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A Pilot Study on Protective Effect of Ambrisentan on Proteinuria in Patients With Alport Syndrome

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INTRODUCTION

Alport syndrome (AS) is the most common inherited glomerular disease caused by *COL4A3/4/5* variants, which is a leading cause of kidney failure worldwide, yet the only standard care available is renin-angiotensin-aldosterone system inhibition.[1] An unmet need exists for AS treatment. In disease models of AS and other glomerular diseases, the involvement of angiotensin II and endothelin-1, either individually or in concert, in mediating glomerular injury has been well documented, leading to the development of proteinuria and kidney damage.[2,3] Previous studies revealed that treatment of Alport mice with sitaxentan, an endothelin A receptor antagonist, resulted in delayed onset of proteinuria, prevention of fibrosis and glomerulosclerosis, and prolonged life span in treated animals compared with controls.[4] More recent DUPLEX trial in focal segmental glomerulosclerosis (Study of Sparsentan in Patients With Primary Focal Segmental Glomerulosclerosis) and PROTECT trial in IgA nephropathy (Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy) showed promising results in significant reductions in proteinuria and preservation of kidney function by sparsentan, a dual endothelin angiotensin receptor antagonist.[5,6] This raises the question of whether the therapeutic in AS is the same as in these forms of glomerular diseases, and whether other endothelin receptor antagonists available on the market are effective as well, such as ambrisentan, a selective endothelin receptor antagonist, which has been approved at a dose of 5 to 10 mg, once daily for patients with pulmonary arterial hypertension.[7] Thus, this pilot study explores the efficacy and safety of ambrisentan on lowering proteinuria in patients with AS.

RESULTS

Efficacy and Safety of Short-Term Medication

In total, 12 patients with AS were included in this real-world study (Table 1). The mean baseline 24-hour urinary protein (± SD) was 2.73 ± 1.56 g/d. After adding ambrisentan for 2 months, the mean urinary protein decreased to 2.14 ± 1.32 g/d ($P = 0.001$). The mean ratio reduction from baseline in the urinary protein was 23.43% ± 5.11%. As for the renal function, the mean estimated glomerular filtration rate was 59.0 (range 31.0–118.9) ml/min per 1.73 m^2 at the baseline, which was stable during the 2 months (mean 57.1, range 30.8–125.6 ml/min per 1.73 m^2). A slight increase of estimated glomerular filtration rate was observed in most patients, although a fluctuation may not be ruled out. In contrast, as reported in most studies, initiation of a sodium-glucose cotransporter-2 inhibitor or a mineralocorticoid receptor antagonist was often associated with a small dip in estimated glomerular filtration rate of 3 to 6 ml/min per 1.73 m^2.[8,9] It seemed that

Table 1. Basic information and changes in 12 patients with Alport syndrome

	Demographic information	Gene information	Baseline medication			Baseline		Second month		Sixth month	
Patient number	Age/Gender	Variants	RAASi	SGLT2i	MRA	UTP	eGFR	UTP	eGFR	UTP	eGFR
1	27 F	COL4A3 c.3751 + 1G > A	✓			1.04	31.9	1.11	32.1	1.01	31.0
2	45 F	COL4A5 c.1094_1095delinsAC p.G365D	✓	✓	✓	1.75	47.1	1.2	60.2	1.13	51.9
3[a]	49 M	COL4A3 c.2990G > A p.G997E	✓	✓	✓	2.85	31.3	1.73	31.9		
4	26 F	COL4A3 homozygote c.40_63del p.Leu14_Leu21del	✓	✓	✓	4.96	66.3	4.57	53.2		
5	52 F	COL4A3 c.3716G > A p.G1239E	✓			0.55	38.6	0.23	38.5	0.11	40.7
6[a]	21 M	COL4A5 c.2969delC p.P990Qfs*6	✓	✓	✓	2.97	31.0	2.7	31.6		
7[a]	21 M	COL4A5 c.4078G > T p.G1360*	✓	✓		4.2	47.2	3.36	33.9		
8	34 M	COL4A5 c.367G > A p.G123R	✓	✓	✓	3.22	45.3	2.8	41.4		
9	21 M	COL4A5 c.170G > A p.G1057E	✓	✓		4.73	107.6	3.06	95.2		
10[a]	38 M	COL4A5 c.4803 + 2T > C	✓			4.07	32.7	3.19	30.8		
11	39 F	COL4A5 c.5030G > A p.R1677Q	✓	✓		1.28	109.8	1.1	110.6	0.92	111.9
12	27 M	COL4A4 c.1334G > A p.G445E	✓	✓		1.08	118.9	0.67	125.6		

[a]These patients discontinued the drug due to an adverse reaction.
eGFR, estimated glomerular filtration rate, ml/min per 1.73 m^2; F, female; M, male; MRA, mineralocorticoid receptor antagonists; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; UTP, 24-hour urine protein (g/24 h).

adverse effects presented with individual differences. Two patients discontinued due to edema in the second month of follow-up, and 2 patients discontinued due to headache. The rest of the patients did not report any side effects.

Efficacy and Safety of Prolonged Medication

Among the patients, 4 patients have been followed for over 6 months with an additional 4-month follow-up data. We observed a continued trend of decrease in urinary protein (Figure 1), an additional reduction of 20.85% ± 10.67% from the second month in the urinary protein, and 36.61% ± 16.06% reduction from the baseline (mean 1.16 g/d, 0.91 g/d, and 0.79 g/d at baseline, 2-month and 6-month follow-up, respectively). The estimated glomerular filtration rate remained stable (meaning of 58.9 ml/min per 1.73 m^2 at the sixth month vs. 56.9 ml/min per 1.73 m^2 at baseline) after this regimen regarding a 6-month follow-up.

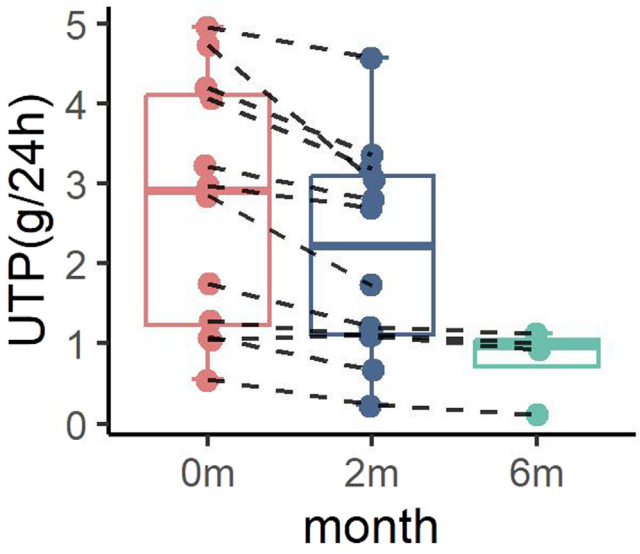

Figure 1. Changes in UTP during treatment. The UTP shows decreasing trends of proteinuria during treatment. The dots and connecting lines represent the changes of one patient's urinary protein. The error bar of each box and whiskers mean minimum to maximum. UTP, 24-hour urine protein.

CONCLUSION

This pilot study suggests that introducing a highly selective antagonist for ET_A on top of renin-angiotensin-aldosterone system inhibition, with or without sodium-glucose cotransporter-2 inhibitors/mineralocorticoid receptor antagonists, provides an additional antiproteinuric effect. A relatively high percentage of patients discontinued the drug in this pilot (4/12) because of adverse reactions, suggesting that clinicians should pay attention to these adverse reactions during the initial period of use. Few effects on renal function were observed. Future prospective large-scale randomized studies are highly warranted to demonstrate the effect and safety of ambrisentan or other endothelin receptor antagonists in AS.

DISCLOSURE

The manuscript has received approval from all authors, who declare no potential conflict of interest.

PATIENT CONSENT

The patients have given consent for their clinical information to be published in the journal.

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DATA AVAILABILITY STATEMENT

All data analyzed in this study were included in the main text. Other source data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Safety data during the study period.

STROBE Statement.

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