Effect of Tonsillectomy Plus Steroid Pulse Therapy on Clinical Remission of IgA Nephropathy: A Controlled Study

Hiroyuki Komatsu, Shouichi Fujimoto, Seiichiro Hara, Yuji Sato, Kazuhiro Yamada, and Kazuo Kitamura

Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

Background and objectives: Few well-designed investigations have examined how tonsillectomy plus steroid pulse therapy affects IgA nephropathy. A prospective, controlled study therefore was performed to compare the effects of combined therapy with those of steroid pulse alone in patients with IgA nephropathy.

Design, setting, participants, & measurements: Fifty-five patients were followed up for 54.0 ± 21.2 mo. Thirty-five of them underwent tonsillectomy and steroid pulse therapy (group C), and 20 received steroid pulse monotherapy (group M). Both groups received methylprednisolone intravenously, followed by oral prednisolone (initial dosage 0.5 mg/kg per d) for 12 to 18 mo. Primary evaluation items were a 100% increase in serum creatinine from baseline levels or the disappearance of urinary protein (UP) and/or occult blood (UOB) indicating clinical remission.

Results: At 24 mo after the initial treatment, the ratios of the UP and UOB disappearance were higher in group C than in group M, and the therapeutic effect persisted until the final observation. None of group C achieved a 100% increase in serum creatinine from the baseline level, whereas one patient in group M developed ESRD during the observation period. The histologic findings of repeated biopsy specimens from 18 patients revealed that mesangial proliferation and IgA deposition were significantly more reduced in group C than in group M. The Cox regression model showed that the combined therapy was approximately six-fold more effective in causing the disappearance of UP than steroid pulse monotherapy.

Conclusion: Tonsillectomy combined with steroid pulse treatment can induce clinical remission in patients with IgA nephropathy.

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The most widespread type of glomerulonephritis is IgA nephropathy (IgAN), and the renal outcome is relatively poor: 30 to 40% of patients reach ESRD within 20 yr (1,2). Various treatment strategies have been attempted to improve the renal outcome of IgAN (3), and corticosteroids, immunosuppressive agents, and angiotensin-converting enzyme inhibitors seem to show promise (4–8); however, IgAN treatment remains controversial because study populations and lead-time bias differ considerably among studies (9,10).

Hotta *et al.* (11) initially described tonsillectomy combined with steroid pulse therapy, which then became a popular approach to treating IgAN for several years in Japan. A retrospective analysis showed that approximately 60% of their patients who underwent tonsillectomy combined with steroid administration achieved remission of urinary abnormalities. The results of their recent multicenter, prospective, cohort study (12) indicated that the remission rate of urinary abnormalities depends on clinical severity defined as the level of serum creatinine (sCr) and proteinuria; however, precise information about the effectiveness of the combination therapy against IgAN remains scarce.

Here, we conducted a prospective, nonrandomized, controlled study to assess whether the tonsillectomy combined with steroid pulse therapy is more effective than steroid pulse monotherapy in patients with IgAN. We determined the therapeutic effects on the basis of remission of urinary abnormalities and histologic findings.

Materials and Methods

Patient Selection

Between April 1999 and December 2003, 78 patients received an initial diagnosis of IgAN by renal biopsy at our institution. The inclusion criteria for this study comprised age 15 to 60 yr, sCr at renal biopsy of ≤2.0 mg/dl, and histologic assessment (described in Assessment of Histologic Severity) as grade 2 or more. Exclusion criteria comprised previous therapy with steroids and/or other immunosuppressive agents; contraindication for the use of corticosteroid; and renal lesions caused by systemic diseases such as Henoch-Schönlein purpura nephritis, systemic lupus erythematosus, and liver cirrhosis. Accordingly, 55 patients were eligible for this study.

Treatment Protocol

All patients received intravenous methylprednisolone pulses of 0.5 g/d for three consecutive days, followed by oral prednisolone at an

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Correspondence: Dr. Hiroyuki Komatsu, Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki, 889-1692, Japan. Phone: 81-985-85-0872; Fax: 81-985-85-6596; E-mail: hkomatsu@fc.miyazaki-med.ac.jp

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initial dosage of 0.5 mg/kg per d. The oral prednisolone was gradually tapered by 5 mg every 2 mo during the first 6 mo, then to 5 mg/d over the next 6 mo, and discontinued by 18 mo after the initial therapy. An antiplatelet drug (Dilazep) was also administered to all patients when contraindications were absent. Renin-angiotensin system inhibitors (RAS-I) such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were administered when BP reached ≥130/80 mmHg.

After IgAN was histologically confirmed, 49 patients, including 30 patients who had a history of macroscopic hematuria associated with upper respiratory infection and/or chronic or recurrent tonsillitis, received medical examination by otolaryngologists. The indication for tonsillectomy was determined on the basis of the otolaryngologic findings of chronic tonsillitis (hypertrophic or atrophic tonsils with an irregular mucosal surface and pus in the tonsillar crypts), and 43 patients had fulfilled the indication. We could obtain sufficient informed consent from 35 patients, and they underwent tonsillectomy before steroid pulse therapy. Ultimately, 35 (group C) and 20 (group M) patients underwent combination therapy and steroid pulse monotherapy, respectively. We could not do random allocation of treatment in consideration of the ethical issue because the combined therapy included the surgical procedure.

Data Collection and Evaluation

We measured the BP, urinary findings, and sCr using an ambulatory BP machine, dip-stick test, and blood samples, respectively. These data were collected once every 3 mo during the first year and then once every 6 mo for up to 8 yr after the diagnosis of IgAN was confirmed.

The qualitative findings of urinary protein (UP) and urinary occult blood (UOB) were converted into scores as follows: (−) and (±) to 0, (1+) to 1, (2+) to 2, and (3+) to 3. Remission of UP or UOB was defined as the UP or UOB scores of 0. Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or the use of antihypertensive medication. The level of sCr was measured enzymatically. Creatinine clearance (Ccr) was calculated from 24-h urine samples.

The primary outcome was a 100% increase in sCr from the baseline levels or the disappearance of UP and/or UOB indicating clinical remission. The mean observation period of all patients was 54.0 ± 21.2 mo.

Assessment of Histologic Severity

We assessed the histologic lesions of all of the patients with IgAN according to the guidelines presented by the Special Study Group (IgAN) on Progressive Glomerular Disease in Japan (13). These guidelines separate patients with IgAN into the following groups on the basis of severity:

1. Grade 1: Slight mesangial cell proliferation and increased matrix. Absence of glomerulosclerosis, crescent formation, and adhesion to Bowman's capsule. No prominent changes in the interstitium, renal tubuli, or blood vessels.
2. Grade 2: Slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in <10% of all biopsied glomeruli. Interstitial and vascular findings identical to those with a grade 1.
3. Grade 3: Moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in 10 to 30% of all biopsied glomeruli. Slight cellular infiltration in the interstitium, except around some sclerosed glomeruli; slight tubular atrophy; and mild vascular sclerosis.
4. Grade 4: Severe, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in >30% of all biopsied glomeruli. When sites of sclerosis are totaled and converted to global sclerosis, the sclerosis rate includes >50% of glomeruli. Some glomeruli also show compensatory hypertrophy, interstitial cellular infiltration, and tubular atrophy and fibrosis. Hyperplasia or degeneration in some intrarenal arteriolar walls.

The histologic parameters of repeat renal biopsy specimens that were obtained from 18 patients was semiquantified as described by Hotta *et al.* (14). The extent of glomerular mesangial proliferation and arteriosclerosis were scored as follows: Mild, 1; moderate, 2; and severe, 3. Crescent formation was considered as either present or absent. Lesions of global and/or segmental sclerosis of glomeruli and adhesion to the Bowman's capsule are indicated as ratios (%) of diseased glomeruli. The distribution of IgA deposition in the mesangial area excluding globally sclerotic glomeruli was scored as follows: 0, absent; 1, <40%; 2, 40 to 80%; 3, >80% with segmental deposition; and 4, >80% with global deposition. Interstitial mononuclear cell infiltration and interstitial fibrosis and/or edema in the renal cortex (fractional volume) is indicated as a ratio (%) of the affected area in the normal interstitium. Two pathologists (S.F. and S.H.) reviewed all histology slides from these patients.

Statistical Analysis

All continuous variables are presented as means ± SD. Normality of each continuous variable was initially examined using the Shapiro-Wilk test. We then compared the clinical parameters of the two groups at renal biopsy and after treatment using the unpaired t test for normally distributed continuous variables or the Mann-Whitney U test for non-normally distributed continuous variables and categorical variables. The difference in proportions was evaluated using the χ^2 independent test or Fisher exact test for 2×2 tables, depending on the number of categories. We used Pearson χ^2 test to compare histologic grades between the two groups. Changes in histologic parameters at the time of the first and second renal biopsies in each group were assessed using the paired t test for continuous variables or the McNemar test for categorical data. We used the Cox proportional hazards model to assess the impact of multiple covariates for the remission of urinary protein. All of the independent variables used in univariate and multivariate analyses are expressed in categorical (*e.g.*, absent/present, coded as 0/1) or quantitative forms. Gender (male/female), presence of macroscopic hematuria (yes/no), combined therapy (yes/no), and RAS-I (yes/no) are regarded as categorical variables, whereas age, systolic BP, amount of UP, the value of sCr, and histologic grading are regarded as quantitative variables. The results of the univariate and multivariate analyses are expressed as hazard ratios with 95% confidence intervals and a P value. $P < 0.05$ was considered statistically significant in all calculations, which were performed by the SPSS for Windows, Advance Statistical Release 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the two groups. Age, distribution of gender, presence of macroscopic hematuria, and systolic and diastolic BP did not differ between them. Five (14.3%) and six (30.0%) patients in groups C and M, respectively, had hypertension. The distribution of the UP and UOB scores was almost identical, and proteinuria for 24 h exceeded 1.0 g/d in both groups. The sCr concentration and Ccr did not significantly differ, with three (8.6%) patients in group C and two (10.0%) in group M having <60 ml/min Ccr. The mean serum IgA concentration was >300 mg/dl in both

Table 1. Baseline characteristics of groups treated with monotherapy and combined therapy[a]

Characteristic	Group C ($n = 35$)	Group M ($n = 20$)	P^b
Age (yr; mean ± SD)	30.9 ± 12.3	27.0 ± 10.7	0.362
Gender (M/F)	11/24	10/10	0.173
Presence of macroscopic hematuria (*n* [%])	16 (45.7)	8 (40.0)	0.681
SBP (mmHg; mean ± SD)	122.0 ± 12.9	127.6 ± 16.6	0.169
DBP (mmHg; mean ± SD)	73.1 ± 11.7	76.3 ± 11.9	0.344
patients with >140/90 mmHg (*n* [%])	5 (14.3)	6 (30.0)	0.147
UOB score (mean ± SD)	2.17 ± 0.86	2.40 ± 0.75	0.352
UP score (mean ± SD)	2.17 ± 0.79	2.35 ± 0.75	0.412
Proteinuria (g/d; mean ± SD)	1.06 ± 1.01	1.41 ± 1.05	0.136
patients with UP >1.0 g/d (*n* [%])	13 (37.1)	12 (60.0)	0.101
Serum creatinine (mg/dl; mean ± SD)	0.72 ± 0.29	0.84 ± 0.30	0.142
patients with sCr >1.2 mg/dl (*n* [%])	3 (8.6)	3 (15.0)	0.377
Creatinine clearance (ml/min; mean ± SD)	96.7 ± 33.6	95.6 ± 34.7	0.806
patients with Ccr <60 ml/min (*n* [%])	3 (8.6)	2 (10.0)	0.752
Serum uric acid (mg/dl; mean ± SD)	5.36 ± 1.24	5.98 ± 1.52	0.128
Serum total cholesterol (mg/dl; mean ± SD)	202.2 ± 45.4	208.8 ± 52.1	0.643
Serum IgA (mean ± SD)	317.9 ± 125.0	326.5 ± 108.4	0.694
Serum C3 (mean ± SD)	94.5 ± 19.3	91.0 ± 23.9	0.549
Histologic grade[c]			0.217
1	0	0	
2	13	3	
3	19	15	
4	3	2	

[a]DBP, diastolic BP; Group C, combined therapy (steroid pulse with tonsillectomy); group M, monotherapy (steroid pulse); SBP, systolic BP; UOB, urinary occult blood; UP, urinary protein.
[b]Data compared using Mann-Whitney *U* test, unpaired *t* test, and χ^2 test.
[c]Histologic grading in both groups compared using Pearson χ^2 test.

groups. The histologic score in more than half of all patients in both groups was grade 3.

Changes in Clinical Findings over Time after Treatment

We separately investigated changes in proteinuria and hematuria after the initial treatment over time according to the UP and UOB scores. The distribution of the UP score gradually shifted to 0 in group C but persisted for 6 mo after starting treatment in group M (Figure 1A). At 24 mo after the initial treatment, the ratio of the UP disappearance was higher in group C than in group M (76.5 *versus* 41.2%; $P = 0.013$).

As with the UP score, the ratio of the UOB disappearance gradually increased within 24 mo after the combination therapy in group C, whereas the distribution of the UOB score moved sideways after 6 mo of monotherapy in group M (Figure 1B). The ratio of the UOB disappearance was higher in group C than in group M (79.4 *versus* 17.6%; $P < 0.001$). Surprising, both UP and UOB remained absent in 23 (65.7%) and in 27 (77.1%) of the patients in group C until the final observation at 4 yr after the initial treatment, and urinary abnormalities went into remission in 19 (54.3%) patients (Table 2).

A subanalysis based on the histologic severity showed that the therapeutic effect on the remission of UP at the final observation was almost equivalent between groups C and M in grade 2, indicating mild lesion (84.6 *versus* 66.7%; $P = 0.929$). In contrast, the patients in group C had a higher rate of remission of UP than those in group M in grade 3, indicating moderate lesion (63.2 *versus* 33.3%; $P = 0.083$). None of patients in groups C and M attained remission of UP in grade 4, indicating severe lesion.

An antiplatelet drug (Dilazep) was administered to 33 (94.3%) patients in group C and to all patients in group M at the onset of treatment. RAS-I was also administered to 16 (45.7%) patients in group C and to 13 (65.0%) patients in group M ($P = 0.168$, χ^2 test) after completing the initial therapy. The BP levels were controlled well during the observation period in both groups, and renal function was also preserved in group C. The sCr value doubled from that of the baseline in one patient in group M, and this patient eventually developed ESRD (Table 2).

Histologic Changes after Treatment

Eighteen of the 55 patients (11 in group C and seven in group M) underwent a repeat renal biopsy at 23.6 ± 7.9 mo after the initial treatment. Table 3 shows the histologic changes before and after treatment in each group. The ratio (%) of patients with crescent formation decreased from 55 to 9% in group C and from 43 to 14% in group M. The extent of mesangial proliferation was significantly improved after as compared with before

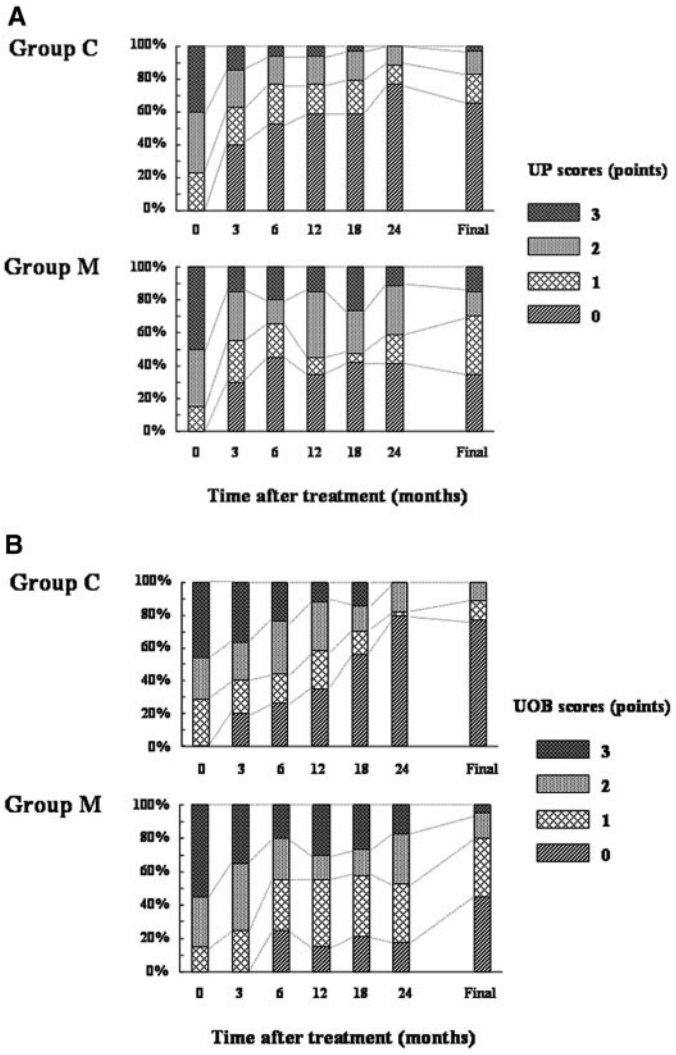

Figure 1. Change in urinary findings over time after treatment. (A) Urinary protein (UP) scores. (B) Urinary occult blood (UOB) scores. Group C, combined therapy (steroid pulse with tonsillectomy); group M, monotherapy (steroid pulse).

treatment in group C (from 2.64 ± 0.67 to 1.55 ± 0.52; $P < 0.001$) but not in group M (from 2.57 ± 0.54 to 2.00 ± 1.00; $P = 0.231$). The distribution of IgA deposition in the mesangial area of group C was significantly reduced from 3.09 ± 0.70 to 2.45 ± 0.69 (assessed as IgA deposition score, $P = 0.011$), and the serum IgA concentration was also significantly reduced from 349.4 ± 136.8 to 252.5 ± 75.0 mg/dl ($P = 0.002$). In contrast, the IgA deposition score and the serum IgA concentration did not change between the first and second biopsies in group M.

Multivariate Analysis of Factors that Contribute to the Remission of UP

We used the Cox proportional hazards model to evaluate the effects of combined therapy on UP remission. The known risk factors for the progression of IgAN as well as combined therapy and RAS-I were selected as imperative independent variables in the model (Table 4). In the univariate analysis, a higher UP value before treatment and histologic severity were risk factors for persistent UP thereafter; meanwhile, combined therapy was a favorable factor to induce remission of UP. In the multivariate analysis, combined therapy was approximately six-fold more effective in causing the disappearance of UP than steroid pulse monotherapy (hazard ratio 6.20; 95% confidence interval 1.98 to 19.5, $P = 0.002$).

Discussion

Our previous retrospective study found that steroid therapy and tonsillectomy could independently contribute to improving renal outcome in 237 patients with IgAN (15); however, that study mainly focused on renal survival. This study, therefore, investigated whether tonsillectomy combined with steroid pulse therapy is more effective than steroid pulse monotherapy in improving renal outcome, particularly in terms of urinary remission. We found that the combination therapy was superior to monotherapy in inducing clinical remission and that the therapeutic effect persisted for approximately 5 yr after the initial treatment. Our histologic examinations of repeat biopsy specimens also showed improved mesangial proliferation and IgA deposition in the group that was treated with combined therapy.

The effects of steroid pulse therapy on IgAN have already been investigated (16). Pozzi *et al.* (5,6) administered a 6-mo course of steroid therapy including intravenous methylprednisolone to 86 patients with 1.0 to 3.5 g/dl UP excretion and sCr <1.5 mg/dl. After 1 yr, the level of UP in 26% of the patients who were treated with the steroid fell to <0.5 g/d, and the 10-yr renal survival rate (sCr doubling from baseline as an end point) was significantly higher in the steroid than in control group (97 *versus* 53%). We found here that UP in 35% of the patients who received only steroid monotherapy went into remission after 1 yr; however, the remission rate of urinary abnormalities was considerably higher after combined therapy compared with only monotherapy.

The value of tonsillectomy in treating IgAN remains controversial. Rasche *et al.* (17) revealed that tonsillectomy did not affect the renal survival of patients with advanced IgAN (mean sCr 208 μmol/L) within a mean follow-up period of 3.4 yr. On the contrary, Xie *et al.* (18) indicated that tonsillectomy favorably affects renal survival over the long term (mean follow-up >15 yr), according to Kaplan-Meier estimates and analyses using the Cox regression; however, regardless of tonsillectomy, the survival rates at 10 yr seemed similar between the groups (with *versus* without tonsillectomy 97.6 *versus* 88.8%), and patients with moderate to severe renal injury progressed to ESRD. Although Chen *et al.* (19) also could not prove the effect of tonsillectomy on renal survival within their follow-up of approximately 11 yr, they indicated that tonsillectomy had a favorable effect on urinary findings from patients with IgAN and mild renal injury. These retrospective studies indicate that the effect of tonsillectomy alone is restrictive and that renoprotective outcomes do not become evident until much later.

Here, we confirmed a powerful and possibly synergistic effect of combined therapy on urinary remission. A mechanism for IgAN onset and progression was proposed as follows (20). The initial phase of the pathogenic mechanism is continuous

Table 2. Comparison of clinical findings at 24 mo after biopsy and at final observation

Parameter	24 Mo after Biopsy			Final Observation		
	Group C (n = 34)	Group M (n = 17)	P[a]	Group C (n = 35)	Group M (n = 20)	P[a]
Observation period (mo; mean ± SD)				49.3 ± 15.6	62.4 ± 27.0	0.060
SBP (mmHg; mean ± SD)	117.5 ± 12.8	120.9 ± 10.0	0.364	116.2 ± 13.7	116.4 ± 18.0	0.969
DBP (mmHg; mean ± SD)	73.0 ± 9.1	75.2 ± 8.3	0.438	70.5 ± 13.5	71.8 ± 12.9	0.721
Patients with BP >140/90 mmHg (n [%])	2 (5.9)	0 (0.0)	0.477	2 (5.7)	1 (5.0)	0.703
Serum creatinine (mg/dl; mean ± SD)	0.86 ± 0.22	1.01 ± 0.91	0.517	0.84 ± 0.28	1.24 ± 1.82	0.344
Patients with 100% increased sCr (n [%])	0 (0.0)	1 (6.7)	0.306	0 (0.0)	1 (5.0)	0.364
Disappearance of UP (n [%])	26 (76.5)	7 (41.2)	0.013[b]	23 (65.7)	7 (35.0)	0.028[b]
Disappearance of UOB (n [%])	27 (79.4)	3 (17.6)	<0.001[b]	27 (77.1)	9 (45.0)	0.016[b]
Remission of urinary abnormalities (n [%])	21 (61.8)	3 (17.6)	<0.001[b]	19 (54.3)	5 (25.0)	0.033[b]

[a]Data compared using unpaired t test, χ^2 test, and Fisher exact test.
[b]Statistically significant.

Table 3. Histologic changes before and after treatment in each group

Parameter	Combination Therapy (n = 11)			Monotherapy (n = 7)		
	Before	After	P[a]	Before	After	P[a]
Glomerulus						
no. of glomeruli (mean ± SD)	24.80 ± 13.70	22.50 ± 7.71	0.488	17.70 ± 7.10	25.60 ± 11.70	0.189
mesangial proliferation (mean ± SD)	2.64 ± 0.67	1.55 ± 0.52	<0.001[b]	2.57 ± 0.54	2.00 ± 1.00	0.231
crescent formation (n [%])	6 (55)	1 (9)	0.063	3 (43)	1 (14)	0.500
global sclerosis (%; mean ± SD)	8.82 ± 8.32	10.10 ± 11.20	0.704	9.37 ± 20.70	4.17 ± 5.83	0.563
segmental sclerosis (%; mean ± SD)	4.73 ± 8.95	9.80 ± 18.20	0.423	2.50 ± 0.44	2.04 ± 0.98	0.244
adhesion (%; mean ± SD)	12.00 ± 17.10	10.50 ± 17.00	0.819	16.80 ± 15.20	7.04 ± 9.97	0.086
IgA deposits (mean ± SD)	3.09 ± 0.70	2.45 ± 0.69	0.011[b]	3.14 ± 0.38	3.43 ± 0.54	0.356
Tubulointerstitium						
mononuclear cell infiltration (%; mean ± SD)	4.55 ± 6.50	4.09 ± 6.25	0.676	0.71 ± 1.89	7.14 ± 9.06	0.078
fractional volume (mean ± SD)	5.91 ± 7.69	7.73 ± 14.00	0.588	5.00 ± 7.64	9.29 ± 11.70	0.308
arteriosclerosis (mean ± SD)	0.45 ± 0.52	0.55 ± 0.82	0.724	0.00 ± 0.00	0.57 ± 0.98	0.172

[a]Data compared using paired t test and McNemar χ^2 test.
[b]Statistically significant.

antigenic stimulation of the innate immune system by the tonsillar mucosa *via* the "mucosa-bone marrow axis." Thereafter, aberrantly glycosylated IgA1 produced as a result of the anomalous stimulated immune response in the bone marrow is deposited within the mesangial area. Such deposition correlates with the severity of glomerular IgAN lesions *in situ* (21). Tonsillectomy might act upstream of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa, whereas steroid pulse therapy acts downstream of the mechanism by suppressing the abnormal immune response in the bone marrow and leading to subsequent inflammation in renal glomeruli. Thus, intervention against both pathogenic mechanisms might have a better therapeutic effect on IgAN than steroid monotherapy. In fact, we confirmed that IgA deposition decreased in the mesangial area of the group that received combined therapy, and this might have improved mesangial proliferation.

We also could show a certain level of effect of the combined

Table 4. Univariate and multivariate analysis of factors that contribute to UP remission in 55 patients with IgAN[a]

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (per 10 yr of age)	0.82	(0.58 to 1.17)	0.278	0.71	(0.46 to 1.10)	0.135
Male (*versus* female)	0.69	(0.32 to 1.49)	0.348	0.93	(0.32 to 2.68)	0.885
Macroscopic hematuria (*versus* no macrohematuria)	0.84	(0.41 to 1.74)	0.637	0.60	(0.26 to 1.38)	0.229
SBP (per 10 mmHg)	0.78	(0.60 to 1.03)	0.076	0.97	(0.70 to 1.33)	0.835
Urinary protein (per 0.5 g/d)	0.72	(0.55 to 0.95)	0.018[b]	0.74	(0.54 to 1.02)	0.063
Serum creatinine (per 0.5 mg/dl)	0.61	(0.36 to 1.04)	0.071	0.84	(0.43 to 1.64)	0.607
Histologic severity (per grade)	0.46	(0.23 to 0.90)	0.023[b]	0.98	(0.39 to 2.45)	0.969
Combined therapy (*versus* monotherapy)	5.19	(2.01 to 13.40)	0.001[b]	6.20	(1.98 to 19.50)	0.002[b]
RAS-I (*versus* absence of RAS-I)	0.52	(0.25 to 1.07)	0.076	0.80	(0.37 to 1.73)	0.571

[a]CI, confidence interval; HR, hazard ratio; RAS-I, renin-angiotensin system inhibitors.
[b]Statistically significant.

therapy on the eradication of crescentic lesions in this study, although the efficacy was not statistically significant compared with steroid alone because of small sample size. IgAN with crescent formation is a high-risk case developed to ESRD (22), and steroid and concomitant use of immunosuppressive agents such as cyclophosphamide are useful for the eradication of the lesions (23,24). The combined therapy might have an advantage from the aspect of the adverse effect caused by drug toxicity, although tonsillectomy is a surgical procedure.

This study has several limitations. First, we evaluated renal outcome on the basis of proteinuria remission, which is a surrogate marker; however, recent long-term follow-up studies indicated that proteinuria remission improves the true renal outcome in IgAN. Reich *et al.* (25) showed that the 15-yr renal survival rate of patients with IgAN and ≤0.3 g/d time-averaged proteinuria was >95%, and they underscored the importance of urinary remission. We therefore believe that urinary remission is a reliable predictor of renal outcome. Second, none of our patients had advanced IgAN with sCr levels of ≥2.0 mg/dl. In fact, the ratio (%) of patients with histologic grade 4 was only 9% in this study population, and the sCr value doubled from baseline within approximately 5 yr in only one patient. Sato *et al.* (26) pointed out that the combined therapy did not confer a benefit on patients with IgAN and sCr values of ≥2.0 mg/dl. Patients with advanced IgAN might have difficulties in achieving clinical remission because nonimmunologic mechanisms are mainly involved at this stage of the disease, and such patients have a high probability of exceeding the "point of no return" (27). Finally, we could not control the selection bias for treatment because this study was not designed for a randomized, controlled trial. In consequence, the severity of the background risk factors between the two groups was not adequately equal, although the difference did not reach statistical significance. The limitation might be considerable even if we applied a multivariate analysis to control some confounding factors such as proteinuria and histologic grade in this study.

Conclusions

Tonsillectomy combined with steroid pulse therapy significantly and positively affected the likelihood of achieving clinical remission compared with steroid pulse therapy alone among patients with a relatively early phase of IgAN. Moreover, the combined therapy seemed to preserve stable renal function over the long term *via* the maintenance of urinary remission. Further studies are required to clarify whether the combined therapy is effective at the advanced stage of IgAN and to confirm whether it actually improves renal outcome over the long term. Although tonsillectomy is a surgical procedure and its arbitrary application is accompanied by ethical concerns, a randomized, controlled trial should address these issues. To understand the mechanism between tonsillitis and IgAN progression in detail is also an urgent necessity.

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Disclosures

None.

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