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NEPHROLOGY – ORIGINAL PAPER

Severity of nephrotic IgA nephropathy according to the Oxford classification

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Abstract
Background IgA nephropathy with nephrotic syndrome (nephrotic IgAN) is a rare form of IgAN. Its prognosis and response to steroid therapy are still controversial because the differential diagnosis between nephrotic IgAN and minimal change nephrotic syndrome with IgA depositions is sometimes confused.
Methods In this retrospective cohort analysis, we accurately diagnosed 42 cases of nephrotic IgAN (4.4%) from 954 IgAN patients, according to the Oxford classification. We analyzed the clinical and histological data, prognosis, and response to steroid therapy.
Results In nephrotic IgAN, mean estimated glomerular filtration rate (eGFR) was 51.1 ± 24.6 ml/min, proteinuria was 5.71 ± 2.56 g/day, and urinary red blood cells were 51.0 ± 37.8 high power field. Both active and chronic histological lesions were observed. Cumulative renal survival rate was significantly lower in nephrotic IgAN than in non-nephrotic IgAN (the control group consisted of 47 non-nephrotic IgAN patients diagnosed between 1995 and 1996) (log-rank test: $P < 0.0001$). The cases with steroid therapy significantly improved their prognosis, though their male-to-female ratio and blood pressure level measured at renal biopsy were significantly lower than in the cases without steroid therapy. Steroid therapy was particularly effective in cases with low-grade tubular atrophy and interstitial fibrosis (T-grade in Oxford classification). Without steroid therapy, lower eGFR and higher T-grade were independent risk factors for severe outcome by multivariate Cox regression.
Conclusion Nephrotic IgAN is a very severe form of IgAN, with renal dysfunction, massive hematuria, and active and chronic histopathological lesions. Renal outcome is severe; however, steroid therapy can improve prognosis in cases with higher eGFR and lower T-grade, according to the Oxford classification.

Keywords IgA nephropathy · Nephrotic syndrome · Oxford classification · Steroid

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Introduction

Urinary findings in patients with IgA nephropathy (IgAN) usually consist of mild-to-moderate proteinuria and mild-to-severe hematuria, and it rarely presents as nephrotic syndrome. However, some cases of IgAN do present with nephrotic syndrome (nephrotic IgAN), whose prevalence varies from 5 to 20% [1–9]. Some previous studies might have included patients who were suspected of minimal change nephrotic syndrome

(MCNS) with IgA depositions. Mesangial IgA deposition appears in about 16% of healthy individuals [10], which make difficult accurate differential diagnosis between nephrotic IgAN and MCNS with IgA depositions. Some studies of nephrotic IgAN have shown a good response to steroid therapy and good prognosis, although proteinuria is widely recognized as a risk factor in patients with IgAN [11, 12]. Therefore, it is important to differentiate nephrotic IgAN from MCNS with IgA depositions.

The Oxford classification, created in 2009, is a novel method for evaluation of histological findings of IgAN [13, 14]. This classification has good reproducibility and can be used to evaluate prognosis and response to therapy. In this retrospective cohort study, we used the Oxford classification to accurately diagnose nephrotic IgAN and to evaluate the clinical findings, pathological background, response to steroid therapy, and prognosis.

Patients and methods

Patients

From 1974 to 2009, 954 patients were diagnosed with primary IgAN by renal biopsy at Tokyo Women's Medical University. The range of patient's age was 15–79 years old. The diagnosis of IgAN was generally based on the light-microscopic findings of mesangial proliferative changes, immunofluorescence of mesangial IgA deposition, and electron-microscopic findings of electron-dense deposits in the mesangial area. Nephrotic syndrome was defined by the following criteria: (1) proteinuria was >3.5 g/day; (2) serum total protein was <6.0 g/dl or serum albumin was <3.0 g/dl; and/or (3) expression of edema. The following criteria were used to exclude MCNS with IgA deposition: (1) total grade was zero by the Oxford classification; (2) selectivity index was <0.1; (3) urinary red blood cell count was <10/high power field (HPF); and (4) deficiency of C3 deposition. We excluded patients who met at least two of these criteria, because it was possible that some of the features of nephrotic syndrome were due to MCNS. Also, patients with systemic diseases such as diabetes mellitus, collagen diseases, abnormal hypergammaglobulinemia, and chronic liver diseases were excluded.

Evaluation of clinical and histological findings

From 954 IgAN patients, we diagnosed 42 (4.4%) with nephrotic IgAN. To compare the survival analysis between nephrotic IgAN and non-nephrotic IgAN, we selected 47 patients with non-nephrotic IgAN diagnosed in 1995 and 1996, because the maximal observation period in nephrotic IgAN patients was 16 years, and we selected patients according to the observation period. We divided nephrotic IgAN into two groups according to treatment: (A) steroid group ($n = 27$) and (B) non-steroid group ($n = 15$), and compared the clinical and histological data between the groups. To evaluate steroid therapy, we also divided the 27 patients treated with steroids into two groups according to prognosis: (A) responder group ($n = 14$), which was defined as patients who reached to the incomplete remission (proteinuria was under 1.0 g/day) by the steroid therapy; and (B) non-responder group ($n = 13$), which was defined as patients who did not reach the incomplete remission despite steroid therapy. Prescription of steroid treatment was decided individually by each doctor. Initial dose of prednisolone was 41.2 ± 9.9 mg/day (0.5–0.8 mg/kg/day), eight cases were treated with steroid pulse therapy, and the mean duration of therapy was 4.0 ± 3.3 years. Inhibitors of the renin angiotensin system were employed in 13 cases (48.1%) in the steroid group and in five cases (33.3%) in the non-steroid group.

The clinical data that were analyzed included sex, age, body mass index, systolic, and diastolic blood pressure (SBP and DBP). The laboratory data included serum total protein, serum albumin, blood urea nitrogen, serum creatinine (S–Cr), estimated glomerular filtration rate (eGFR), serum uric acid (UA), serum total cholesterol (T-Cho), serum LDL-cholesterol and triglyceride, serum IgA, serum complement component C3, urinary protein excretion, urinary red blood cell count (URBC), urinary β-2 microglobulin (U-β2MG), and urinary N-acetylglutamate (NAG).

All biopsy specimens were obtained by the percutaneous needle biopsy method. The specimens were fixed with 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin, and cut into 4-μm-thick sections. The sections were stained with hematoxylin and eosin, periodic acid Schiff, silver methenamine, and Masson trichrome for light-microscopic examination. The histological findings such as mesangial and endothelial hypercellularity, segmental glomerular

sclerosis, and tubular atrophy/interstitial fibrosis were graded according to the Oxford classification [13, 14]. Biopsies containing <8 glomeruli were excluded from the analysis which criteria was as same as Oxford classification.

Statistical analysis

Data were expressed as means ± standard deviation and analyzed using JMP® 8.0.1 (SAS institute Inc, NC, USA). Unpaired Student's *t*-test for normally distributed data and Mann–Whitney's *U*-test for non-normally distributed data were used to compare the clinical and histological findings. The χ^2 test was used to compare the histological grades according to the Oxford classification and the sex distribution at the time of renal biopsy. The cumulative renal survival rate until ESRD was calculated according to the Kaplan–Meier method and the log-rank test. In multivariate analysis, we used Cox proportional hazards model to analyze the risk to deteriorate to the end-stage renal disease (ESRD: required hemodialysis or renal transplantation). Differences with P values <0.05 were considered to be statistically significant in all the analyses.

Results

Clinical and histological findings in all cases, steroid group and non-steroid group at the time of renal biopsy

Table 1 shows the clinical background of all cases and the steroid and non-steroid groups. The male/female ratio was even for all cases of nephrotic IgAN; however, the proportion of female patients was significantly higher in the steroid group than in the non-steroid group (χ^2; $P = 0.024$). SBP and DBP were significantly lower in the steroid group than in the non-steroid group by Student's *t*-test (SBP, $P = 0.0035$, DBP, $P = 0.0015$). None of the other clinical data differed significantly between the both groups. The clinical data for all the cases of nephrotic IgAN showed that the disease was already advanced, because renal function had deteriorated, such as higher S–Cr (1.33 ± 0.73 mg/dl) and lower eGFR (51.1 ± 24.6 ml/min), and severe interstitial changes were suspected from as the high levels of U-β2MG and NAG (988 ± 1,508 μg/l and 18.9 ± 10.1 U/l, respectively). However, high U-RBC (51.0 ± 37.8 cells/HPF) was indicative of active glomerular lesions.

Table 1 also shows the histological evaluation according to the Oxford classification. Tubular atrophy/interstitial fibrosis (T-Grade) tended to be higher, and endocapillary hypercellularity tended to be lower in the steroid than in the non-steroid group. However, there was no significant difference in Oxford classification grade between the steroid and non-steroid group by the χ^2 test. Seven cases were excluded from the histological evaluation by Oxford classification because the number of glomeruli was <8.

Outcome of nephrotic IgAN in the steroid and non-steroid group

The cumulative survival rate until ESRD was significantly higher in non-nephrotic than nephrotic IgAN (log-rank test: $P < 0.0001$) (Fig. 1). Mean survival was 5.3 years in nephrotic IgAN and 8.6 years in non-nephrotic IgAN. In the nephrotic IgAN group, the cumulative survival rate until ESRD was significantly higher in the steroid group than in the non-steroid group (log-rank test: $P = 0.0002$) (Fig. 2). All cases in the non-steroid group developed ESRD, and the mean survival was only 4.3 years, compared with 7.37 years in the steroid group. Cases with complete remission in which proteinuria was under 0.3 g/day was 0% in the non-steroid group and only 14.8% (4/27 cases) in the steroid group. Incomplete remission (IR) in which proteinuria was under 1.0 g/day throughout the observation period was 0% in the non-steroid group and 51.8% (14/27 cases) in the steroid group.

Difference between steroid responder and non-responder groups

Table 2 shows the clinical findings in the steroid responder group ($n = 14$), which reached to the IR and the non-responder group ($n = 13$), which did not reach the IR. The responder group showed significantly better blood urea nitrogen ($P = 0.02$), but the other clinical findings were not different between the groups. According to the Oxford classification, tubular atrophy/interstitial fibrosis (T-grade) was significantly lower in the responder group ($P = 0.012$).

Table 1 Clinical and histological findings of nephrotic IgAN at the time of renal biopsy

	All cases	Steroid group	Non-steroid group	*P* value
Clinical findings				
Sex (male/female)	21/21	10/17	11/4	0.024
Age (years)	34.2 ± 12.6	32.7 ± 12.3	36.7 ± 12.0	NS
BMI	23.0 ± 3.73	23.1 ± 3.4	22.9 ± 4.5	NS
SBP (mmHg)	133.2 ± 18.4	127.2 ± 17.9	143.9 ± 14.5	0.0035
DBP (mmHg)	82.5 ± 12.6	79.1 ± 12.4	88.7 ± 10.8	0.0015
TP (g/dl)	5.22 ± 0.52	5.17 ± 0.53	5.31 ± 0.51	NS
Alb (g/dl)	2.83 ± 0.37	2.80 ± 0.36	2.89 ± 0.40	NS
BUN (mg/dl)	20.6 ± 8.53	18.7 ± 6.99	23.9 ± 10.2	NS
S-Cre (mg/dl)	1.33 ± 0.73	1.24 ± 0.81	1.48 ± 0.56	NS
e-GFR (ml/min)	51.1 ± 24.6	55.8 ± 27.6	42.8 ± 16.2	NS
UA (mg/dl)	6.9 ± 1.5	6.8 ± 1.3	7.1 ± 1.7	NS
T-Cho (mg/dl)	268.1 ± 66.6	277.0 ± 73.5	252.7 ± 51.3	NS
LDL-C (mg/dl)	176.3 ± 66.0	184.1 ± 69.1	160.8 ± 58.8	NS
TG (mg/dl)	189.5 ± 110.8	178.5 ± 106.5	208.5 ± 119.3	NS
IgA (mg/dl)	320.4 ± 133.7	333.9 ± 137.4	292.3 ± 126.1	NS
C3 (mg/dl)	86.0 ± 22.5	86.8 ± 24.2	84.4 ± 19.5	NS
U-Prot (g/day)	5.71 ± 2.56	5.73 ± 2.05	5.66 ± 3.37	NS
U-RBC (counts/HF)	51.0 ± 37.8	57.8 ± 35.9	38.9 ± 39.4	NS
U-β2MG (μg/l)	988 ± 1,508	1,051 ± 1,224	896 ± 1,908	NS
NAG (U/l)	18.9 ± 10.1	20.6 ± 10.8	14.9 ± 7.2	NS
S.I.	0.25 ± 0.12	0.24 ± 0.14	0.26 ± 0.07	NS
Histological findings (*Oxford classification*)				
Mesangial hypercellularity				
M0/M1 (number)	14/21	9/14	5/7	0.88
Endocapillary hypercellularity				
E0/E1 (number)	20/15	11/12	9/3	0.12
Segmental glomerulosclerosis				
S0/S1 (number)	6/29	4/19	2/10	0.96
Tubular atrophy/interstitial fibrosis				
T0/T1/T2(number)	12/14/9	10/7/6	2/7/3	0.20
Out of evaluation	7	4	3	

BMI, body mass index; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *TP,* total protein; *Alb,* albumin; *BUN,* blood urea nitrogen; *S-Cre,* serum creatinine; *TG,* triglyceride; *C3,* complement component C3; *SI,* selectivity index

Multivariate analysis of factors to deteriorate to ESRD

We evaluated by Cox proportional hazards model the clinical findings at the time of biopsy and histological findings of nephrotic IgAN patients with a risk of progression to ESRD. In the clinical findings, male (vs. female), lower eGFR, without steroid therapy, and higher T-grade were independent risk factors for deterioration to ESRD [male: hazard ratio (HR) 4.45, $P = 0.0241$, eGFR: HR 2.78, $P < 0.0001$, without steroid therapy: HR 6.7, $P = 0.0024$, T-grade: HR 2.31, $P = 0.0138$] (Table 3).

Discussion

Nephrotic IgAN is a rare form of IgAN, and there is still controversy over whether it responds well to steroid therapy and has a good prognosis. Some

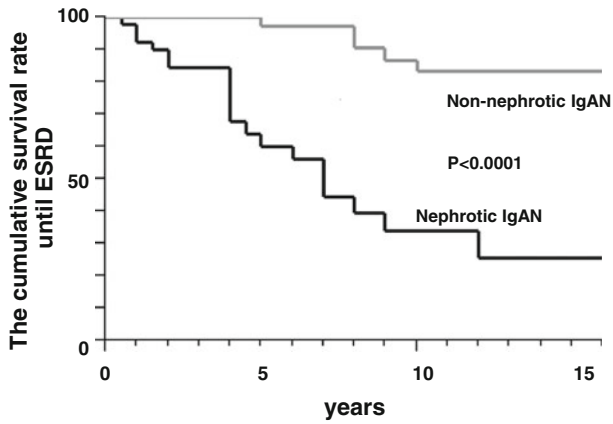

Fig. 1 Cumulative survival rate until ESRD of nephrotic and non-nephrotic IgAN. The survival rate was significantly higher in non-nephrotic than nephrotic IgAN (log-rank test, $P < 0.0001$)

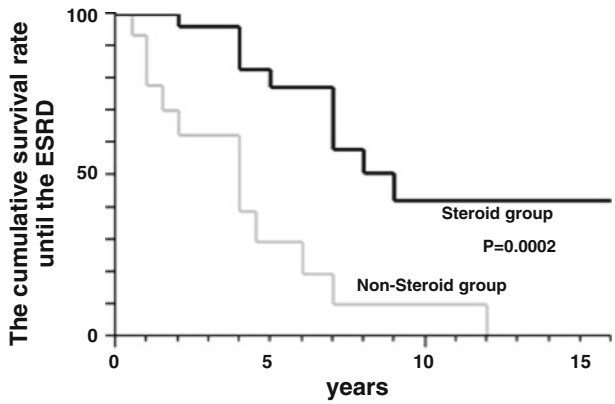

Fig. 2 Cumulative survival rate until ESRD of the steroid and non-steroid groups in nephrotic IgAN. The survival rate of the steroid group was significantly higher than that of the non-steroid group (log-rank test, $P < 0.0002$)

previous studies of nephrotic IgAN have indicated the presence of MCNS with IgA depositions [2–4, 6–9]. These previous studies have included IgAN with minimal to mild histological change, absence of hematuria and complement component C3 deposition, early response to steroid therapy, and frequent relapse, and they have also reported the possibility of MCNS with IgA depositions. We previously have reported that latent mesangial IgA deposition was present in 82 (16.1%) of 510 renal allografts [10], and 15 (23.8%) of 63 patients with MCNS [15], as well as mild hematuria. Therefore, it has been difficult to make an accurate diagnosis between MCNS with IgA deposition and nephrotic IgAN, and there could have been some confusion between the two conditions previously. In the present study, we used criteria based on the Oxford classification to make an accurate diagnosis of nephrotic IgAN and exclude MCNS with IgA deposition.

In the present study, we diagnosed 42 cases of nephrotic IgAN (4.4%) in 954 IgAN patients. There were fewer cases than in previous studies, as we expected, because MCNS with IgA deposition was excluded from the present study. On the other hand, we diagnosed 30 cases (15.5%) as MCNS with deposition from 194 MCNS patients. For clinical findings, we observed proteinuria in the nephrotic range and a high level of U-RBC, and renal function had already deteriorated in most cases of nephrotic IgAN. For histological findings, the Oxford classification showed severe IgAN with active, progressive, and deteriorated lesions. Also, renal survival rate was significantly lower than that with non-nephrotic IgAN. These results indicate that nephrotic IgAN is a very severe form of IgAN, and different from that in several previous studies [1–4, 6–9]. For the non-nephrotic IgAN, Pozzi et al. reported the beneficial effect of steroid pulse therapy by the randomized controlled trial. They have reported that 6 month course of steroid therapy (1 g of methylprednisolone intravenously for three consecutive days every other month and oral prednisolone 0.5 mg/kg every other day for

Table 2 Clinical and histological findings of responder group and non-responder group at the time of renal biopsy

	Responder group	Non-responder group	*P* value
Clinical findings			
Sex (male/female)	5/9	5/8	NS
Age (years)	34.2 ± 13.3	31.2 ± 11.6	NS
BMI	23.3 ± 3.3	23.7 ± 3.3	NS
SBP (mmHg)	122.1 ± 18.1	132.6 ± 16.7	NS
DBP (mmHg)	77.0 ± 14.0	81.4 ± 10.6	NS
TP (g/dl)	5.09 ± 0.48	5.26 ± 0.59	NS
Alb (g/dl)	2.84 ± 0.41	2.76 ± 0.31	NS
BUN (mg/dl)	15.8 ± 4.43	21.8 ± 8.02	0.02
S-Cre (mg/dl)	1.00 ± 0.33	1.51 ± 1.06	NS
e-GFR (ml/min)	60.4 ± 24.5	50.8 ± 30.8	NS
UA (mg/dl)	6.70 ± 1.28	6.95 ± 1.44	NS
T-Cho (mg/dl)	259.4 ± 82.9	294.6 ± 60.8	NS
LDL-C (mg/dl)	169.2 ± 70.8	198.9 ± 66.8	NS
TG (mg/dl)	189.4 ± 128.0	167.7 ± 83.5	NS
IgA (mg/dl)	319.7 ± 171.8	365.2 ± 90.7	NS
C3 (mg/dl)	93.6 ± 29.1	80.6 ± 17.6	NS
U-Prot (g/day)	6.17 ± 2.49	5.26 ± 1.39	NS
U-RBC (counts/HF)	65.0 ± 38.0	50.0 ± 33.2	NS
U-β2MG (μg/l)	1,153.0 ± 1,556.6	1,005.1 ± 1,128.7	NS
NAG (U/l)	19.8 ± 11.0	21.3 ± 11.0	NS
S.I.	0.21 ± 0.17	0.27 ± 0.09	NS
Histological findings (Oxford classification)			
Mesangial hypercellularity			
M0/M1 (number)	4/8	5/6	0.55
Endocapillary hypercellularity			
E0/E1 (number)	6/6	6/5	0.82
Segmental glomerulosclerosis			
S0/S1 (number)	2/10	2/9	0.92
Tubular atrophy/interstitial fibrosis			
T0/T1/T2 (number)	7/5/0	3/2/6	0.012
Out of evaluation	2	2	

6 months) significantly decreased proteinuria and improved 10-year renal survival in comparison to the supportive therapy [16]. On the other hand, for the nephrotic IgAN, Lai et al. have reported a randomized controlled trial of steroid therapy. They have shown that 4-month steroid therapy (40–60 mg daily oral prednisolone for first 2 months and 20–30 mg dairy for latter 2 months) has a beneficial effect to decrease proteinuria on cases with minimal to mild histological changes; however there was no effect on renal function after 38 months [7]. Other studies have also shown a good response to steroid therapy in patients with minimal histopathological changes [3, 6, 8, 9]. However, these studies also shown resistance to steroid therapy in patients with severe histological change. Then, Barratt et al. [17] did not recommend steroid therapy for nephritic IgAN, other than nephrotic IgAN patients with minimal histological change. However, our study indicates a little possibility that steroid therapy could improve renal survival rate and decrease the risk to progress to ESRD in some cases of nephrotic IgAN with severe histological lesion. All 15 patients in the non-steroid group developed ESRD within 12 years, but 18 of the 27 patients in the steroid

Table 3 Hazard ratio of possible reaching ESRD risk factors in multivariate Cox regression

	Hazard ratio	95% CI	*P* value
Clinical findings			
Male (vs. female)	4.45	1.22–18.26	0.0241
Age (per 1 year)	0.95	0.90–1.00	0.0503
Without steroid therapy (vs. with steroid)	6.70	1.91–28.8	0.0024
Mean blood pressure (per 10 mmHg)	1.07	0.64–1.84	0.7993
U-Prot (per 1.0 g/day)	1.21	0.91–1.59	0.1924
U-RBC (per 25/HPF)	0.97	0.69–1.32	0.8316
e-GFR (per 10 ml/min lower)	2.78	1.46–5.71	<0.0001
Histological findings (*Oxford classification*)			
Mesangial hypercellularity	0.55	0.18–1.45	0.2062
Endocapillary hypercellularity	0.87	0.15–3.94	0.8608
Segmental glomerulosclerosis	0.70	0.11–4.41	0.6918
Tubular atrophy/interstitial fibrosis	2.31	1.18–4.88	0.0138

U-Prot urinary protein excretion

group showed prevention from ESRD though the baseline data about the sex and blood pressure was different between the groups. Moreover, 15-year survival rate in the steroid group was 46.8%; although this survival rate was much less than that of non-nephrotic IgAN (74.6%), steroid therapy might prevent from ESRD in some cases of nephrotic IgAN. The cases that responded to steroid therapy showed lower grade of tubular atrophy and interstitial fibrosis according to the Oxford classification and higher grade of tubular atrophy, and interstitial fibrosis was an independent risk factor for the deterioration to ESRD by multivariate analysis. To adapt steroid treatment to IgAN, it is important to analyze the renal biopsy findings, if the clinical findings demonstrate nephrotic syndrome. The Oxford classification can be useful for the adaptation of steroid therapy. The effectiveness of immunosuppressive agents for nephrotic IgAN has also been reported in recent years [1, 4]. These immunosuppressive agents, and combined therapy of tonsillectomy and steroid pulse therapy, which have become standard treatment for IgAN in Japan, may have some beneficial effects for nephrotic IgAN and should be evaluated.

The present study had some limitations. First, the study design was a retrospective cohort analysis. We compared the effectiveness of steroid and non-steroid therapy in nephrotic IgAN, and found a possible beneficial effect of steroid therapy. However, clinical background at the time of renal biopsy was different between both groups. In the steroid group, blood pressure was significantly better, and the female ratio was significantly higher than in the non-steroid group. These differences were the most important for prediction of prognosis, because hypertension and gender were one of the independent risk factors for progression of IgAN to ESRD. Also, in the steroid group, renal function was better, and more patients were treated with inhibitors of the renin angiotensin system than in the non-steroid group, although the differences were not significant. We could not rule out the possibility that these differences might have some effect on progression to ESRD. Moreover, prescription of steroid therapy was decided individually. To show strong evidence for steroid therapy of nephrotic IgAN, a randomized controlled trial should be conducted.

Second, the sample size of this study was very small. It would have been better to perform a large study; however, nephrotic IgAN is a very rare form of IgAN. We can observe only 42 cases (4.4%) from 954 IgAN cases in the past 35 years. Therefore, we suspect that it would be difficult to conduct a large, long-term controlled study.

In conclusion, nephrotic IgAN shows advanced and severe nephropathy with chronic and active histopathological lesions. Supportive therapy could not prevent from progression to ESRD; however, steroid therapy has the possibility to be effective in some cases of nephrotic IgAN with better renal function, and

lower interstitial change and tubular atrophy. Adaptation of steroid therapy should be carefully carried out.

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