Optimal level of proteinuria reduction for renoprotection in patients with IgA nephropathy

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The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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<ABSTRACT>

Optimal level of proteinuria reduction for renoprotection in patients with IgA nephropathy

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(Directed by Professor Seung Hyeok Han)

Proteinuria is a target for renoprotection in various glomerular diseases. However, optimal level of proteinuria reduction is unknown in patients with IgA nephropathy (IgAN). Therefore, I conducted a retrospective observational cohort study to investigate whether reducing proteinuria below the level that the current guideline suggests may confer a more renoprotective advantage in these patients. Among 644 participants who were pathologically diagnosed with IgAN in Yonsei University Severance Hospital and National Health Insurance Corporation Ilsan Hospital between 2000 and 2010, 500 subjects were eligible for the study. Time-averaged proteinuria (TA-P) was calculated as an average of the mean of every 6 month period of measurements of spot urine protein-to-creatinine ratio. The study endpoints were a

doubling of the baseline serum creatinine concentration (D-sCr) and the onset of end-stage renal disease (ESRD). ESRD was defined as initiation of dialysis or receiving transplantation. There were 221 (44.2%), 135 (27.0%), 96 (19.2%), and 48 (9.6%) patients with TA-P of < 0.5, 0.5-0.99, 1.0-1.99, and ≥ 2.0 g/g, respectively. During a median follow-up duration of 65 (12-154) months, D-sCr was reached in 1 (0.5%), 3 (2.2%), 18 (18.8%), and 30 (62.5%) patients of each group (P < 0.001). There was no difference in the development of D-sCr between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g. ESRD did not occur in these two groups compared to 11 (11.5%) and 23 (47.9%) patients with TA-P of 1.0-1.99 and ≥ 2.0 g/g, respectively. In the multivariable Cox model after adjustment for age, estimated glomerular filtration rate, blood pressure, pathologic findings, and treatment, risk of reaching D-sCr did not differ between patients with TA-P of < 0.5 g/g and those with 0.5-0.99 g/g [hazard ratio (HR), 3.34; 95% confidence interval (CI), 0.33 to 34.22; P = 0.310], whereas it was markedly increased in patients with TA-P of 1.0-1.99 g/g (HR, 33.92; 95% CI, 4.25 to 270.49; P = 0.001) and those with TA-P > 2.0 g/g (HR, 171.52; 95% CI 20.85 to 411.01; P < 0.001). These findings suggest that the optimal anti-proteinuric goal is < 1.0 g/g in patients

with IgAN. Further studies are required to clarify whether reduction of proteinuria of < 0.5 g/g may confer a more renoprotective advantage.

Key words : proteinuria, IgA nephropathy, long-term outcome

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I. INTRODUCTION

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide and still the main cause of end-stage renal disease (ESRD). Clinical presentation of IgAN covers a wide range from asymptomatic urinary abnormalities to acute or chronic renal failure. Long-term studies of the natural history have shown that IgAN generally exhibits a slowly progressive nature and about 20 to 30% of patients with IgAN will eventually require renal replacement therapy within 20–25 years after disease onset.[1, 2]

Because it is not a totally benign condition, a number of studies have identified risk factors associated with progression of IgAN. Among these, proteinuria is considered a strong predictor of adverse renal outcome.[3-13] In fact, not only in IgAN but in many other glomerular diseases, proteinuria is significantly related to clinical and pathological factors that affect the future

outcome, thus is a therapeutic target for kidney protection although treatment options differ according to types and severity of diseases. As aforementioned, unlike idiopathic nephrotic syndrome or crescentic glomerulonephritis showing abrupt onset or rapid progressive decline in renal function, IgAN is characterized by slowly progressive nature without symptoms over time. Therefore, it is difficult to determine when we should begin to treat or who should be treated among patients with IgAN. In addition, therapeutic options are limited and role of immunosuppressive drugs has not yet been clearly defined. Nevertheless, remission of proteinuria is of paramount importance to improve prognosis in these patients. However, optimal threshold of proteinuria reduction to attenuate progression of kidney disease is currently unknown. Interestingly, such threshold appears to differ depending on types of proteinuric glomerular diseases.[14] Moreover, although patients with IgAN are considered to have favorable outcome if they have proteinuria < 1 g/d throughout the disease course, there is controversy on whether further reduction of proteinuria below this level is more beneficial.[11, 12] The purpose of this study was, therefore, to identify the optimal level of proteinuria reduction for renoprotection in patients with IgAN. To this end, I used time-averaged proteinuria (TA-P) and classified patients into four groups according to TA-P levels. In particular, I aimed to investigate whether reducing proteinuria below the level that the current guideline suggests may confer a more renoprotective advantage.

II. MATERIALS AND METHODS

1. Patient selection

Flow chart of participants is shown in Figure 1. A total of 644 patients were pathologically diagnosed with IgAN in Yonsei University Severance Hospital and National Health Insurance Corporation Ilsan Hospital between 2000 and 2010. All patients had definite pathologic findings with predominant mesangial deposition of IgA with at least 1+ on immunofluorescent staining and electron-dense deposits within the mesangium detected by electron microscopy. Patients with Henoch-Schonlein purpura nephritis were considered ineligible. Exclusion criteria were as follows: aged < 18 years (n = 18); follow-up duration < 12 months (n = 89); inadequate biopsy sample with the number of glomeruli ≤ 7 (n = 13); secondary causes of mesangial IgA deposition, such as IgA-dominant acute post-infectious glomerulonephritis (n = 4); systemic lupus erythematosus (n = 8); liver cirrhosis (n = 7); or malignancy (n = 5). Therefore, a total of 500 patients were analyzed in this study.

2. Data collection

All data were obtained from database of the two institutions. Baseline data

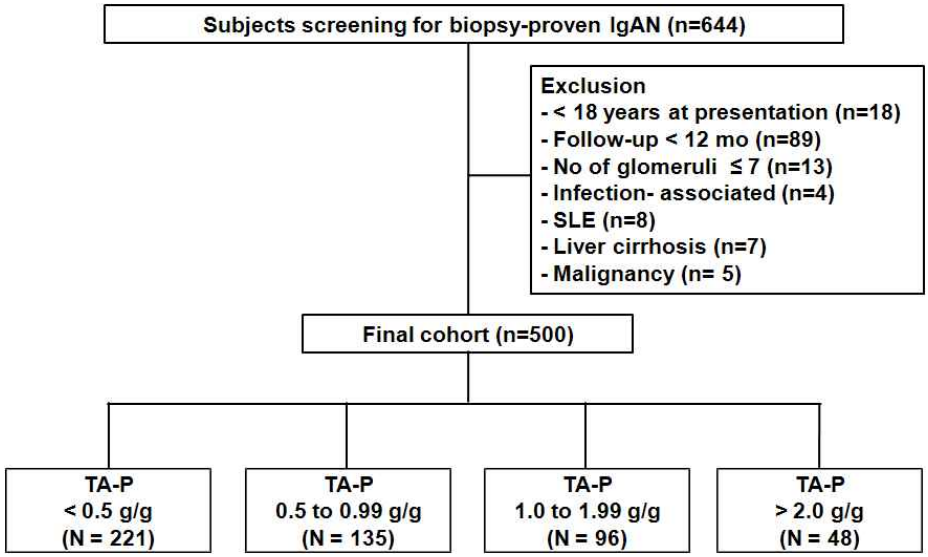

Figure 1. Flow chart of participants

Abbreviations: IgAN, Immunoglobulin A nephropathy; SLE, systemic lupus erythematosus; TA-P, time-averaged proteinuria

was collected at the time of renal biopsy. These included gender, age, systolic and diastolic blood pressure, comorbid disease, date of renal biopsy, pathologic findings on renal biopsy, and laboratory parameters including serum blood urea nitrogen, creatinine, albumin, total cholesterol, triglyceride, hemoglobin, random urine protein-to-creatinine ratio (UPCR), and 24-h urinary protein excretion. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[15] During follow-up, proteinuria was assessed by UPCR because measurement of 24-h protein excretion was not feasible at all

visits. Using these data, I calculated TA-P, as an average of the mean of every 6 month period of proteinuria measurements.[11] In addition, medications including anti-hypertensive medications, renin-angiotensin system (RAS) blockers, steroids, and other immunosuppressants were recorded. In this study, I presented pathologic findings using the Oxford classification criteria.[16, 17]

3. Study endpoints

Study endpoints were a doubling of the baseline serum creatinine concentration (D-sCr) and the onset of ESRD. The former was defined as a sustained, greater than a two-fold increase in serum creatinine for at least three consecutive measurements. Point of D-sCr was taken as the first among these measurements. ESRD was defined as initiation of dialysis or receiving transplantation. Patients who reached D-sCr or ESRD were considered 'progressors'.

4. Statistical analyses

All variables with normal distribution were expressed as mean ± standard deviation. Comparisons were made by Student's t-tests or one-way ANOVA for continuous variables and by the Chi-square test for categorical variables as required. The Kolmogorov-Smirnov test was used to determine the normality

of the distribution of parameters. If data did not show normal distribution, they were expressed as median and interquartile range and were compared using the Mann–Whitney test or Kruskal–Wallis test. The cumulative renal survival rates were estimated by the Kaplan-Meier method and differences between survival curves were compared with log-rank test. Renal survival time was considered as the interval between the time of biopsy and last follow-up. Cox proportional hazards model was used to identify independent variables for renal survival. The results were expressed as a hazard ratio (HR) and 95% confidence interval (CI). All P-values were two-tailed and values <0.05 were considered statistically significant. Data analysis was performed using SPSS software for Windows, version 20 (SPSS, Chicago, IL).

III. RESULTS

1. Baseline characteristics according to time-averaged proteinuria

Baseline characteristics of the study population are shown in Table 1. The mean age at the time of renal biopsy was 37.0 ± 12.0 years and 215 patients (43%) were male. 122 (24.4%) patients were hypertensive before renal biopsy. The median of 24-h protein excretion was 1.1 (0.5-2.2) g/day and mean eGFR was 80.2 ± 23.4 ml/min per 1.73 m^2. When pathologic findings were analyzed using the Oxford classification system, there were 238 (47.6%), 46 (9.2%), 184 (36.8%), 46 (9.2%) and 30 (6.0%) patients with M1, E1, S1, T1, and T2,

respectively.

Patients were categorized into four groups according to TA-P (Table 1). 221 (44.2%), 135 (27.0%), 96 (19.2%), and 48 (9.6%) patients had TA-P of < 0.5, 0.5-0.99, 1.0-1.99, and ≥ 2.0 g/g, respectively. There were no differences in age, sex, comorbid diseases, and blood pressure among four groups (P for trend = NS). However, serum concentrations of total cholesterol (P for trend < 0.001) and triglyceride (P for trend = 0.001), 24-h urine protein excretion (P for trend <0.001), and UPCR (P for trend <0.001) were significantly higher, whereas eGFR (P for trend = 0.002) and serum albumin levels (P for trend <0.001) were lower as patients had greater amount of TA-P. Regarding pathologic features, each component of the Oxford-MEST lesion was more commonly observed in patients with higher grades of TA-P. During follow-up, patients with TA-P < 0.5 g/g were less treated with RAS blockers than other groups. In addition, corticosteroids were most commonly prescribed to patients with TA-P ≥ 2.0 g/g.

2. Renal outcome according to time-averaged proteinuria

Median follow-up of the cohort was 65 (12-154) months. As shown in Table 2, 52 (10.4%) patients reached D-sCr during follow-up. Among these, 35 (7.0%) patients developed ESRD. There was no patient who progressed to ESRD before reaching D-sCr.

I further analyzed renal outcomes according to TA-P. D-sCr was most commonly reached in patients with TA-P ≥ 2.0 g/g (62.5%), followed by those with TA-P of 1.0-1.99 g/g (18.8%). There was no significant difference in the development of D-sCr between patients with TA-P < 0.5 g/g (0.5%) and those with TA-P of 0.5-0.99 g/g (2.2%). In addition, ESRD occurred in 23 (47.9%) and 11 (11.5%) patients with TA-P ≥ 2.0 g/g and 1.0-1.99 g/g, respectively, whereas it did not occur in patients with TA-P < 1.0 g/g. A Kaplan–Meier curve also showed that renal survival rates were lower as patients had greater amount of TA-P (Figure 2), particularly from TA-P > 1.0 g/g. There was no significant difference in renal survival rate between patients with TA-P < 0.5 g/g and TA-P of 0.5-0.99 g/g. Their 10-year survival rates were excellent, which were 99.5% and 92.5%, respectively.

3. Clinical features and renal outcome between progressors and non-progressors

Clinical characteristics and renal outcome were also evaluated between progressors and non-progressors (Table 3). Compared with non-progressors, progressors exhibited higher level of systolic blood pressure and proteinuria, and lower eGFR. In addition, M, E, and T lesions by the Oxford classification were more commonly observed in progressors. During follow-up, progressors received more RAS blockers and corticosteroids than non-progressors.

Table 1. Baseline characteristics according to time-averaged proteinuria

Variables	Total	TA-P < 0.5 g/g	TA-P 0.5–0.99 g/g	TA-P 1.0–1.99 g/g	TA-P ≥ 2.0 g/g	P-for trend
Number	500	221 (44.2%)	135 (27.0%)	96 (19.2%)	48 (9.6%)	
Male (n, %)	215 (43%)	109 (49.3%)	52 (38.5%)	37 (38.5%)	17 (35.4%)	0.085
Age (years)	37.0±12.0	36.2±12.5	37.3±11.0	37.3±11.2	48±13.2	0.165
Hypertension (n, %)	122 (24.4%)	43 (19.5%)	37 (27.4%)	25 (26.0%)	17 (35.4%)	0.076
SBP (mmHg)	126.1±15.6	124.8±15.5	127.2±15.8	124.7±14.8	131.7±15.6	0.119
DBP (mmHg)	78.3±11.1	78.2±10.8	77.8±11.8	78.5±11.6	79.7±9.3	0.483
MAP (mmHg)	94.2±11.7	93.7±11.6	94.2±12.2	94.0±11.6	97.1±10.2	0.255
BUN (mg/dl)	15.4±11.6	13.7±4.2	15.1±5.5	18.4±6.4	18.2±8.5	<0.001
S-Cr (mg/dl)	1.0±0.4	0.9±0.2	1.0±0.4	1.1±0.4	1.2±0.5	<0.001
eGFR (ml/min per 1.73m^2)	80.2±23.4	86.0±19.2	77.5±22.0	76.5±26.3	68.2±30.0	0.002
Serum albumin (g/dl)	4.0±0.6	4.2±0.5	4.0±0.6	3.9±0.6	3.5±0.7	<0.001
Total cholesterol (mg/dl)	190.0±50.0	177.2±41.7	191.2±36.4	202.7±68.2	189.9±49.9	<0.001
Triglyceride (mg/dl)	140.5±114.5	123±79.1	132.24±98.8	163.4±155.0	190.8±161.6	0.001
Hb (g/dl)	13.1±2.0	13.8±1.5	13.1±1.7	13.3±1.8	10.6±3.0	<0.001
UPCR (g/g)*	0.9 (0.4-1.8)	0.6 (0.2-1.0)	1.2 (0.7-1.8)	1.9 (1.1-3.2)	3.0 (1.6-5.0)	<0.001
Proteinuria (g/24h)*	1.1 (0.5-2.2)	0.6 (0.2-1.1)	1.1 (0.6-1.8)	1.7 (1.0-3.3)	2.7 (1.6-3.9)	<0.001
Treatment						
RAS blockers	388 (77.9%)	132 (59.7%)	122 (90.4%)	89 (92.7%)	45 (97.8%)	<0.001
Corticosteroids	56 (11.2%)	14 (6.3%)	17 (12.6%)	12 (12.5%)	13 (28.3%)	<0.001
Oxford-MEST						
M1	238 (47.6%)	83 (37.6%)	66 (48.9%)	57 (59.4%)	32 (66.7%)	<0.001
E1	46 (9.2%)	17 (7.7%)	10 (7.4%)	10 (10.4%)	9 (18.8%)	0.036
S1	184 (36.8%)	66 (29.9%)	59 (43.7%)	37 (38.5%)	22 (45.8%)	0.018
T1	46 (9.2%)	9 (4.1%)	14 (10.4%)	10 (10.4%)	13 (27.1%)	<0.001
T2	30 (6.0%)	4 (1.8%)	5 (3.7%)	12 (12.5%)	9 (18.8%)	<0.001

All data are expressed as mean ± SD or *median (and interquartile range)

Abbreviations: TA-P, time-averaged proteinuria; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BUN, blood urea nitrogen; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; UPCR, urine protein-to-creatinine ratio; RAS, renin-angiotensin system

Table 2. Clinical renal outcomes according to time-averaged proteinuria

			TA-P < 0.5 g/g		TA-P 0.5-0.99 g/g		TA-P 1.0-1.99 g/g		TA-P ≥ 2.0 g/g		
	All	/100 Patient-years	N (%)	/100 Patient-years	N (%)	/100 Patient-years	N (%)	/100 Patient-years	N (%)	/100 Patient-years	P-value
D-sCr	52 (10.4%)	1.88	1 (0.5%)	0.08	3 (2.2%)	0.38	18 (18.8%)	3.35	30 (62.5%)	14.38	<0.001
ESRD	35 (7.0%)	1.24	0 (0%)	0	0 (0%)	0	11 (11.5%)	2.33	23 (47.9%)	5.08	<0.001

Abbreviations: D-sCr, doubling of the baseline serum creatinine concentrations; ESRD, end-stage renal disease

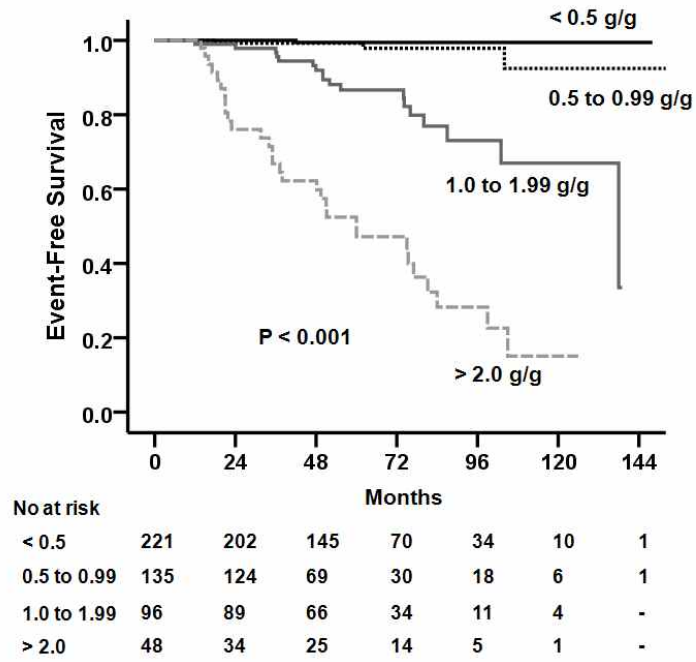

Figure 2. The Kaplan–Meier renal survival curve of patients with IgAN according to time-averaged proteinuria

Table 3. Clinical and laboratory differences in baseline characteristics between progressors and non-progressors

Variables	Total	Non-progressors	Progressors	P-value
Number	500	448 (89.6%)	52 (10.4%)	
Age (years)	37.0±12.0	36.9±11.8	38.4±13.6	0.453
Male (n, %)	215 (43%)	187 (41.7%)	28 (53.8%)	0.095
Hypertension (n, %)	122 (24.4%)	100 (22.3%)	22 (42.3%)	0.001
SBP (mmHg)	126.1±15.6	125.6±15.5	131.0±15.7	0.020
DBP (mmHg)	78.3±11.1	78.2±11.2	79.3±10.2	0.467
MAP (mmHg)	94.2±11.7	94.0±11.7	96.6±11.1	0.127
BUN (mg/dl)	15.4±11.6	14.9±5.0	19.9±8.4	0.002
S-Cr (mg/dl)	1.0±0.3	0.99±0.32	1.4±0.52	<0.001
eGFR (ml/min per 1.73m^2)	80.2±23.4	83.3±21.4	58.3±25.6	<0.001
Serum albumin (g/dl)	4.0±0.6	4.0±0.57	3.5±0.59	<0.001
Total cholesterol (mg/dl)	190.0±50.0	188.3±49.8	203.1±49.3	0.043
Triglyceride (mg/dl)	140.5±114.5	134.4±106.2	188.3±160.3	0.050
UPCR (g/g)*	0.9 (0.4-1.8)	1.0 (0.5-1.9)	2.9 (1.6-4.2)	<0.001
Proteinuria (g/24h)*	1.0 (0.5-2.2)	0.9 (0.5-1.7)	2.9 (1.8-3.8)	<0.001
Treatment				
RAS blockers	388 (77.9%)	340 (75.9%)	48 (96.0%)	0.001
Corticosteroids	56 (11.2%)	46 (10.3%)	10 (20%)	0.039

All data are expressed as mean ± SD or *median (and interquartile range)
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BUN, blood urea nitrogen; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; UPCR, urine protein-to-creatinine ratio

4. Multivariable Cox models for study endpoint

To determine the optimal level of proteinuria, I constructed multivariable Cox models where four groups of TA-P were entered after adjustment of clinical parameters and pathologic findings (Table 4). A risk of reaching D-sCr did not differ between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g in a model 1 adjusted for age, mean arterial pressure, the

Table 4. Multivariable Cox regression models for study endpoint

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (1 year)	0.97 (0.94 to 0.99)	0.018	0.96 (0.94 to 0.99)	0.012	0.96 (0.93 to 0.99)	0.012
eGFR (1 ml/min/1.73 m^2)	0.97 (0.96 to 0.98)	<0.001	0.98 (0.97 to 0.99)	<0.001	0.98 (0.96 to 0.99)	<0.001
MAP (1 mmHg)	1.00 (0.97 to 1.02)	0.849	1.00 (0.98 to 1.03)	0.999	1.00 (0.97 to 1.03)	0.999
Hypertension (vs. no)	1.25 (0.68 to 2.29)	0.482	1.13 (0.59 to 2.18)	0.709	1.16 (0.60 to 2.24)	0.657
TA-P (g/g)						
< 0.5	reference		reference		reference	
0.5 to 0.99	3.91 (0.40 to 37.89)	0.240	3.85 (0.39 to 37.63)	0.247	3.34 (0.33 to 34.22)	0.310
1.0 to 1.99	40.82 (5.40 to 309.16)	<0.001	38.9 (5.07 to 298.36)	<0.001	33.92 (4.25 to 270.49)	0.001
≥ 2.0	202.29 (26.86 to 523.73)	<0.001	205.5 (26.46 to 596.74)	<0.001	171.52 (20.85 to 411.01)	<0.001
Pathologic findings						
M1 (vs. M0)	-	-	0.73 (0.36 to 1.47)	0.376	0.76 (0.37 to 1.57)	0.461
E1 (vs. E0)	-	-	1.60 (0.61 to 4.23)	0.344	1.42 (0.51 to 3.97)	0.499
S1 (vs. S0)	-	-	1.19 (0.65 to 2.17)	0.569	1.17 (0.64 to 2.14)	0.611
T1 (vs. T0)	-	-	1.44 (0.58 to 3.59)	0.434	1.47 (0.59 to 3.68)	0.407
T2 (vs. T0)	-	-	2.78 (1.16 to 6.64)	0.022	2.72 (1.13 to 6.55)	0.026
Treatment						
RAS blockers (vs. no)	-	-	-	-	1.35 (0.28 to 6.39)	0.709
Corticosteroids (vs. no)	-	-	-	-	1.44 (0.68 to 3.06)	0.341

Abbreviations: HR, hazard ratio; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; RAS, renin-angiotensin system

presence of hypertension, and eGFR (HR, 3.91; 95% CI, 0.40-37.89; P = 0.240). Although pathologic findings were added to model 1, a HR was not significantly altered (HR, 3.85; 95% CI, 0.39-37.63; P = 0.247) (Table 4, Model 2). Furthermore, the fully adjusted model including the use of RAS blockers and corticosteroids revealed no significant increase in risk of reaching D-sCr in patients with TA-P of 0.5-0.99 g/g, as compared to those with TA-P < 0.5 g/g (HR, 3.34; 95% CI, 0.33-34.22; P = 0.310) (Table 4, Model 3). Of note, risk of progression was markedly increased from patients with TA-P of 1.0-1.99 g/g and highest in patients with TA-P > 2.0 g/g. Such increased risks in these groups were consistently noted in all three models.

5. Proteinuria reduction and renal outcome

I further evaluated renal outcome of patients categorized according to initial proteinuria and TA-P (Table 5). Among 267 patients with baseline UPCR < 1.0 g/g, 171, 65, and 31 patients had TA-P of < 0.5, 0.5-0.99, and > 1.0 g/g, respectively. There was no difference in the development of D-sCr between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g. However, compared to these two groups, 4 (12.9%) patients with TA-P > 1.0 g/g reached D-sCr (P < 0.001). In addition, among 233 patients with baseline UPCR ≥ 1.0 g/g, 50, 70, and 113 patients had TA-P of < 0.5, 0.5-0.99, and ≥ 1.0 g/g, respectively. There were no patients with TA-P of < 0.5 g/g who reached D-

sCr. In addition, only one (2.9%) patient among the group with 0.5-0.99 g/g attained this endpoint. However, compared to these two groups, 44 (38.9%) patients with TA-P ≥ 1.0 g/g reached D-sCr ($P < 0.001$). A Kaplan-Meier curve also showed that the 10-year renal survival rates were comparable between patients with TA-P of < 0.5 g/g and those with TA-P of 0.5-0.99 g/g irrespective of their baseline UPCR. However, if patients had TA-P ≥ 1 g/g during follow-up, their 10-year survival rates were significantly decreased although they had the baseline UPCR < 1.0 g/g (Figure 3).

Table 5. Proteinuria reduction and renal outcome

	All	UPCR < 1.0 g/g			P-value	UPCR ≥ 1.0g/g			P-value
		TA-P < 0.5 g/g	TA-P 0.5-0.99 g/g	TA-P ≥ 1.0 g/g		TA-P < 0.5 g/g	TA-P 0.5-0.99 g/g	TA-P ≥ 1.0 g/g	
Total	500	171	65	31		50	70	113	
Non-progressors	448 (89.6%)	170 (99.4%)	64 (98.5%)	27 (87.1%)	<0.001	50 (100%)	68 (97.1%)	69 (61.1%)	<0.001
Progressors	52 (10.4%)	1 (0.6%)	1 (1.5%)	4 (12.9%)		0 (0%)	2 (2.9%)	44 (38.9%)	

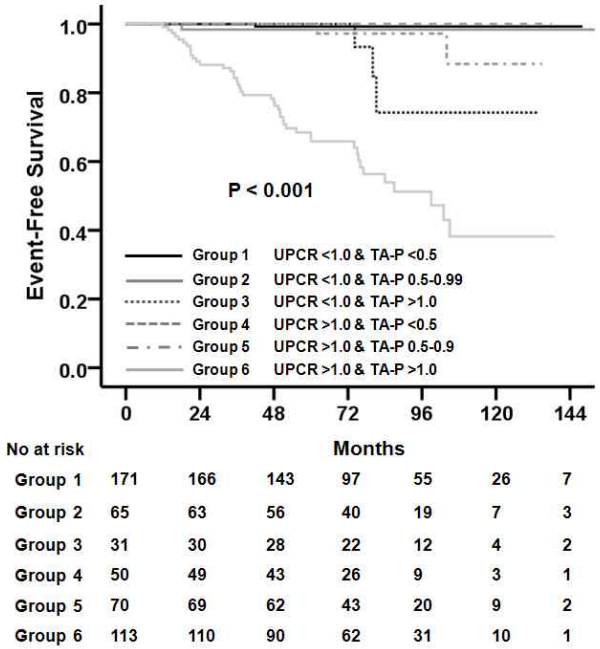

Figure 3. The Kaplan–Meier renal survival curve of patients with IgAN according to baseline urine protein-to-creatinine ratio and time-averaged proteinuria

IV. DISCUSSION

In this study, I sought to identify the optimal level of proteinuria reduction to attenuate kidney disease progression in patients with IgAN. I showed that risk of progression was comparable between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g. In addition, although patients presented proteinuria > 1.0 g/g at disease onset, their renal outcome was favorable if they achieved TA-P < 1.0 g/g, which was similar to patients with TA-P < 1.0 g/g throughout the follow-up period. These findings suggest that the optimal anti-proteinuric goal is < 1.0 g/g in patients with IgAN.

Proteinuria has long been not only a marker of kidney damage but a therapeutic target in the management of various kidney diseases. In diabetic nephropathy, albuminuria is the first clinical sign of diabetic kidney injury. Many studies have consistently shown that improved renal outcome was concordant to reduction of proteinuria conferred by RAS blockers in patients with overt diabetic nephropathy.[18-20] Similar effect of proteinuria reduction was also evident in non-diabetic kidney diseases.[21, 22] Not surprisingly, therefore, proteinuria is considered a modifiable risk factor for kidney disease progression. However, excluding some glomerulonephritis which are well responsive to immunosuppressive drugs or undergo spontaneous remission, it is difficult to achieve complete resolution of proteinuria. Moreover, it is also unknown the optimal level of proteinuria reduction to halt progression of

kidney disease.

To date, in patients with IgAN, a number of studies have suggested that proteinuria should be decreased < 1.0 g/day because risk of progression is remarkably increased beyond this point.[23-25] However, there has been emerging concern whether further reduction of proteinuria is required because residual proteinuria remains. Several studies addressed this issue with conflicting results. In a Chinese cohort study by Le et al., TA-P 0.5-1.0 g/day were associated with a 9.1-fold increased risk of progression compared to TA-P < 0.5 g/day, suggesting that target for proteinuria reduction should be lowered to 0.5 g/day.[12] On the other hand, using the Toronto Glomerulonephritis Registry, Reich et al. reported that renal survival was similar between patients with TA-P < 0.3 g/day and TA-P of 0.3-1.0 g/day.[11] A recent Spanish study of 141 IgAN patients with minor abnormalities at presentation also supported this finding because TA-P > 0.5 g/day was no longer associated with developing a > 50% increase of baseline serum creatinine levels in the adjusted multivariable analysis as compared to TA-P < 0.5 g/day.[26] In keeping with findings of the latter two studies, I showed that there was no difference in renal outcome between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g. Only 4 patients with TA-P < 1.0 g/g developed D-sCr and none of them reached ESRD during follow-up. Their 10-year survival rates were excellent. Furthermore, renal outcome was comparable between patients with baseline proteinuria > 1.0 g/g who achieved

TA-P < 1.0 g/g and patients with TA-P < 1.0 g/g throughout the follow-up period. These findings together suggest that the cut-off level of proteinuria suggested by the current guideline is reasonable.

In the Chinese cohort study, it is unclear why patients with TA-P of 0.5-1.0 g/day were at greater risk of progression than those with TA-P < 0.5 g/day. Unfortunately, tubulointerstitial fibrosis or glomerulosclerosis that is widely accepted as most important pathologic factors affecting renal outcome was not evaluated in their study. Therefore, their finding should be interpreted with caution. Of note, only the Spanish cohort study and the present study incorporated pathologic findings in the multivariable analyses and these two studies did not find a significant advantage conferred by further reduction of proteinuria among patients with TA-P < 1.0 g/day or 1.0 g/g. However, initial kidney biopsy findings at disease onset may not reflect time-dependent changes of clinical parameters during the course of IgAN. Interestingly, in the present study, the Oxford M-, S-, and T-scores were higher in patients with TA-P of 0.5-0.99 g/g than in those with TA-P < 0.5 g/g although there was no difference in the development of D-sCr between the two groups. Thus, it remains to be determined whether such moderate amount of proteinuria may increase risk of progression in the end.

The present study also supported the previous findings that threshold of proteinuria reduction differs depending on types of proteinuric glomerular diseases.[14, 27] In other glomerulonephritis such membranous nephropathy

(MGN) or focal segmental glomerulosclerosis, patients with proteinuria of 1.0-2.0 g/day had similar eGFR decline rate to those with proteinuria of 0.5-1.0 g/day.[14] In particular, eGFR decline rate in patients with MGN who had proteinuria < 3.5 g/day was only -0.93 ml/min/1.73 m^2 and 12.0% of these patients developed a 50% decrease in creatinine clearance during a median follow-up of 82 months.[27] In contrast, in the Toronto study by Reich et al, renal survival sharply began to decline from TA-P of 1-2 g/day in patients with IgAN.[11] This finding was corroborated by my study showing that risk of reaching D-sCr remarkably began to increase from TA-P > 1.0 g/g. A 10-year renal survival rate of patients with TA-P < 1.0 g/g was > 90% and none of these patients developed ESRD, whereas that of patients with TA-P of 1.0-1.99 g/g was 67.0% and 11 (11.5%) patients developed ESRD. Therefore, unlike other types of primary glomerulonephritis in which subnephrotic proteinuria is not associated with higher risk of loss of kidney function, aggressive treatment to lower proteinuria to 1.0 g/g can be justified in patients with IgAN.

In this study, I used TA-P instead of baseline proteinuria. Although several cohort studies showed that baseline proteinuria independently predicted renal outcome,[3, 5] there is concern that it may not reflect the course of disease or the effect of treatment. In fact, I showed that patients with baseline proteinuria < 1.0 g/g, if their TA-P achieved > 1.0 g/g during follow-up, had decreased renal survival rate. Of note, Szeto CC et al. reported that one-third of IgAN patients

with minimal proteinuria developed proteinuria > 1g/day during a median follow-up of 7 years.[28] In addition, many recent studies have suggested that proteinuria over time is more closely associated with renal outcome compared to baseline proteinuria.[8, 9, 11-13] These findings can provide a rationale for the use of TA-P, particularly when we intent to offer the optimal level of proteinuria reduction.

Several shortcomings of this study should be discussed. First, this study was retrospective in nature, thus the effects of therapeutic interventions such as RAS blockers or corticosteroids could not be accurately assessed. The KDIGO guideline suggests the use of corticosteroids in patients with persistent proteinuria > 1.0 g/day and preserved kidney function.[23, 29, 30] In this study, corticosteroids were prescribed in 56 (11.2%) patients. Of note, 14 (6.3%) and 17 (12.6%) of patients with TA-P < 0.5 g/g and 0.5-0.99 g/g received corticosteroids, respectively. 23 (74.2%) of these patients initially had persistent proteinuria > 1 g/g, despite optimized supportive care at least for 3 months and the remaining 8 (25.8%) showed nephrotic syndrome at presentation. All these patients responded to corticosteroids and achieved a favorable outcome. Although this finding may favor the use of corticosteroids, it was not associated with an improved renal outcome in the fully adjusted multivariable model. More well-designed prospective studies are required to validate the effect of corticosteroids. Second, I used UPCR for the calculation of TA-P. In fact, 24-h urine collection, a gold standard method to assess

proteinuria, was burdensome and thus not feasible at all visits. It is usually repeated only when proteinuria substantially increases. Because UPCR is easily performed in the setting of outpatient clinics and can be reliably used to monitor proteinuria,[31] my institution performs UPCR at every visit instead of 24-h urine collection. Therefore, in this study, calculating TA-P based on UPCR is more correct to reflect the average proteinuria during follow-up period. Finally, median follow-up duration was 65 months, which is relatively shorter than previous studies.[11, 26] During this period, only 4 patients reached D-sCr and none developed ESRD among patients with TA-P < 1.0 g/g. Given the very slow progressive nature of IgAN, a longer period of observation is required to evaluate whether more renal events will occur in these patients with moderate proteinuria.

V. CONCLUSION

In conclusion, this study showed that risk of progression was comparable between patients with TA-P < 0.5 g/g and those with TA-P of 0.5-0.99 g/g. In addition, irrespective of initial proteinuria, if they achieved TA-P < 1.0 g/g, their renal outcome was favorable. These findings suggest that the optimal anti-proteinuric goal is < 1.0 g/g in patients with IgAN. Further studies are required to clarify whether reduction of proteinuria of < 0.5 g/g may confer a more renoprotective advantage.

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ABSTRACT (IN KOREAN)

IgA 신병증 환자에서 신기능 보존을 위한 단백뇨 감량의 적정 수준

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남 기 헌

단백뇨는 다양한 사구체 질환에서 신기능 보존을 위한 치료 표적이다. 그러나 IgA 신병증 환자에서 단백뇨 감량의 적정 수준에 대해서 명확히 알려진 바가 없다. 따라서 본 연구는, 현재 진료 지침에서 제시하고 있는 수준인 1일 1 g의 단백뇨 보다 더 감량하는 것이 IgA 신병증 환자의 신기능 보존에 유리할 것인지를 알아보고자 하였다. 본 후향적 관찰 코호트 연구는, 2000년 1월부터 2010년 12월까지 세브란스 병원과 국민건강보험 일산병원을 방문하여 신생검으로 IgA 신병증을 진단받은 644명의 환자 중 500명을 선별하여 진행하였다. 추적 관찰 기간 동안의 무작위 소변의 단백과 크레아티닌 비율을 조사하여 평균치 단백뇨 (Time-averaged proteinuria, TA-P)를 구하였으며, 연구 종결점은 혈중 크레아티닌 수치가 기저치로부터 2배 이상으로 증가한 경우 (D-sCr)와 말기 신질환 (ESRD)의 발생이었다. ESRD는 투석을 시작하거나, 신이식을 받는 경우로 정의하였다. 분석을 시행한 결과, TA-P < 0.5, 0.5-0.99, 1.0-1.99, ≥ 2.0 g/g인 군이 각각 221명 (44.2%), 135명 (27.0%), 96명 (19.2%), 48명 (9.6%)이었다. 중앙값 65개월의 추적 관찰 기간 동안, 각각의 군에서 D-sCr이 1명 (0.5%), 3명 (2.2%), 18명 (18.8%),

30명 (62.5%)에서 발생하였다 (P < 0.001). TA-P < 0.5 g/g와 TA-P 0.5-0.99 g/g의 두 군을 비교하였을 때, D-sCr 발생의 통계학적인 차이는 없었다. 이 두 군에서는 ESRD가 발생하지 않았으나, TA-P 1.0-1.99, ≥ 2.0 g/g인 군에서는 각각 11명 (11.5%)과 23명 (47.9%)의 환자에서 ESRD가 발생하였다. Cox 회귀 분석 결과, 환자들의 나이, 사구체여과율, 혈압, 병리학적 소견, 그리고 환자가 받은 치료를 보정하였을 때에도, TA-P < 0.5 g/g 군에 비해 TA-P 0.5-0.99 g/g 군의 D-sCr 발생의 위험도에 차이는 없었으나 [hazard ratio (HR), 3.34; 95% confidence interval (CI), 0.33-34.22; P = 0.310], TA-P 1.0-1.99 군 (HR, 33.92; 95% CI, 4.25-270.49; P = 0.001)과 TA-P > 2.0 g/g 군 (HR, 171.52; 95% CI 20.85-411.01; P < 0.001)에서는 그 위험도가 급격하게 증가하였다. 이러한 결과들은 IgA 신병증 환자에서 적정 단백뇨의 감량 수준이 < 1.0 g/g 이라는 것을 시사하고 있다. IgA 신병증 환자에서 < 0.5 g/g로 단백뇨를 감량하는 것이 신기능 보존에 더 유리할 것인지에 대해서는, 추후 많은 연구가 이루어져야 하겠다.

핵심되는 말 : IgA 신병증, 단백뇨, 예후