Tonsillectomy and Steroid Pulse Therapy Significantly Impact on Clinical Remission in Patients With IgA Nephropathy

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• **We conducted a retrospective investigation of renal outcome in 329 patients with immunoglobulin A (IgA) nephropathy with an observation period longer than 36 months (82.3 ± 38.2 months) in our renal unit between 1977 and 1995. Clinical remission, renal progression, and the impact of covariates were estimated by Kaplan-Meier analysis and a Cox regression model. In 157 of 329 patients (48%), disappearance of urinary abnormalities (clinical remission) was obtained. None of these 157 patients showed progressive deterioration, defined as a 50% increase in serum creatinine (Scr) level from baseline, during the observation period. Conversely, in patients without clinical remission, the Kaplan-Meier estimate of probability of progressive deterioration was 21% ± 5% at 10 years. In the multivariate Cox regression model with 13 independent covariates, initial Scr level, histological score, tonsillectomy, and high-dose methylprednisolone therapy had a significant impact on clinical remission, whereas proteinuria, age, sex, levels of hematuria, blood pressure, conventional steroid therapy, angiotensin-converting enzyme inhibitor therapy, and cyclophosphamide therapy had no significant effect. These findings indicate that interventions aimed at achieving clinical remission have provided encouraging results applicable to managing patients with IgA nephropathy.**

INDEX WORDS: Immunoglobulin A (IgA) nephropathy; clinical remission; tonsillectomy; steroid pulse therapy.

IMMUNOGLOBULIN A (IgA) nephropathy is the most common form of glomerulonephritis worldwide,[1] and it tentatively has been established that 30% to 40% of patients reach end-stage renal failure (ESRF) within 10 to 25 years of diagnosis as a result of the progressive nature of this disease.[2,3]

The proportion of patients experiencing clinical remission during the course of IgA nephropathy has been uncertain.[2,4] Recently, Yoshikawa et al[5] reported that clinical remission is often observed in children with IgA nephropathy after immunosuppressive therapy. Moreover, we have experienced a similar phenomenon after intensive therapy, even in adult patients.[6] In contrast to the large amount of knowledge about unfavorable clinical and pathological prognostic factors associated with ESRF,[1,7,8] little is known about factors that contribute to clinical remission.

Chauveau and Droz[2] reported that most patients who had not achieved clinical remission over a 20-year period developed chronic renal failure or ESRF in the long run. In their report, approximately 30% of patients with IgA nephropathy experienced spontaneous clinical remission during long-term follow-up (10 to 40 years). To our knowledge, there is no evidence showing that clinical remission terminates the progression of nephropathy. Considering the life-long prognosis of patients with IgA nephropathy, if clinical remission terminates progressive deterioration, whether clinical remission is obtained thus appears to be very important. In this regard, factors influencing clinical remission merit elucidation.

In the present study, we test the hypothesis that clinical remission may terminate subsequent progressive deterioration. We also analyzed multiple covariates, including clinical and pathological findings at the time of renal biopsy and therapeutic strategies, from the viewpoint of clinical remission.

METHODS

Patients

Among 3,625 patients who underwent renal biopsy in our renal unit at Sendai Shakaihoken Hospital (Sendai, Japan) between 1977 and 1995, we identified 821 patients who had histologically proven IgA nephropathy. The diagnosis was limited to primary mesangial proliferative glomerulonephritis with a predominant deposition of IgA in the mesangium. No patient had clinical or histological evidence of such systemic diseases as systemic lupus erythematosus, Henoch-Schönlein purpura, or chronic liver disease. Exclusion crite-

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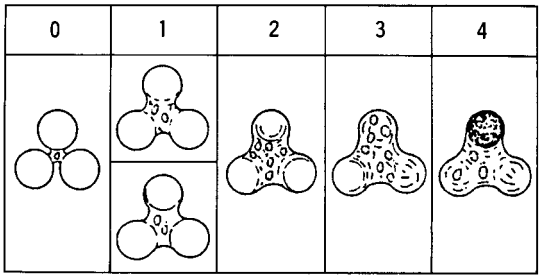

Fig 1. Calculation of IGL. The degree of morphological damage in each glomerulus was graded from 0 to 4 according to the percentage of injured lobules as the result of mesangial proliferation and sclerosis. The average for all glomeruli was calculated and registered as IGL. Abbreviations: N_0-N_4, numbers of glomeruli showing changes of grade 0 to 4, respectively: N, $N_0 + N_1 + N_2 + N_3 + N_4$.

ria for the present study were: (1) age younger than 15 years or older than 60 years, (2) 24-hour urinary protein excretion less than 0.5 g, (3) insufficient number of glomeruli (<5 glomeruli) in a biopsy specimen for light microscopic study, (4) follow-up period less than 36 months, and (5) incomplete data in the medical records. As a result, 329 of the 821 patients were included on the present study.

Clinical, Laboratory, and Pathological Data

Baseline data at the time of the diagnostic renal biopsy were compiled from medical records by three trained extractors who were blinded to patients' outcomes. Patient characteristics included age, sex, blood pressure, serum creatinine (Scr) level, degree of proteinuria and hematuria, and histological score. Severity of the glomerular lesion (ie, histological score) in each case was evaluated using the index of the glomerular lesion (IGL) according to the method originally proposed by Suwa and Takahashi,[9] with a modification to evaluate sclerotic changes as previously described[10-12] (Fig 1).

In addition to baseline data, annual follow-up data were assessed in the outpatient department of our institute.

Treatment

Supportive or immunosuppressive therapy was administered at the treating physician's discretion. Specific treatment regimens in individual patients are listed in Table 1. The following immunosuppressive therapies were used: (1) high-dose methylprednisolone (0.5 g/d for 3 days for three courses) followed by oral prednisolone at an initial dose of 0.6 mg/kg on alternate days, with a gradual decrease in dosage over 1 year (steroid pulse therapy); (2) 1- to 1.5-year course of oral prednisolone at an initial dose of 0.6 mg/kg/d for 1 month (conventional steroid therapy) followed by a gradual decrease in dosage; and (3) a 4-month course of cyclophosphamide at a dose of 1 mg/kg/d.

Antiplatelet drugs (dipyridamole, 150 to 300 mg/d, or dilazep dihydrochloride, 150 to 300 mg/d) were administered to all 329 patients, at least during the initial follow-up year. The duration of administration of antiplatelet drugs was 31.3 ± 23.2 months.

Immunosuppressive therapy basically was administered when active glomerular lesions, such as crescents and tuft necrosis, were present. In some patients without active glomerular lesions, steroids, especially steroid pulse therapy, were administered when patients sought clinical remission, after informed consent was obtained.

In the vast majority of patients, tonsils were examined by an otolaryngologist (S.T.). We recommended tonsillectomy when pus was observed in tonsillar crypts. In addition, for some patients who desired clinical remission, tonsillectomy was performed after sufficient informed consent was obtained regardless of the gross appearance of tonsils and even in the absence of episodes of recurrent tonsillitis or gross hematuria with tonsillitis. Two hundred fifty patients underwent tonsillectomy. Eighteen patients had a history of transient gross hematuria synchronizing with pharyngitis. Pus was observed in tonsillar crypts in most cases, but in some patients, palatine tonsils had a normal gross appearance.

Antihypertensive drugs were administered when hypertension was present. Angiotensin converting-enzyme (ACE) inhibitors were administered to 155 patients (47.1%; Table 1).

Outcomes

The primary outcome for multiregression analysis was either remission of urinary abnormalities or deterioration of

Table 1. Specific Treatment Regimens in Individual Patients

Therapy	Tonsillectomy (+)	Tonsillectomy (−)	Total
Steroid pulse (n = 197)			
Cyclophosphamide (+)	54 (24)*	8 (4)	62 (28)
Cyclophosphamide (−)	125 (59)	10 (6)	135 (65)
Conventional steroid (n = 78)			
Cyclophosphamide (+)	19 (10)	14 (9)	33 (19)
Cyclophosphamide (−)	29 (17)	16 (5)	45 (22)
Steroids (−) and cyclophosphamide (−) (n = 54)	23 (8)	31 (13)	54 (21)
Total	**250 (118)**	**79 (37)**	**329 (155)**

NOTE. Numbers in parentheses indicate number of patients who were given ACE inhibitors.

renal function. Remission of urinary abnormalities or clinical remission was defined as negative proteinuria and hematuria by dipstick and urinary erythrocytes of 4/high-power field or less. Deterioration of renal function or progression was defined as a 50% increase in baseline Scr values. In addition, total deaths and ESRF requiring renal replacement therapy were included in the category of deterioration of renal function.

Statistical Analysis

We used the Cox proportional hazards model, choosing a backward stepwise procedure[13] to assess the impact of multiple covariates for clinical remission. Variables used in multivariable analysis were expressed using a binary scale, such as absent/present, and coded as 0/1. The variables age, sex, proteinuria, hematuria, hypertension, Scr level, histological score, tonsillectomy, steroid pulse therapy, conventional steroid therapy, ACE inhibitor therapy, and cyclophosphamide therapy were treated as categorical variables. Multivariable analysis results were expressed by hazard ratio as an index of quantitative significance and 95% confidence intervals and *P* as an index of statistical significance. The influence of categorical variables on clinical remission was tested using Cox regression analysis for each independent variable by the enter method and for all variables by the backward stepwise likelihood ratio method. In the Cox analysis, exp (β) is the hazard ratio for a case with the characteristic compared with a case without the characteristic.

To clarify the problem of whether clinical remission (disappearance of prolonged urinary abnormalities) relates to the termination of progressive deterioration of renal function, we conducted a bivariate analysis. The clinical remission rate was estimated by means of survival analysis according to the Kaplan-Meier method.[14] The log-rank test was used for comparison of survival curves. For all analyses, a two-tailed *P* less than 0.05 is considered statistically significant. Correlations between dichotomous variables were expressed by Spearman's correlation coefficients.

All statistical analyses, including chi-square test, Cox proportional hazards model, and Kaplan-Meier analysis, were performed using the Statistical Package for the Social Sciences program, version 9.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline Characteristics

The median duration of follow-up for the 329 patients with IgA nephropathy was 75 months (range, 36 to 261 months). The man-woman ratio was 1.2:1. Median age at renal biopsy was 36 years. Mean daily urinary protein excretion was 1.40 ± 1.09 (SD) g. Massive proteinuria, defined as 24-hour urinary protein excretion greater than 1.5 g, was observed in 33.1% of patients. Renal dysfunction, defined as Scr level greater than 1.3 mg/dL, was observed in 20.7% of patients at the time of renal biopsy. Elevated blood pressure, defined as systolic blood pressure greater than 130 mm Hg or diastolic blood pressure greater than 80 mm Hg, was present in 156 patients (47.4%) and 111 patients (33.7%), respectively. A high histological score, defined as IGL of 2.0 or greater, was observed in 43.5% of patients (Table 2).

Initial values for degree of proteinuria and histological score (IGL) were significantly greater in patients treated with steroid pulse therapy (n = 197) in contrast to the other patients (n = 132) (proteinuria, 1.5 ± 1.2 versus 1.2 ± 0.8 g/d; $P = 0.022$; IGL, 2.03 ± 0.63 versus 1.88 ± 0.61; $P = 0.040$).

Clinical Remission and Outcomes

One hundred fifty-seven patients (48%) had achieved clinical remission at the final observation, whereas another 172 patients still had prolonged urinary abnormalities at the end of the observation period. Thirteen patients showed a relapse of urinary abnormalities after transient or prolonged remission. These 13 patients were

Table 2. Baseline Characteristics of 329 Patients With IgA Nephropathy

		Cutoff for Cox Hazard
Sex (men/women)	178/151	Men (54.1)
Age (y)	36.1 ± 12.8	≤40 189 (57.4)
Scr (mg/dL)	1.14 ± 0.48	≤1.3 261 (79.3)
Proteinuria (g/24 h)	1.40 ± 1.09	<1.5 220 (66.9)
Urinary red blood cells (/HPF)	Median 10-29	≤29 175 (53.2)
Systolic blood pressure (mm Hg)	132.3 ± 17.2	≤130 173 (52.5)
Diastolic blood pressure (mm Hg)	78.0 ± 12.3	≤80 218 (66.3)
IGL	1.97 ± 0.63	<2.0 186 (56.5)
Observation (mon)	82.3 ± 38.2 (36-261)	

NOTE. Data shown as mean ± SD (range) or number (percent).
Abbreviation: HPF, high-power field.

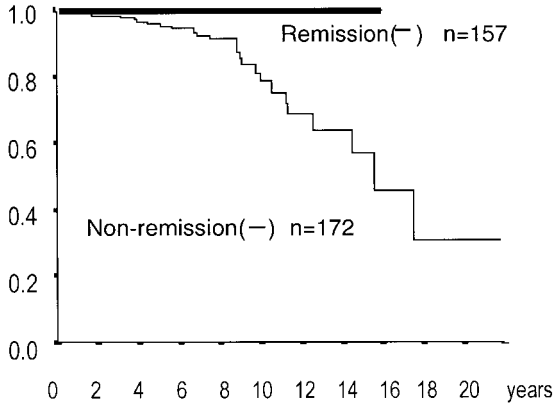

Fig 2. Kaplan-Meier analysis comparing remission with nonremission patients regarding the probability of progressive renal dysfunction, ie, final Scr/initial Scr > 1.50. *P* < 0.001, log-rank test.

included with the 172 patients in the non–clinical remission category. Among patients with clinical remission, including 14 patients with impaired renal function (Scr $>$ 1.3 mg/dL) at the time of renal biopsy, none showed progressive renal dysfunction, defined as a 50% increase in baseline Scr values. Treatment regimens used in the 14 remission cases with initial Scr levels greater than 1.3 mg/dL were steroid pulse therapy with tonsillectomy in 7 patients (cyclophosphamide, 4 of 7 patients; ACE inhibitor, 2 of 7 patients), conventional steroids with tonsillectomy in 5 patients (cyclophosphamide, 3 of 5 patients; ACE inhibitor, 2 of 5 patients), and steroid pulse therapy without tonsillectomy in 2 patients (cyclophosphamide, 1 of 2 patients; ACE inhibitor, 1 of 2 patients).

Twenty-four of 172 nonremission patients (14%) showed progressive renal dysfunction, and 14 of the 24 patients developed ESRF requiring dialysis therapy. Seven of 118 nonremission patients (6%) with Scr levels of 1.3 mg/dL or less and 17 of 54 nonremission patients (31%) with Scr levels greater than 1.3 mg/dL showed progressive renal dysfunction (versus remission patients, chi-square test, $P < 0.05$). Five nonremission patients died of cardiomyopathy, subarachnoid hemorrhage, cerebral infarction, abdominal aortic aneurysm rupture, and interstitial pneumonitis before the development of ESRF.

In addition, we performed a Kaplan-Meier analysis comparing remission and nonremission patients regarding the probability of progressive renal dysfunction. The estimated probability of progressive renal dysfunction at 10 years in nonremission patients was 77.4%, but was 0% in remission patients (log-rank test, $P < 0.001$; Fig 2).

Thirty-eight of 250 patients (15.2%) showed transient macroscopic hematuria after tonsillectomy. In terms of the time to clinical remission and percentage of patients who reached clinical remission, there were no significant differences between those with and without macroscopic hematuria after tonsillectomy.

Cox Regression Analysis

Multivariate Cox regression analysis with 13 variables showed histological score (IGL) and

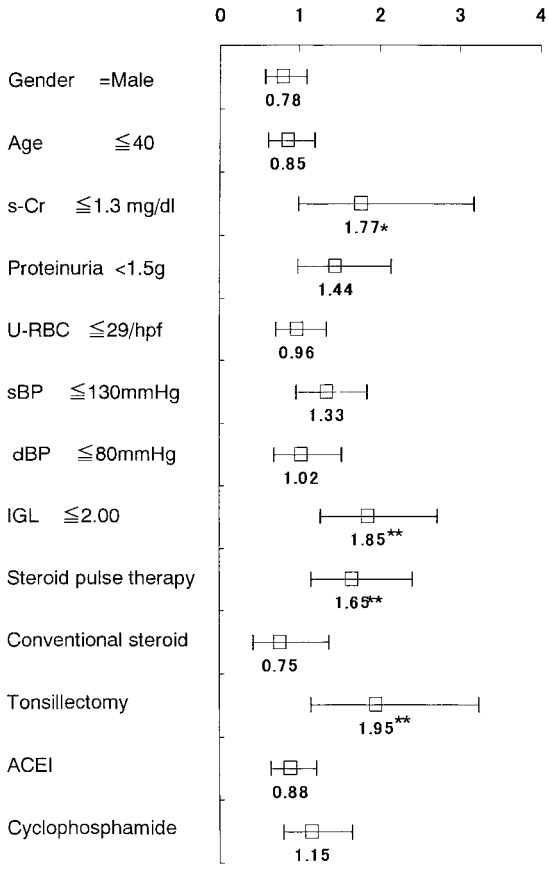

Fig 3. Hazard ratios for the Cox regression model in IgA nephropathy. Numbers are hazard ratios, with 95% percent confidence intervals (0.95 CI). Abbreviations: U-RBC, urinary red blood cells; hpf, high-power field; sBP, systolic blood pressure; dBP, diastolic blood pressure; ACEI, ACE inhibitor.**P* **< 0.05. *****P* **< 0.01.**

Scr level at biopsy to be significant factors in predicting clinical remission. Age, sex, and proteinuria had no impact on clinical remission. Systolic blood pressure less than 130 mm Hg and diastolic pressure less than 80 mm Hg also had no impact on clinical remission. Among characteristics at the time of renal biopsy in the Cox regression analysis with all covariates, IGL was the predictor with the greatest influence on clinical remission when the backward stepwise likelihood ratio method was used. With respect to treatment regimens, tonsillectomy and steroid pulse therapy had significant impacts on clinical remission. Conversely, conventional steroid, ACE inhibitor, and cyclophosphamide therapies had no impact on clinical remission (Fig 3).

Correlations Between Clinical Remission Rate and Parameters

Because Cox analysis showed Scr level and IGL to be significant covariates in clinical remission, we analyzed relationships between these covariates and clinical remission rates. More than half the men and women patients with Scr levels of 1.3 mg/dL or less and 1.0 mg/dL or less experienced clinical remission, respectively (Fig 4). Clinical remission rates decreased in parallel with an increase in histological score (IGL; Fig 5).

Because Cox analysis showed tonsillectomy and steroid pulse therapy had a significant impact on clinical remission, the remission rate in steroid-treated patients with Scr levels of 1.4 mg/dL or less was compared between those with and without tonsillectomy. Baseline data for these two groups were statistically matched in terms of Scr level, proteinuria, and degree of histological score. The clinical remission rate was greater in patients treated with the combination of steroids (steroid pulse therapy, 153 patients; conventional steroids, 38 patients) with tonsillectomy than steroids (steroid pulse therapy, 12 patients; conventional steroids, 22 patients) without tonsillectomy (59.7% versus 35.3%; $P < 0.01$; Table 3).

Conversely, regarding the incidence of progressive renal functional loss, there were no significant differences between the steroid pulse therapy versus non–steroid pulse therapy group or the tonsillectomy versus nontonsillectomy group (Fig 6).

Time between starting treatment and entering clinical remission in 157 patients is shown in Fig 7. Ninety-four of 157 patients (59.9%) reached clinical remission within 1 year after the initiation of treatment, and 67 of these 94 patients (71.3%) were treated with tonsillectomy and steroid pulse therapy. Conversely, time to clinical remission was more than 2 years in 36 of 157 patients (22.9%), of whom a combination of tonsillectomy and steroid pulse therapy was used in 16 patients (44.4%; incidence of tonsillectomy with steroid pulse therapy for <1 versus >2 years, chi-square test, $P < 0.01$).

DISCUSSION

This is the first report to address the clinical remission of IgA nephropathy. Although clinical characteristics of patients with IgA nephropathy may be influenced by race, according to reports by the Japanese Ministry of Health and Welfare[15] and Japanese Society of Dialysis,[16] IgA nephropathy onset peaks in persons aged in the teens and

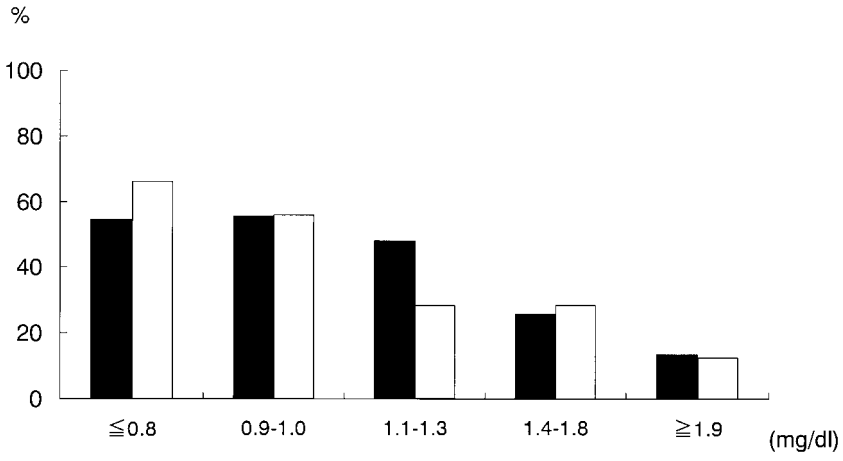

Fig 4. Correlation between serum creatinine level at renal biopsy and percentage of patients experiencing clinical remission. (■), Men (n = 178); (□), women (n = 151).

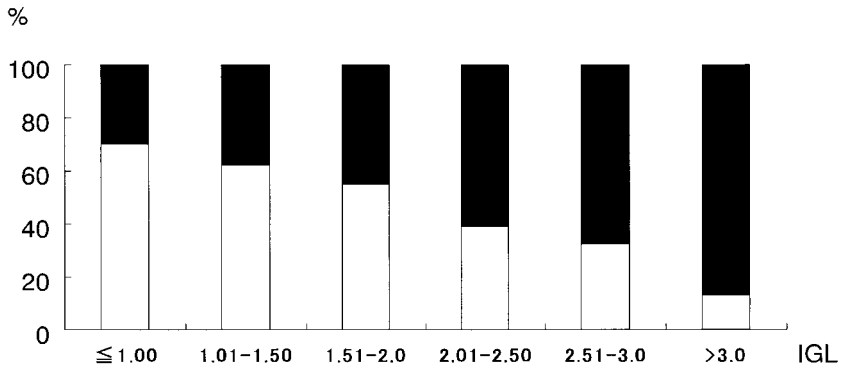

Fig 5. Correlation between histological score (IGL) and percentage of patients experiencing clinical remission. (□), Remission (n = 157); (■), nonremission (n = 172).

20s,[15] and the average age at which dialysis therapy is required because of ESRF caused by chronic glomerulonephritis (with IgA nephropathy presumably the major cause) is approximately 60 years.[16] Based on these two reports, we can assume that the duration of IgA nephropathy from onset to ESRF is 30 to 40 years in many cases. At present, predicting the course of nephropathy beyond 30 years is essentially impossible, especially for patients with IgA nephropathy who do not have unfavorable prognostic factors, such as impaired renal function, massive proteinuria, or an advanced histological score,[1,7,8] at the time of diagnosis. However, in the absence of clinical remission, nephropathy may show an essentially progressive course, although the speed of this progression varies among patients.[2] Conversely, after clinical remission is obtained, termination of the progressive decline in renal function can be expected. This concept has been supported in other forms of glomerular disease, such as focal segmental sclerosis[17-19] and membranous nephropathy.[20] Our present study confirms this hypothesis.

In multivariate Cox regression analysis, Scr level and histological score had a significant impact on clinical remission. Regarding therapeutic strategies for achieving clinical remission of IgA nephropathy, tonsillectomy, and steroid pulse therapy, but not conventional steroid, ACE inhibitor, or cyclophosphamide therapy, had a significant impact on clinical remission of IgA nephropathy.

The clinical benefit of tonsillectomy in patients with IgA nephropathy remains controversial. With respect to clinical remission, several studies, mostly by Japanese groups, have shown positive results.[21-24] In accordance with these findings, the clinical remission rate was significantly greater in patients administered steroids with tonsillectomy than without tonsillectomy. Conversely, with respect to progression of nephropathy, a recent study using Cox regression analysis by Rasche et al[25] showed no benefit.

In Japan, the system for annual health examination is well developed. Approximately 70% of Japanese patients with IgA nephropathy were found to have renal disease on routine health

Table 3. Clinical Remission Rate in Steroid-Treated Patients With Scr of 1.4 mg/dL or Less With and Without Tonsillectomy

	Tonsillectomy + Steroids	Steroids
No. of patients	**191**	**34**
Remission rate (%)	**59.7**	**35.3***
Age (y)	33.5 ± 12.2	39.6 ± 13.6*
Scr (mg/dL)	0.96 ± 0.22	1.01 ± 0.17
Proteinuria (g/24 h)	1.38 ± 1.17	1.35 ± 0.75
Systolic blood pressure (mm Hg)	127.9 ± 15.0	136.3 ± 16.8†
Diastolic blood pressure (mm Hg)	75.5 ± 11.1	78.5 ± 13.5
IGL	1.89 ± 0.55	1.85 ± 0.50

*$P < 0.01$ at chi square test.
†$P < 0.05$, at chi square test.

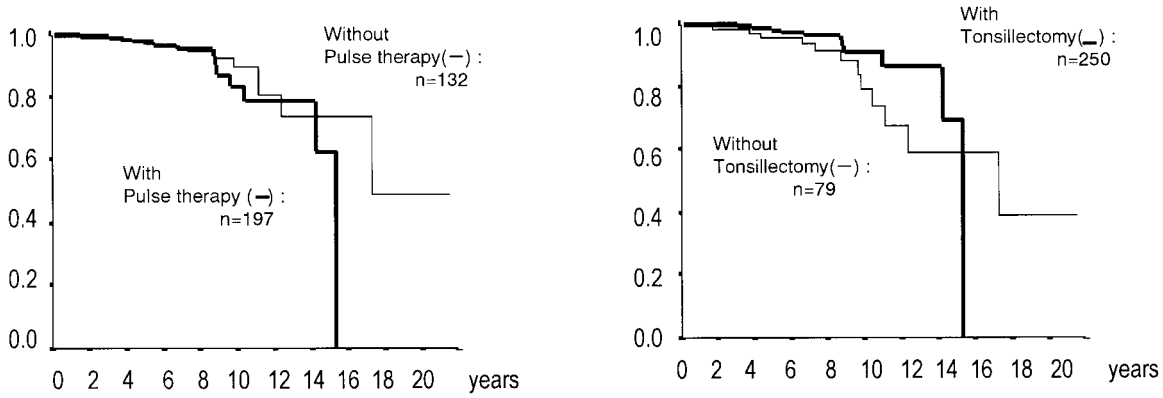

Fig 6. (A) Kaplan-Meier analysis comparing patients with and without steroid pulse therapy regarding the probability of progressive renal dysfunction, ie, final Scr/initial Scr > 1.50. Not significant in log-rank test, *P* = 0.40. (B) Kaplan-Meier analysis comparing patients with and without tonsillectomy. Not significant in log-rank test, *P* = 0.15.

examinations,[15] and renal biopsies often are performed even for patients with a mild degree of proteinuria. Under such circumstances, early-stage IgA nephropathy is found more often than in countries with limited and strict indications for renal biopsy, such as the United States and Germany.

Regarding the stage of nephropathy in our patients, only 7% reached the end point of a 50% increase from baseline Scr level. In the study of Pozzi et al,[26] in which the same end point was used but patients with proteinuria less than 1.0 g/d of protein were excluded, 21% of patients on steroid pulse therapy and 33% of controls had reached the same end point by year 5 of follow-up. In the study by Donadio et al,[27] in which the efficacy of fish oil for IgA nephropathy was shown, 33% of control patients (proteinuria ≥ 1.0 g/d of protein) showed an increase in Scr level of 50% or greater by 2.2 years. Therefore, it is conceivable that the stage of nephropathy in our patients as a whole was earlier than those in previous studies. It is obvious that spontaneous clinical remission is seen rather frequently in mild IgA nephropathy. However, to avoid excessive representation of mild IgA nephropathy, we excluded patients with proteinuria less than 0.5 g/d of protein. Moreover, clinical remission was observed even in patients with impaired renal function, in whom spontaneous clinical remission is unlikely. In addition, degrees of proteinuria and histological scores were significantly greater in patients treated with steroid pulse therapy in contrast to the others. Finally, in patients who entered clinical remission in the early observation period (<1 year), the combination of tonsillectomy and steroid pulse therapy was used more often than in patients who achieved clinical remission later (>2 years; Fig 7). We therefore speculate that the clinical remission observed in the present study was, at least in a considerable proportion of cases, a result of treatment intervention, especially tonsillectomy and steroid therapy, rather than the natural course of this disease.

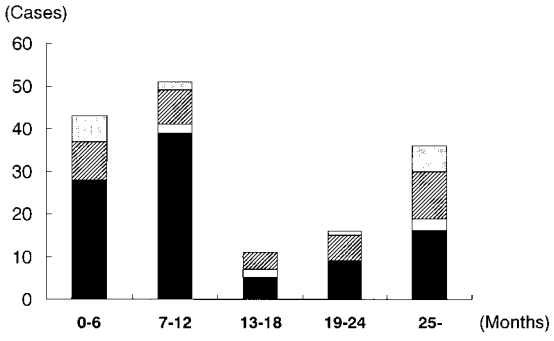

Fig 7. Time between the initiation of therapy and clinical remission in 157 remission patients. (■), Steroid pulse therapy with tonsillectomy (n = 97); (□), steroid pulse therapy without tonsillectomy (n = 7); (▨), tonsillectomy without steroid pulse therapy (n = 38), among whom conventional steroids were administered to 27 patients; (▩), without tonsillectomy and steroid pulse therapy (n = 15), among whom conventional steroids were administered to 6 patients.

Despite the significant impact of tonsillectomy and steroid pulse therapy on clinical remis-

sion, clinical outcome data failed to reach significance. This may have occurred partly because patients in the present study were at an early stage of disease and the overall rate at which a 50% increase in Scr level occurred was too low, or the population was still too small to allow the detection of improved outcomes.

Although the present study was retrospective, our results may provide useful information for conducting a future prospective study. Namely, treatment strategies leading to clinical remission should be encouraging for patients with IgA nephropathy. Terminating the progressive deterioration of renal function is the goal of effective therapy.

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REFERENCES

1. D'Amico G, Imbasciati E, Barbiano D, Belgioioso G, Bertoli S, Fogazzi G, Ferrario F, Fellin G, Ragni A, Colasanti S, Minetti L, Ponticelli C: Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. Medicine 64:49-60, 1985

2. Chauveau D, Droz D: Follow-up evaluation of the first patients with IgA nephropathy described at Necker Hospital. Contrib Nephrol 104:1-5, 1993

3. Galla JH: IgA nephropathy. Kidney Int 47:377-387, 1995

4. Costa RS, Droz D, Noel LH: Long-standing spontaneous clinical remission and glomerular improvement in primary IgA nephropathy (Berger's disease). Am J Nephrol 7:440-444, 1987

5. Yoshikawa N, Ito H, Sakai T, Takekoshi Y, Honda M, Awazu M, Ito K, Iitaka K, Koitabashi Y, Yamaoka K, Nakagawa K, Nakamura H, Matsuyama S, Seino Y, Takeda N, Hattori S, Ninomiya M: Controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. J Am Soc Nephrol 10:101-109, 1999

6. Hotta O, Taguma Y, Yoshizawa N, Oda T, Nishiyama J, Yusa N, Chiba S, Horigome I, Sudo K, Tomioka S: Long-term effects of intensive therapy combined with tonsillectomy in patients with IgA nephropathy. Acta Otolaryngol 523:S165-S168, 1996 (suppl)

7. Koyama A, Igarashi M, Kobayashi M: Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis 29:526-532, 1997

8. Yoshida H, Mitarai T, Kawamura T, Kitajima T, Miyazaki Y, Nagasawa R, Kawaguchi Y, Kubo H, Ichikawa I, Sakai O: Role of the deletion polymorphism of angiotensin-converting enzyme gene in the progression and therapeutic responsiveness of IgA nephropathy. J Clin Invest 96:2162-2169, 1995

9. Suwa N, Takahashi T: Morphological and Morphometrical Analysis of Circulation in Hypertension and Ischemic Kidney. München-Berlin-Wien, Germany, Urban & Schwarzenberg, 1971, pp 108-116

10. Sato Y, Hotta O, Taguma Y, Takasaka T, Nose M: IgA nephropathy with poorly development lymphoepithelial symbiosis of the palatine tonsils. Nephron 74:301-308, 1996

11. Hotta O, Taguma Y, Kurosawa K, Sudo K, Suzuki K, Horigome I: Predictive value of small crescents in IgA nephropathy: Analysis of four patients showing a deteriorated renal function during a long follow-up period. Clin Nephrol 40:125-130, 1993

12. Ootaka T, Suzuki M, Sudo K, Sato H, Seino J, Saito T, Yoshinaga K: Histological localization of terminal complement complexes in renal diseases: An immunohistochemical study. Am J Clin Pathol 91:144-151, 1989

13. Cox DR: Regression models and life tables. J R Stat Soc 34:187-220, 1972

14. Kaplan EL, Meier P: Nonparametric estimation for incomplete observation. J Am Stat Assoc 53:116-122, 1958

15. Endoh M: Epidemiologic analysis of IgA nephropathy in Japan [Japanese]. Kidney Dial 46:29-32, 1999

16. Japanese Society for Dialysis Therapy: An Overview of Regular Dialysis Treatment in Japan (as of December 31, 2000) [Japanese]. Tokyo, Japan, Japanese Society for Dialysis Therapy, 2001

17. Kobet SM, Schwartz MM, Lewis EJ: Primary focal segmental glomerulosclerosis: Clinical course and response to therapy. Am J Kidney Dis 23:773-783, 1994

18. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P: Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. Am J Med 82:938-944, 1987

19. Banfi G, Moriggi M, Sabadini E, Fellin G, D'Amico G, Ponticelli C: The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. Clin Nephrol 36:53-59, 1991

20. Passerini P, Pasquali S, Cesana B, Zucchelli P, Ponticelli C: Long-term outcome of patients with membranous nephropathy after complete remission of proteinuria. Nephrol Dial Transplant 4:525-529, 1989

21. Lagrue G, Sardreoux T, Laurant J, Hirbec G: Is there a treatment of mesangial IgA nephropathy. Clin Nephrol 14:161, 1981 (letter)

22. Sanai A, Kudoh F: Effects of tonsillectomy in children with IgA nephropathy, purpura nephritis, or other chronic glomerulonephritis. Acta Otolaryngol 523:S172-S174, 1996 (suppl)

23. Sugiyama N: Clinicopathological study of the effectiveness of tonsillectomy in IgA nephropathy accompanied by chronic tonsillitis. Acta Otolaryngol 508:S43-S48, 1993 (suppl)

24. Iino Y, Ambe K, Kato Y, Nakai A, Toriyama M, Saima K, Yoshimoto K: Chronic tonsillitis and IgA nephropathy. Acta Otolaryngol 508:S29-S35, 1993 (suppl)

25. Rasche FM, Schwarz A, Keller F: Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin Nephrol 51:147-152, 1999

26. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, Locatelli F: Corticosteroids in IgA nephropathy: A randomized controlled trial. Lancet 353:883-887, 1999

27. Donadio JV Jr, Bergstralh EJ, Offord KP, Spencer DC, Holley KE: A controlled trial of fish oil in IgA nephropathy. N Engl J Med 331:1194-1199, 1994