Prognostic Value of Urinary Interleukin 6 in Patients with IgA Nephropathy: An 8-Year Follow-Up Study

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Key Words

IgA nephropathy · Interleukin 6 · Prognosis · Predictor

Abstract

We evaluated the significance of urinary IL-6 levels in the prediction of long-term renal outcome in patients with IgA nephropathy (IgAN). Fifty-nine patients with biopsy-proven IgAN were enrolled in this study. All patients had a creatinine clearance (Ccr) greater than 80 ml/min and normal serum creatinine concentration (Scr) on enrollment and were followed for 8.07 ± 1.72 years. Twenty-four-hour urine samples were obtained and urinary IL-6 was measured by ELISA. Fifteen patients exhibited a worsening of renal function (progressor). Renal function of the remaining 44 patients was stable during follow-up (non-progressor). The urinary IL-6 levels of progressors on enrollment were significantly higher than those of non-progressors (3.8 ± 3.8 and 1.8 ± 1.5 ng/day, respectively, $p = 0.0138$). We calculated the risk ratio for the progression to renal failure. Patients with a urinary IL-6 level greater than 2.5 ng/day at diagnosis had a 7.8-fold higher risk for the progression of the disease (95% CI 1.31–46.47, $p = 0.024$) compared with those whose urinary IL-6 level was less than 1.0 ng/day. In conclusion, urinary IL-6 levels could be used as a predictor of long-term renal

outcome in patients with IgAN. Patients with a urinary IL-6 level greater than 2.5 ng/day at diagnosis may have a worse prognosis.

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Introduction

IgA nephropathy (IgAN) was previously considered to be relatively benign and to have a reasonable long-term prognosis. However, a recent study indicated that 30–50% of patients with IgAN progress to end-stage renal disease over 20 years [1–3]. Prognostic factors for the future development of renal failure included the presence of nephrotic range proteinuria, an elevated serum creatinine level at diagnosis and the presence of hypertension [3]. The presence of severe disease on renal biopsy such as crescent formation and severe tubulointerstitial involvement is the most reliable predictor of unfavorable prognosis [3, 4]. However, some patients without any severe lesions on renal biopsy reached end-stage renal failure during the long-term follow-up period. Therefore, it is difficult to predict the individual prognosis. We have reported that patients with IgAN exhibited elevated levels of urinary IL-6, which correlated with the progression of renal involvement during a 10-month follow-up period

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0028-2766/02/0924-0824\$18.50/0

Accessible online at:
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[5]. However, the significance of urinary IL-6 excretion in the long-term follow-up of patients with IgA nephropathy remains unknown. Therefore, in this prospective study we investigated the relationship between urinary IL-6 levels and long-term renal outcome in patients with IgAN.

Patients and Methods

Fifty-nine patients with biopsy-proven IgAN (26 males, 33 females; mean age on enrollment 34.6 ± 11.3 years) were enrolled in this study and gave fully informed consent. Two renal pathologists determined the severity of disease according to Lee pathologic grading [4]. We excluded the patients according to the following exclusion criteria in order to minimize the effect of known prognostic indices; (1) patients with severe disease on renal biopsy such as crescent formation, segmental glomerulosclerosis and severe tubulointerstitial lesions (grade IV and V in Lee pathologic grading), and (2) patients with renal insufficiency [creatinine clearance (Ccr) of <80 ml/min]. All patients were followed up in the Nephrology Clinic at Nara Medical University Hospital for 8.07 ± 1.72 years. Twenty-four-hour urine samples were collected on enrollment and at the end of the follow-up period. Urinary IL-6 was measured using an ELISA system developed by Fuji Rebio Inc. (Tokyo, Japan) according to the manufacturer's instructions.

Results are expressed as mean $\pm$ SD. Statistical analysis was performed using the Wilcoxon signed rank test. The risk ratio for the progression to renal failure was calculated in a multiple logistic regression model.

Table 1. Characteristics of patients with IgAN

Variables	Progressors	Non-progressors	
Patients	15 (25.9%)	44 (71.1%)	
Age, years	31.3 ± 12.1	35.8 ± 10.9	n.s.
Presence of hypertension	5 (33.3%)	11 (25.0%)	
Creatinine clearance, ml/min	91.6 ± 7.1	93.2 ± 14.0	n.s.
Proteinuria, g/day	0.7 ± 0.2	0.9 ± 0.8	n.s.
Data are given as mean $\pm$ SD. n.s. = Statistically not significant.			

Table 2. Risk ratio of the independent factor for the renal failure

Independent variables	Risk ratio	95% CI
High urinary IL-6 excretion (>2.5 ng/day)	7.8	(1.31–46.47) ($p = 0.024$)
Moderate IL-6 excretion (1.0 – 2.5 ng/day)	3.3	(0.50–21.69) ($p = 0.217$)
Observation period (>8.1 years)	2.4	(0.66–9.08) ($p = 0.181$)
Hypertension (SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg)	1.2	(0.28–5.13) ($p = 0.798$)
Proteinuria (>1.0 g/day)	1.2	(0.31–4.58) ($p = 0.801$)

Results

During follow-up, 15 patients exhibited a deterioration of renal function which was defined as a Ccr of less than 60 ml/min (range: 20–56 ml/min) (progressor group). Percent reduction of Ccr during follow-up is more than 30% and percent reduction of Ccr per year is more than 3% in all patients belonging to the progressor group. The remaining 44 patients maintained stable renal function, i.e. Ccr remained above 80 ml/min (non-progressor group) and percent reduction of Ccr is less than 10% during follow-up. There was no difference in the age, gender, prevalence of hypertension, Ccr, degree of proteinuria, and histologic grade between the two groups on enrollment (table 1).

The urinary IL-6 excretion on enrollment in the progressor group was significantly higher than in the non-progressor group (3.8 ± 3.8 vs. 1.8 ± 1.5 ng/day, respectively, $p = 0.0138$). Furthermore, the urinary IL-6 excretion at the end of the follow-up period was also significantly higher in the progressor group (5.6 ± 5.8 vs. 1.9 ± 1.6 ng/day; progressors vs. non-progressors respectively, $p = 0.0040$). The urinary IL-6 excretion was significantly elevated at the end of the follow-up only in the progressor group ($p = 0.040$).

We studied the effect of treatment on the excretion of urinary IL-6. Twenty-four patients (41%) were treated with oral prednisolone and 26 patients (44%) were treated with angiotensin-converting enzyme inhibitor during the follow-up period. No difference of the urinary IL-6 excretion was observed after treatment.

We performed multiple logistic regression analysis in order to determine whether urinary IL-6 excretion was an independent risk factor for the progression to renal failure and calculated the risk ratio. Patients were divided into 3 groups according to the value of urinary IL-6 excretion on enrollment; 18 cases with urinary IL-6 excretion greater than 2.5 ng/day, 21 cases with urinary IL-6 excretion from 1.0 to 2.5 ng/day, and 20 cases with urinary IL-6 excretion

Fig. 1. Urinary IL-6 and change of renal function. Percent reduction of Ccr in patients with high urinary IL-6 excretion (>2.5 ng/day) is significantly higher than in patients with low urinary IL-6 excretion (≤ 1.0 ng/day).

less than 1.0 ng/day. As shown in table 2, a high level of urinary IL-6 excretion was an independent risk factor for the development of renal failure with a risk ratio for the progression of the disease of 7.8 compared with patients with low excretion of urinary IL-6 excretion (95% CI 1.31–46.47, $p = 0.024$). As shown in figure 1, percent reduction of Ccr is significantly higher in patients with high urinary IL-6 excretion compared with patients with low urinary IL-6 excretion.

Discussion

The main finding of this study is that the urinary IL-6 level at diagnosis is closely associated with the progression of IgAN over an 8-year follow-up period. To our knowledge, this is the first report which has demonstrated the clinical significance of urinary IL-6 levels in the long-term

renal outcome of patients with primary glomerulonephritis.

Most of the currently published studies regarding various prognostic markers for IgAN have followed patients for less than 3 years. However, although IgAN was initially believed to be a benign glomerulonephritis, the progression of IgAN typically occurs gradually as demonstrated by several previous studies [1–3]. In the report by Kusumoto et al. [1], the renal survival 3 years after the diagnosis of IgAN was 99% whereas the renal survival at 10 years was significantly lower at 80%. In addition, a further study by D'Amico et al. [3] demonstrated an actuarial renal survival rate in adult patients with IgAN of 50% over 20 years. It is therefore apparent that longer periods of follow-up are required in order to evaluate the roles of potentially important prognostic indicators, particularly when studying patients with normal renal function as in this study.

Multivariate analysis in this study revealed that higher urinary IL-6 excretion on enrollment, i.e. >2.5 ng/day had a 7.8-fold higher risk for the deterioration of renal function. Traditional prognostic factors, such as hypertension and proteinuria were weaker prognostic indicators for the risk of developing progressive disease. This may be partly because we excluded patients with renal insufficiency or severe renal disease on renal biopsy (grade IV and V in Lee pathologic grading) on enrollment. The development of renal insufficiency is frequently complicated by severe hypertension. Therefore, as a result of our rigorous inclusion criteria this study population could include fewer patients with severe hypertension or massive proteinuria. Therefore, in patients without renal insufficiency or severe renal disease on renal biopsy, urinary IL-6 levels may be a better prognostic indicator for the long-term renal outcome.

In conclusion, our findings suggest that urinary IL-6 levels could be a better long-term prognostic indicator for predicting renal outcome. Further studies are required to clarify the exact role of urinary IL-6 in the clinical course of IgAN.

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