exert a therapeutic effect and reduce the proteinuria due to nephrotic syndrome in membranous nephropathy.

KEYWORDS
angiotensin II receptor blocker, membranous nephropathy, mineralocorticoid receptor antagonist, nephrotic syndrome, saireito

INTRODUCTION

Nephrotic syndrome is a group of diseases in which hypoalbuminemia occurs due to a marked proteinuria of 3.5 g/day (alternatively, spot urine protein/urine creatinine ratio of 3.5) or higher, and edema develops. Types of nephrotic syndrome include membranous nephropathy, which is common in adults, minimal-change nephrotic syndrome, which is common in the younger generation, and focal glomerulosclerosis, which is often steroid-resistant. The degree of proteinuria affects renal prognosis depending on the amount of urinary protein. Complete remission is a reduction to less than 0.3 g/day and incomplete remission type 1 is a reduction to 0.3 g/day or more but less than 1.0 g/day. After remission, the prognosis is expected to improve. We present a case of nephrotic syndrome due to membranous nephropathy in which the mineralocorticoid receptor antagonist (MRA) eplerenone and saireito were sequentially used in combination with an angiotensin II receptor blocker.
receptor blocker (ARB), and urinary protein decreased gradually, reaching the level of remission.

CASE PRESENTATION

A 25-year-old Japanese female, with a history of Crohn’s disease at 19 years of age, gained 3 kg of body weight in two weeks and presented with anasarca. Crohn’s disease was in remission during the onset of nephrotic syndrome. Laboratory tests demonstrated normal renal function and marked nephrotic syndrome, with an occasional urinary protein/urinary creatinine ratio of 6.07, daily urinary protein of 4.6 g, serum creatinine of 0.6 mg/dL, serum albumin of 1.0 g/dL, and total cholesterol of 297 mg/dL. The fibrinogen level, 815 mg/dL, was markedly high. We did not evaluate PLA2R antibody. Renal biopsy revealed pathological membranous nephropathy (Figs 1, 2). The complication of malignant disease and infectious disease was excluded. Treatment was started for primary membranous nephropathy. Previously, she had a history of anaphylaxis with infliximab and adalimumab (each genetical recombination), during the treatment of Crohn’s disease. Therefore, the use of rituximab, which, like infliximab and adalimumab, is a genetic recombination antibody drug, was postponed for the specific treatment of membranous nephropathy.

As the initial treatment, prednisolone at 50 mg, ciclosporin at 75 mg, the ARB losartan at 12.5 mg, and atorvastatin at 20 mg were administered. After four months, as shown in Figure 3, prednisolone was tapered to 20 mg, and her urinary protein/creatinine mildly decreased to 2.2 and serum albumin recovered to 2.4 g/dL, but no further improvement was noted.

Next, the MRA eplerenone at 50 mg was added and the dose was further increased to 100 mg. Four months after the addition of eplerenone, the urinary protein/urinary creatinine ratio fluctuated but slightly decreased, and the serum albumin level recovered mildly to 2.8 g/dL. At this point, her blood pressure was 123/76 mm Hg and the massive edema almost disappeared. Regarding the medical evaluation of Kampo at this point, she had the complaints of thirst and

FIGURE 1 Immunohistochemistry for IgG. Fine granular IgG deposits are continuously observed along the glomerular capillary loops (×400)

FIGURE 2 Electron microscopic study of the glomerulus. Electron-dense deposits were observed side by side in the subepithelium (arrows, ×16,000)

FIGURE 3 Clinical course. After the addition of eplerenone, the serum albumin level recovered mildly to 2.8 g/dL. After the combined use of saireito, the urinary protein/urinary creatinine ratio was 0.31 and the serum albumin level increased to 3.2 g/dL, leading to the remission of nephrotic syndrome

| Month after eplerenone | Alb, g/dl | Urine protein/urinary Cre, mg/mg |
|------------------------|-----------|--------------------------------|
| 0                      | 2.2       | 1.0                            |
| 1                      | 2.4       | 0.9                            |
| 2                      | 2.8       | 0.3                            |
| 3                      | 3.0       | 0.1                            |
| 4                      | 3.2       | 0.0                            |
| 5                      | 3.4       | not done                       |
| 6                      | 3.6       | not done                       |
unsmooth urination. The abdomen showed discomfort in the hypochondrium. Abdominal muscle tonus was moderate, and deviation to deficiency or excess in Kampo medicine was suggested scarce. Therefore, we chose and added saireito treatment. Although it was not measured one month later, after two months of the combined use of saireito, the urinary protein/urinary creatinine ratio markedly decreased to 0.31 and the serum albumin level increased to 3.2 g/dL (Fig 3). These values were maintained at the next visit. The patient recovered from nephrotic syndrome. Furthermore, the serum creatinine level was 0.6 mg/dL and renal function remained stable. Crohn’s disease maintained in remission even at the final observation when the nephrotic syndrome was in remission, and no special treatment was given.

**DISCUSSION**

In the present case, remission of nephrotic syndrome was not achieved with steroid, ciclosporin, and ARB administration. However, after a relatively short period of six months, it was achieved after first adding a MRA and then saireito. The remission time was the two-month period immediately after the last administration of saireito. Moreover, as no measurement after one month was performed in the outpatient clinic, the recovery period may have been less than two months. Therefore, we considered this suggestive of the effect of saireito, rather than assuming that natural remission occurred at the same time by chance. Furthermore, at the time of remission, the renal function was normal and blood pressure was stable.

We previously reported an 83-year-old Japanese male with a history of angina pectoris treated using ARB, nitrate, beta blocker, Ca antagonist, clopidogrel, and rosuvastatin [1]. He developed edema, and renal biopsy confirmed idiopathic membranous nephropathy with a urinary protein/urinary creatinine ratio of 6.8 and a low serum albumin level of 2.8 g/dL. Steroids were not prescribed due to old age. After the additional prescription of saireito for six months, the urinary protein/creatinine ratio decreased to 1.4. Further addition of the MRA eplerenone at 50 mg for two years further reduced the urinary protein/creatinine ratio to below 0.3 and the serum albumin level recovered to 3.8 g/dL. Because of these two cases of recovery from nephrotic syndrome, we supposed the effects were due to the combination of three drugs: saireito, ARB, and MRA.

Waldman and Austin reported that almost 32% of membranous nephropathy patients experience spontaneous remission, usually within the first two years of diagnosis [2]. They recommended that patients with stable, normal renal function and persistent moderate proteinuria (>4 g per day but <8 g per day) during the six-month observation period have a medium risk of progression. Japanese guidelines do not specify such a six-month observation period, and steroids and immunosuppressive therapy are suggested for patients with high proteinuria [3]. Indeed, in the guidelines by the Japanese Society of Nephrology developed on the basis of a retrospective study on Japanese patients with membranous nephropathy, the remission rates did not significantly differ among three treatment groups (steroids alone, steroids and cyclophosphamide, and supportive treatment); however, steroids alone and the combination of steroids and cyclophosphamide were significantly effective in preventing the deterioration of the renal function when compared with supportive treatment. Of note, in the present case, after starting saireito, a rapid decrease in urinary protein and amelioration of the nephrotic syndrome were observed two months after the preceding eight months before the administration of saireito. Therefore, rapid remission after the use of saireito suggested its usefulness in avoiding the risk of decreased renal function.

Saireito is a traditional Japanese herbal medicine [4] and is occasionally administered to patients with IgA nephropathy with focal mesangial proliferation to reduce proteinuria [5]. In rat glomerulonephritis induced by anti-rat thymocyte serum, saireito reduced urinary protein, and proliferating cell nuclear antigen (PCNA) and ED-1-positive cells (macrophages) together with the deposition of extracellular matrix protein [6]. In multicenter open trials, saireito has been reported to be effective for nephrotic syndrome [7]. Steroids are often used in patients with primary nephrotic syndrome and are effective at suppressing inflammation. However, their long-term use occasionally induces inherent, unavoidable side effects. Furthermore, steroids induce fibrosis through connective tissue growth factor (CTGF), a profibrotic cytokine [8]. On the other hand, it was reported that saireito involves suppression of the upregulation of the proinflammatory cytokines IL-1β and IL-6, and improvement of the lymphatic function in the early stage of inflammation, using a mouse model irradiated with ultraviolet B [9].

Rituximab, a genetical recombination antibody drug, is occasionally used for nephrotic syndrome membranous nephropathy [10]. Although genetical recombination drugs have excellent therapeutic effects, serious adverse events such as anaphylaxis are known. It seems that the option of using saireito, which has far fewer side effects, might be considered in advance.

ARBs are considered effective to reduce urinary protein in chronic kidney diseases, including nephrotic syndrome [11]. Increased aldosterone after ARB administration is termed aldosterone breakthrough and MRAs are useful against this phenomenon [12,13]. ARBs were originally used in the present case and the previous case, and eplerenone and saireito were used in combination, although the order was opposite. Saireito contains
licorice as an ingredient and eplerenone may suppress the licorice-induced pseudoaldosteronism [14]. In addition, eplerenone may suppress aldosterone breakthrough in ARB.

In conclusion, the combination of ARB, MRA, and saireito may exert therapeutic effects to reduce proteinuria due to nephrotic syndrome in membranous nephropathy. A limitation remains for the interpretation of this case, and evaluation in a large number of cases is required in the future.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

- Approval of the research protocol by an Institutional Reviewer Board and the approval number: Yes, No. R3-9.
- Informed consent: not applicable.
- Registry and the registration no. of the study/trial: not applicable.
- Animal studies: not applicable.

ORCID
Takahiko Ono https://orcid.org/0000-0002-0767-9963

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