Drugs controlling proteinuria of patients with Alport syndrome

Jian-Guo Li, Jie Ding, Fang Wang, Hong-Wen Zhang

Beijing, China

Background: **Proteinuria is one of the risk factors for the progression of renal diseases including Alport syndrome (AS), a hereditary glomerular renal disease. This study aimed to evaluate the efficacy of angiotensin converting enzyme inhibitors (ACEIs) and/or tripterygium, a Chinese herbal medicine widely used in Chinese patients with hematuria and proteinuria, on proteinuria in patients with AS.**

Methods: **Twenty-nine children were enrolled into this retrospective study. Patients were divided into 3 therapy groups: ACEI group, tripterygium group, and ACEI plus tripterygium group.**

Results: **In the 29 children, 23 were male and 6 female. In the ACEI group and the tripterygium group, the effective rate was 87.5% and 25.0%, respectively and in the ACEI plus tripterygium group was 42.9%.**

Conclusions: **ACEI is effective in controlling proteinuria of AS patients. Tripterygium should be carefully administered in controlling proteinuria of AS patients.**

World J Pediatr 2009;5(4):308-311

Key words: **Alport syndrome;**
angiotensin converting enzyme inhibitor;
herbal medicine;
tripterygium

Introduction

Alport syndrome (AS) is a hereditary nephritis manifested by hematuria, sensorineural hearing loss, ocular lesions and progressive renal failure.[1] Almost all male patients with X-linked AS (XLAS) and all patients with autosomal recessive AS (ARAS) present proteinuria during the progression of the disease.[1] Studies have shown that the degree of proteinuria is related to the progression of renal function.[2] Thus efforts have been made to control proteinuria for a slow progression of AS, such as the application of ACEI/ARB, cyclosporine, or mineralocorticoid receptor antagonist spironolactone (SP) in patients or animal models of AS.[3-10] Tripterygium, a cheap Chinese herbal medicine, is also effective to decrease proteinuria in some renal diseases. The present retrospective study aimed to evaluate the effects of ACEI and tripterygium on proteinuria of children with AS.

Methods

Diagnostic criteria

The diagnosis of AS was based on the clinical manifestations and laboratory investigation, including sensorineural hearing loss, eye abnormality, positive family history of chronic renal failure, the characteristic ultrastructural changes of the glomerular basement membrane shown by an electron microscope, abnormal staining of α chains of type IV collagen in epidermal basement membrane or in glomerular basement membrane, and *COL4A5* mutations.

From June 1998 to December 2007, 29 children who met these criteria were enrolled in the study. These children were divided into three groups according to the administration of different drugs: ACEI group, tripterygium group, and ACEI plus tripterygium group.

Effectiveness criteria for treatment

Effectiveness of treatment was defined as proteinuria decreased after treatment for more than 4 months.

Results

The clinical features of the 29 children are shown in Table.

Author Affiliations: Department of Pediatrics, Peking University First Hospital, Beijing 100034, China (Li JG, Ding J, Wang F, Zhang HW)

Corresponding Author: Jie Ding, MD, PhD, Department of Pediatrics, Peking University First Hospital, No. 1, Xianmen Dajie, Beijing 100034, China (Tel: 8610 66551122 ext 3236; Fax: 8610 66134261; Email: djnc_5855@126.com).

doi:10.1007/s12519-009-0059-5

Table. The clinical features of the 29 patients with Alport syndrome

Group	*n*	Age of starting therapy (y)	Sex		Genotype		Before therapy				Follow-up duration (mon)	Percent of proteinuria reduction		The end of follow-up			
							Proteinuria (mg/24h)			Renal dysfunction		4-6 mon	>9 mon	Proteinuria (mg/d)			Renal dysfunction
			M	F	XLAS	ARAS	<500	500-1000	>1000					<500	500-1000	>1000	
ACEI	12	9.8	11	1	10	2	3	2	7	No record	7.03±3.24	87.5% (7/8)	100.0% (7/7)	6	1	5	1/12
Tripterygium	9	13.1	6	3	7	2	4	1	4	2/9	11.02±5.86	25.0% (2/7)	0.0% (0/4)	2	1	6	2/9
ACEI plus tripterygium	8	11.6	6	2	7	1	0	2	6	No record	16.21±8.93	42.9% (3/7)	42.9% (3/7)	0	1	7	1/8

ACEI: angiotensin converting enzyme inhibitor; XLAS: X-linked Alport syndrome; ARAS: autosomal recessive Alport syndrome; M: male; F: female.

ACEI group

This group included 12 children who received ACEI treatment. Their mean age at diagnosis and initial therapy was 6.7 years and 9.8 years, respectively. The average dose of captopril was 15 mg to 75 mg per day according to the body weight (0.3-0.5 mg/kg, every 8 hours). The dose of monopril was 5 mg or 10 mg per day. After 4 to 6 month treatment, proteinuria increased in 1 child, but decreased in 6 children. After 9 to 12 month treatment, proteinuria decreased in 6 children. The average reduction of proteinuria ranged from 14.0% to 78.0% (Fig. 1). The abnormal renal function was detected in 1 child after 1 year of ACEI treatment. Unfortunately, there were no data on renal function before the treatment.

Tripterygium group

This group consisted of 9 children treated with tripterygium. Their mean age at the detection of proteinuria and beginning of the therapy was 9.4 years and 13.1 years, respectively. The average dose of tripterygium was 20 mg to 60 mg per day according to the body weight of the children (1-2 mg/kg per day). After 4-6 month treatment, proteinuria decreased in 2 children but increased in 6. After 9-12 month treatment, proteinuria increased in 4 children (Fig. 2). The renal function of the 2 children was abnormal before and after the treatment. No children showed renal dysfunction during the follow-up.

ACEI plus tripterygium group

This group comprised 8 children who received ACEI plus tripterygium treatment. Their mean age at detection of proteinuria and initial treatment was 8.3 years and 11.6 years, respectively. The dose of tripterygium ranged from 15 mg to 60 mg per day. The dose of ACEI ranged from 5 mg to 37.5 mg per day. After 4-6 month treatment and 9-12 month treatment, proteinuria increased in 4 children but decreased in 3 (Fig. 3). Only 1 of the 8 children was detected with renal dysfunction after the treatment for 18 months. Unfortunately, there were no data on the renal function before the treatment.

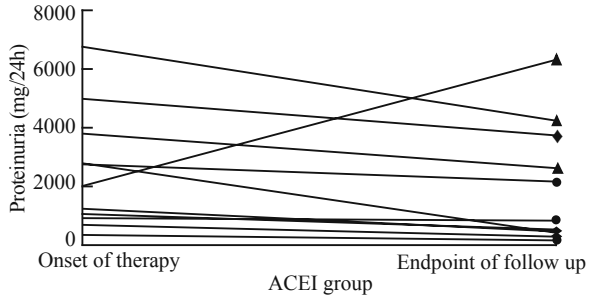

Fig. 1. The effects of drug therapy in the ACEI group. ▲: The patients received ACEI for 4 to 6 months; ●: The patients received ACEI for 9 to 12 months; ♦: The patients received ACEI for more than 12 months. Every line represented the change of proteinuria in 12 patients who received ACEI treatment. After treatment with ACEI, most of the lines showed the tendency of decline.

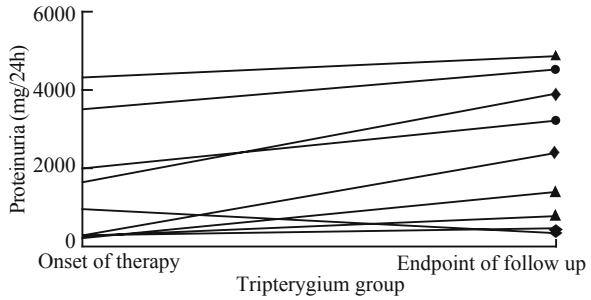

Fig. 2. The effects of drug therapy in the tripterygium group. ▲: The patients received tripterygium for 4 to 6 months; ●: The patients received tripterygium for 9 to 12 months; ♦: The patients received tripterygium for more than 12 months. Every line represented the change of proteinuria in 9 patients who received tripterygium treatment. After treatment with tripterygium, most of the lines showed the tendency of increase.

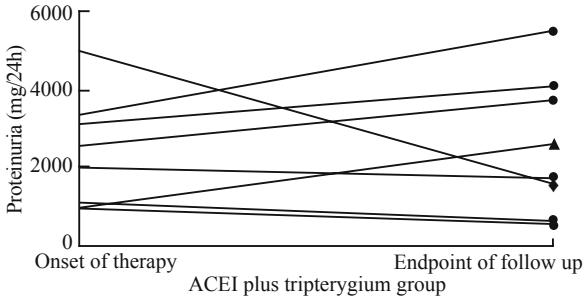

Fig. 3. The effects of drug therapy in the ACEI plus tripterygium group. ▲: The patients received ACEI plus tripterygium for 4 to 6 months; ●: The patients received ACEI plus tripterygium for 9 to 12 months; ♦: The patients received ACEI plus tripterygium for more than 12 months. Every line represented the change of proteinuria in 8 patients who received ACEI plus tripterygium therapy. After treatment with ACEI plus tripterygium, about half of lines showed the tendency of decline.

ACEI related side-effects including cough and renal function deterioration were not observed in the ACEI group. In the tripterygium group, some children presented with irregular menstruation and reduced white blood cell count. Only one girl had to withdraw the treatment with tripterygium because of irregular menstruation.

Discussion

Alport syndrome is a hereditary progressive nephritis.[1] Once proteinuria appeared, the progression of renal function would accelerate.[11] Several drugs have been applied in patients or animal models of AS,[3-6,7-9,12] but their effects on AS are controversial. Cyclosporine is beneficial in slowing the progression of renal function in patients or animal models of AS, whereas the nephrotoxicity caused by cyclosporine would limit the long-term application.[8,13] In other studies, ACEI (0.05-0.5 mg/kg per day) was used to control proteinuria in AS patients. But the effect of ACEI was not consistent in the studies.[3-5,10,14]

Before the therapy in our study, there was no significant difference in demographic data of patients in the three groups. In the ACEI group, the percentage of proteinuria reduction in 4-6 months and 9-12 months was 85.7% and 100.0% respectively. A study[15] found that routine treatment with ACEI was unnecessary in the early stage of AS patients with sub-nephrotic range proteinuria. Another study,[5] however, showed that ACEI was effective in controlling proteinuria when lower than 50 mg/kg per day, but was not effective to nephrotic-range proteinuria. We found that ACEI was effective in controlling proteinuria regardless of the level of proteinuria, the nephrotic range, and the lower level of pretienuria. We suggest that AS patients with proteinuria should be given ACEI as early as possible. Our data showed that the longer ACEI was administered, the better the effect of controlling proteinuria exhibited. Thus we suggest a long-time ACEI treatment for AS patients with proteinuria.

There was no satisfactory therapy for AS. Tripterygium, a Chinese herbal medicine, showed effects in decreasing proteinuria or/and hematuria in patients with renal diseases. The mechanism of tripterygium in the treatment of glomerular diseases was regarded as suppressing immuno-effects, inhibiting glomerular mesangial proliferation and extracellular matrix accumulation, delaying glomerular sclerosis, and ameliorating the podocyte injury.[16-19] In addition, tripterygium is relatively cheap and will increase the compliance of patients. However, our study did not show any significant effects as we expected in controlling the proteinuria of AS patients. Most of the patients showed increase of proteinuria after treatment. Only one girl with AS treated with tripterygium showed good effect except for abnormal menstruation (data not shown). She presented with obvious proteinuria after withdrawal of the tripterygium treatment because of abnormal menstruation, but her proteinuria decreased again when tripterygium was continued. Therefore, the effects of tripterygium need a further study.

In the ACEI group, no side-effects were observed. In the tripterygium group, neutropenia or abnormal menstruation was noticed.

There are some limitations in our study. First, the present study is a retrospective study and did not enroll cases with placebo as controls, because such study design is difficult to be approved by the ethical committee. Second, it will be better if the effect of the therapy was assessed by the change of renal function. Unfortunately the glomerular filtration rate was not regularly detected in the follow up. In addition, the suitable age for starting drug therapies and the proper dosage of drugs are still undecided.

In conclusion, ACEI was an effective and safe drug in controlling proteinuria of AS patients, but tripterygium did not show any significant effects in our study. Tripterygium should be carefully administered in controlling proteinuria of AS patients. A multicenter and prospective trial is needed to evaluate the efficacy of drugs in AS patients.

Acknowledgements

We are grateful to physicians who have referred patients to our department. We also thank all physicians and nurses in the Division of Pediatric Nephrology, Peking University First Hospital including Liu JC, Chen Y, Yao Y, Xiao HJ, Huang JP, Zhong XH and Yang JY.

Funding: This work was supported by grants from the National Natural Science Foundation of China (30170992, 30672259), National 10th Five-Year Project (2003BA712A11-23) and National 11th Five-Year Scientific and Technical Supporting Programs (2006BAI05A07).

Ethical approval: The study was approved by the Ethics Committee of Peking University First Hospital, China (2006023).

Competing interest: None declared.

Contributors: Li JG wrote the main body of the article under the supervision of Ding J. Wang F and Zhang HW provided gene diagnosis of Alport syndrome. Ding J is the guarantor.

References

1 Kashtan CE. Alport syndrome and thin glomerular basement membrane disease. J Am Soc Nephrol 1998;9:1736-1750.

2 Burton C, Harris KP. The role of proteinuria in the progression

of chronic renal failure. Am J Kidney Dis 1996;27:765-775.
3 Proesmans W, Knockaert H, Trouet D. Enalapril in paediatric patients with Alport syndrome: 2 years' experience. Eur J Pediatr 2000;159:430-433.
4 Cohen EP, Lemann J Jr. In hereditary nephritis angiotensin-converting enzyme inhibition decreases proteinuria and may slow the rate of progression. Am J Kidney Dis 1996;27:199-203.
5 Proesmans W, Van Dyck M. Enalapril in children with Alport syndrome. Pediatr Nephrol 2004;19:271-275.
6 Gross O, Beirowski B, Koepke ML, Kuck J, Reiner M, Addicks K, et al. Preemptive ramipril therapy delays renal failure and reduces renal fibrosis in *COL4A3*-knockout mice with Alport syndrome. Kidney Int 2003;63:438-446.
7 Kaito H, Nozu K, Iijima K, Nakanishi K, Yoshiya K, Kanda K, et al. The effect of aldosterone blockade in patients with Alport syndrome. Pediatr Nephrol 2006;21:1824-1829.
8 Charbit M, Gubler MC, Dechaux M, Gagnadoux MF, Grünfeld JP, Niaudet P. Cyclosporin therapy in patients with Alport syndrome. Pediatr Nephrol 2007;22:57-63.
9 Sigmundsson TS, Palsson R, Hardarson S, Edvardsson V. Resolution of proteinuria in a patient with X-linked Alport syndrome treated with cyclosporine. Scand J Urol Nephrol 2006;40:522-525.
10 Proesmans W, Wambeke IV, Dyck MV. Long-term therapy with enalapril in patients with nephrotic-range proteinuria. Pediatr Nephrol 1996;10:587-589.
11 Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, et al. X-linked Alport syndrome: natural history in 195 families and genotype-phenotype correlations in males. J Am Soc Nephrol 2000;11:649-657.
12 Callís L, Vila A, Carrera M, Nieto J. Long-term effects of cyclosporine A in Alport's syndrome. Kidney Int 1999;55: 1051-1056.
13 Chen D, Jefferson B, Harvey SJ, Zheng K, Gartley CJ, Jacobs RM, et al. Cyclosporine a slows the progressive renal disease of alport syndrome (X-linked hereditary nephritis): results from a canine model. J Am Soc Nephrol 2003;14:690-698.
14 Lama G, Luongo I, Piscitelli A, Salsano ME. Enalapril: antiproteinuric effect in children with nephrotic syndrome. Clin Nephrol 2000;53:432-436.
15 Adler L, Mathew R, Futterweit S, Frank R, Gauthier BG, Kashtan CE, et al. Angiotensin converting enzyme inhibitor therapy in children with Alport syndrome: effect on urinary albumin, TGF-beta, and nitrite excretion. BMC Nephrol 2002;3:2.
16 Jiang X. Clinical observations on the use of the Chinese herb Tripterygium wilfordii Hook for the treatment of nephrotic syndrome. Pediatr Nephrol 1994;8:343-344.
17 Zheng CX, Chen ZH, Zeng CH, Qin WS, Li LS, Liu ZH. Triptolide protects podocytes from puromycin aminonucleoside induced injury *in vivo* and *in vitro*. Kidney Int 2008;74:596-612.
18 Sharma M, Li JZ, Sharma R, Artero M, Ge X, McCarthy ET, et al. Inhibitory effect of Tripterygium wilfordii multiglycoside on increased glomerular albumin permeability *in vitro*. Nephrol Dial Transplant 1997;12:2064-2068.
19 Wan YG, Sun W, Wang Y, Zhang J, Li M, Ruan JG, et al. Effects of multi-glycoside of Tripterygium wilfordii Hook. f. on proteinuria and expression of slit diaphragm-associated molecules in rats with anti-thy1.1 glomerulonephritis. Zhong Guo Zhong Xi Yi Jie He Za Zhi 2006;26:1094-1102. [in Chinese]

Received February 12, 2009
Accepted after revision August 11, 2009