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ORIGINAL ARTICLE

Impact of tonsillectomy combined with steroid pulse therapy on immunoglobulin A nephropathy depending on histological classification: a multicenter study

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Abstract

Background In addition to corticosteroids and inhibition of the renin–angiotensin–aldosterone system, tonsillectomy with steroid pulse therapy (TSP) may have a beneficial impact on the clinical course of IgA nephropathy (IgAN). However, there is still much uncertainty regarding the indications for therapy, treatment protocol, and therapeutic options for IgAN.

Methods In this multicenter retrospective cohort study, we enrolled 284 patients with biopsy-proven IgAN who received TSP or corticosteroid therapy or conservative therapy. The effects of TSP on clinical remission (CR) were evaluated after a median follow-up period of 4.1 years in relation to histological classifications.

Results Among the 284 participants, 161 patients received TSP. During the observation time, 141 patients (49.6 %) achieved CR, with a median time to remission of 397 days. In multivariate Cox regression analyses, TSP had an impact on achieving CR in only the group with histological grade 3 defined as glomerulosclerosis, crescent formation or adhesion to Bowman's capsule in 10–30 % of all biopsied glomeruli, or mild cellular infiltration in the interstitium (hazard ratio (HR) 4.29, 95 % confidence interval (95 %CI) 1.88–11.19, $P < 0.001$). TSP independently contributed to a higher incidence of CR, particularly in the patient group showing evident mesangial hypercellularity (HR 2.54, 95 %CI 1.38–5.08, $P = 0.002$).

Conclusions TSP may have a beneficial effect on the clinical course in IgAN patients with mild to moderate glomerular and interstitial lesions, particularly with distinct mesangial cell proliferation.

Keywords IgA nephropathy · Pathological classification · Tonsillectomy

Steering committee for "IgA nephropathy from four universities (IgAN-4U)", Japan.

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Introduction

Immunoglobulin A nephropathy (IgAN), the most prevalent type of primary glomerulonephritis, is a clinically and pathologically heterogeneous disease. Pathologic classification, together with cross-sectional and follow-up clinical data showing proteinuria >1 g/day, decreased glomerular filtration rate (GFR), and presence of hypertension are well-established indicators that identify IgAN patients who are likely to develop progressive disease [1, 2]. Histological lesions, including tubular atrophy/interstitial fibrosis, mesangial cell proliferation, and increased matrix, glomerulosclerosis, and extracapillary proliferation, have been associated with an increased risk for a progressive clinical course [3–5]. In addition to providing prognostic information, determination of a pathologic grade can potentially be used to guide therapy in IgAN [5].

Nonimmunosuppressive treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors has been shown to slow the progression of IgAN independently of the effect of RAAS inhibitors on blood pressure [6, 7]. Corticosteroids remain the first-line immunosuppressive therapy for IgAN, with limited experience using other immunosuppressive agents [8]. Tonsillectomy has been suggested as a possible treatment modality in combination with immunosuppressive therapy for IgAN patients on the basis of the rationale that chronic tonsillitis may lead to increased production of abnormally glycosylated IgA1, resulting in the formation of IgG–IgA immune complexes and their deposition in the glomeruli [9, 10].

Several studies, including one meta-analysis, have reported the efficacy of tonsillectomy combined with steroid pulse therapy (TSP) on the clinical course of IgAN [11–20]. Meanwhile, a recent randomized controlled trial showed that TSP had no significant impact on the incidence of clinical remission in the short term [21]. Although a nationwide survey revealed that TSP is becoming a standard treatment option for adult IgAN patients in Japan [22], there is still uncertainty about treatment alternatives for IgAN, including the criteria for application of TSP.

Against this background, we reviewed the treatment options and protocols for IgAN during the past 10 years in four university hospitals and examined the relatively long-term impact of treatment options on clinical remission, with special emphasis on the pathologic grade and features of renal biopsy.

Patients and methods

Patients

Data were collected retrospectively on patients with biopsy-proven IgAN over a period of 10 years (September 2000 to August 2010) at University of Miyazaki Hospital, Nagasaki University Hospital, Oita University Hospital, and University Hospital of Occupational and Environmental Health. The exclusion criteria for this study were age younger than 15 years or older than 60 years at renal biopsy, follow-up period less than 12 months, incomplete data in medical records, and the presence of secondary causes of mesangial IgA deposits such as systemic lupus erythematosus. From the 323 patients who fit the inclusion criteria, 23 patients who received tonsillectomy without corticosteroid therapy, 12 patients who received tonsillectomy and corticosteroid without steroid pulse therapy, 3 patients who received mizoribine without corticosteroid therapy, and 1 patient who received steroid pulse therapy without subsequent corticosteroid therapy were excluded. A total of 283 patients (161 women) were ultimately enrolled in the outcome analyses, with median follow-up period of 4.1 (1.0–11.7) years. The study protocol was approved by the participating institutional review boards, with the following approval numbers: 874 for the University of Miyazaki Hospital; 11102452-2 for Nagasaki University School of Medicine; 496 for the Faculty of Medicine, Oita University; and H23-89 for the University of Occupational and Environmental Health School of Medicine.

Data collection and evaluation

Clinical and laboratory data collected at the time of diagnosis and follow-up visits included systolic blood pressure (SBP), diastolic blood pressure (DBP), blood test results, and dipstick measurements. Hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg or the use of antihypertensive medication. The quantitative findings of urinary protein and urinary occult blood (UOB) were converted into scores as follows: (−) and (±) to 0, (1+) to 1, (2+) to 2, and 3+ to 3.

Histological classification

Histologic severity of IgAN was categorized according to the classification presented by the Special IgAN Study Group in Japan [23], as follows:

- *Grade 1*: Slight mesangial cell proliferation and increased matrix. Absence of glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule. No prominent changes in the interstitium, renal tubuli, or blood vessels.
- *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 specimens with Grade 1.

- *Grade 3*: Moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in 10–30 % of all biopsied glomeruli. Slight cellular infiltration in the interstitium, except around some sclerosed glomeruli. Slight tubular atrophy. Mild vascular sclerosis.
- *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 is seen in some intrarenal arteriolar walls.

The renal biopsy specimens were re-assessed and scored using the Oxford Classification (MEST score) [3], which includes mesangial hypercellularity (M0, ≤0.5 of mesangial hypercellularity score; M1, >0.5 of mesangial hypercellularity score), endocapillary hypercellularity (E0 absent; E1 present), segmental glomerulosclerosis (S0, absent; S1, present), and tubular atrophy/interstitial fibrosis (T0, <25 %; T1 25–50 %; T2, >50 %). The mesangial hypercellularity score is the mean score for all glomeruli (<4 mesangial cells per mesangial area = 0; 4–5 mesangial cells = 1, 6–7 mesangial cells = 2; ≥8 mesangial cells = 3).

Outcomes

The primary outcome was designated as clinical remission (CR), defined as remission of both proteinuria and hematuria at least two consecutive times. Remission of proteinuria was specified as negative or trace proteinuria on the urine dipstick test or urine protein excretion <0.3 g/g creatinine. Remission of hematuria was defined as the absence of blood on the dipstick test or urine red blood cells (U-RBC) <5/high power field.

Statistical analysis

Values are expressed as mean ± SD or median (range of 10th to 90th percentile) or percentage, as appropriate. Statistical significance was set at the level of $P < 0.05$. Comparisons among the three treatment groups (TSP, CS; corticosteroids without tonsillectomy, CT; conservative therapy with renin–angiotensin–aldosterone system inhibitors and/or antiplatelet agents or observation) were assessed with the nonparametric Wilcoxon signed-rank test for continuous variables and a χ^2 test for nominal variables. Kaplan–Meier analysis was performed to estimate cumulative curves of clinical remission. Cox regression hazards models were fitted to assess the impact of multiple covariates for clinical remission. This model included TSP, CS, and other known clinical variables that influence the clinical course such as age, hypertension during observation, estimated GFR (eGFR), severity of proteinuria, and administration of RAAS-I. The results of the multivariate analyses are expressed as hazard ratios (HR) with 95 % confidence intervals (CI) and a P value. All statistical analyses were performed using JMP version 9 (SAS Institute Inc, Cary, NC, USA).

Results

Treatments

Of the 323 study patients with IgAN, 161 patients (49.8 %) received TSP. Steroid pulse therapy followed by oral prednisolone without tonsillectomy was administered to 29 patients (9.0 %). Oral prednisolone without steroid pulse and tonsillectomy was selected for 14 patients (4.3 %). Tonsillectomy followed by oral prednisolone without steroid pulse therapy was employed for 12 patients (3.7 %). Twenty-three patients (7.1 %) underwent tonsillectomy without steroid therapy. Mizoribine was administered to 16 patients (5.0 %) as an immunosuppressive agent, of whom 3 patients received mizoribine without a steroid. RAAS inhibitors were given to 166 patients (51.4 %), of whom 46 patients (14.2 %) received an RAAS inhibitor without a steroid or tonsillectomy. Antiplatelet agents (dipyridamole or dilazep dihydrochloride) were used for 239 patients (74.0 %), of whom 12 patients (3.7 %) received antiplatelet agents without any other treatment. Twenty-two patients (6.8 %) were observed only by regular follow-up visits. The steroid pulse therapy protocols were administered to the different groups of patients as follows: 0.5 g/d of intravenous methylpredonisolone for 3 consecutive days for 3 courses ($n = 66$), 0.5 g/d for 3 days for 2 courses ($n = 62$), 0.5 g/d for 3 days for 1 course ($n = 45$), and other regimens ($n = 18$). The initial dosage of oral prednisolone was approximately 0.5 mg/kg per day. Subsequently, the prednisolone was gradually tapered. The median administration period was 411 (188–970) days.

Baseline characteristics

The baseline characteristics of the 283 IgAN patients are summarized in Table 1 according to the three treatment options. The patients who received TSP were younger, with more females than males, and a lower incidence of hypertension during the observation time. Significant

Table 1 Baseline characteristics of groups according to therapies

	Treatment groups			*P*
	TSP	CS	CT	
Number	161	43	80	
Age (years)	33 ± 13	38 ± 15	41 ± 15	<0.001
Female, *n* (%)	105 (65)	22 (51)	34 (43)	0.003
SBP (mmHg)	122 ± 16	129 ± 18	121 ± 18	0.04
DBP (mmHg)	74 ± 13	78 ± 12	73 ± 11	0.09
Hypertension at biopsy, *n* (%)	28 (17)	14 (33)	13 (16)	0.08
Hypertension during observation time, *n* (%)	40 (25)	18 (42)	38(48)	0.001
Albumin (g/dl)	4.1 ± 0.5	3.8 ± 0.7	4.2 ± 0.4	0.001
BUN (mg/dl)	14.3 ± 4.2	16.8 ± 6.4	15.0 ± 4.7	0.05
eGFR (ml/min/1.73 m^2)	86 ± 29	71 ± 33	78 ± 28	0.003
Hemoglobin (g/dl)	13.2 ± 1.9	13.2 ± 1.7	13.6 ± 2.1	0.11
CRP (mg/dl)	0.16 ± 0.4	0.16 ± 0.32	0.16 ± 0.27	0.36
IgA (mg/dl)	340 ± 128	345 ± 129	334 ± 130	0.87
C3 (mg/dl)	106 ± 21	108 ± 26	104 ± 23	0.85
Urinary protein score	2.0 ± 0.9	2.5 ± 0.8	1.4 ± 1.0	<0.001
UOB score	2.3 ± 0.9	2.3 ± 0.9	1.8 ± 1.2	0.005
RAAS-I, *n* (%)	72 (44)	31 (72)	46 (57)	0.003

Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation

Treatment groups: *TSP* tonsillectomy combined with steroid pulse therapy, *CS* corticosteroid therapy without tonsillectomy, *CT* conservative therapy (RAAS-I or tonsillectomy antiplatelet agents or observation), *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *CRP* C reactive protein, *C3* Complement component 3, *UOB* urine occult blood, *RAAS-I* Renin– angiotensin–aldosterone system inhibitors

differences among the groups were observed in albumin levels, eGFR, urinary protein scores, UOB scores, and prevalence of RAAS-I administration. The distribution of pathological classification and MEST scores is shown in Table 2.

Effects of TSP on clinical remission depending on the histological classification

There were 141 patients (49.8 %) who achieved CR during a median follow-up period of 4.1 years (minimum 1.0 years to maximum 11.7 years). The median time to remission was 397 (range 61–1855) days. Thirteen patients (4.6 %) showed > 100 % increase in serum creatinine from the baseline level at final observation, of whom 7 patients reached end-stage kidney disease requiring renal replacement therapy.

In the total cohort, a Kaplan–Meier plot revealed a significant difference in CR rates among the three treatment groups (log-rank $\chi^2 = 15.1$, $P < 0.001$, Fig. 1). In a multivariate Cox proportional hazards model predicting clinical remission, TSP (versus CT) independently contributed to a higher incidence of CR [hazard ratio (HR) 2.08, 95 % confidence interval (CI) 1.33–3.33, $P = 0.001$, Table 3]. If the Kaplan–Meier analyses were stratified according to the histological grade, significant differences in attaining CR among the three treatment options were observed only in the patient group with histological grade 3 (Supplementary Figure 1). In this patient group, the multivariate Cox model showed that both TSP (HR 4.29, 95 % CI 1.88–11.19, $P < 0.001$) and CS (HR 4.17, 95 % CI 1.45–12.8, $P = 0.01$) were independently associated with a higher incidence of CR compared to the CT group (Table 3).

When stratified by the histological features according to the Oxford-MEST criteria, univariate Kaplan–Meier analyses showed significant differences in CR rates among the three treatment options in the patient groups with the score of M0, M1, E0, S1, and T0 (Supplementary Figure 2). In the multivariate Cox models stratified by MEST classification, TSP exerted independent and significant effects on reaching CR in all patient groups except those with M0 and S0 (Table 4). When stratified by mesangial hypercellularity, the impact of TSP on CR rate was significant in the patients with M1 (HR 2.54, 95 % CI 1.38–5.08, $P = 0.002$), while no independent effect of TSP was observed in the patients with M0 (HR 1.72, HR 0.76–3.98, $P = 0.20$). When stratified by segmental sclerosis, both TSP (HR 3.60, 95 % CI 1.68–8.66, $P < 0.001$) and CS (HR 2.89, 95 % CI 1.14–7.78, $P = 0.03$) showed

Table 2 Number of histologic findings of groups according to therapies

	Total	Treatments		
		TSP	CS	CT
Histological Classification by IgAN Study Group, number				
Histologic grade 1	44	22	1	21
Histologic grade 2	65	38	5	22
Histologic grade 3	118	70	22	26
Histologic grade 4	57	31	15	11
Oxford Classification (number)				
Mesangial hypercellularity, M0/M1	80/204	31/130	9/34	40/40
Endocapillary hypercellularity, E0/E1	194/90	108/53	29/14	57/23
Segmental glomerulosclerosis, S0/S1	146/138	82/79	15/28	49/31
Tubular atrophy/Interstitial fibrosis, T0/T1-2	215/69	133/28	24/19	58/22

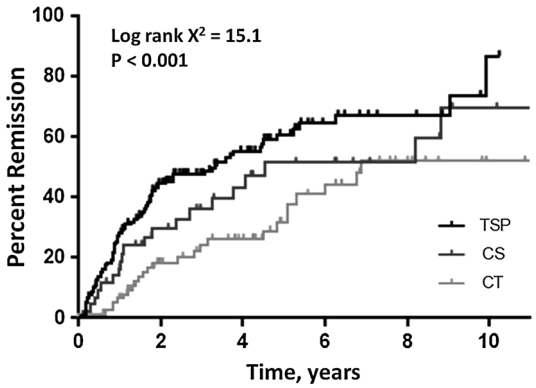

Fig. 1 Kaplan–Meier analysis comparing the clinical remission rate between the tonsillectomy combined with steroid pulse therapy group (TSP), the corticosteroid group (CS), and the group who received conservative therapy (CT), $n = 284$

significant effects on CR rate, with a higher HR of TSP in the patient group with S1, while no independent effect of TSP (HR 1.57, 95 % CI 0.91–2.83, $P = 0.11$) or CS (HR 1.09, 95 % CI 0.37–2.79, $P = 0.87$) was shown in the patients with S0.

Discussion

TSP is becoming a standard treatment option for adult IgAN patients in Japan on the basis of multiple clinical studies that have shown the beneficial impact of TSP on the clinical course of IgAN [22]. Nevertheless, there is still uncertainty regarding the indication of TSP for IgAN patients. The results of this multicenter cohort study, in which 49.8 % of IgAN patients diagnosed during 2000 to 2010 received TSP with several protocols of steroid therapy, indicated that the beneficial effect of TSP on achieving CR was remarkable in the patient group having histological features of moderate glomerular lesions and/or slight to mild interstitial abnormality. Of note, in the patient group with mesangial hypercellularity, a favorable impact of TSP on the clinical course was notable against other treatment options including corticosteroid therapy without tonsillectomy.

In the pathogenic mechanism of IgAN, aberrantly glycosylated IgA1 initially produced in the mucosal immune system, such as the palatine tonsils and immune complexes containing the abnormally glycosylated IgA1, is considered

Table 3 Multivariate Cox regression model predicting clinical remission in total cohort and patients with histological grade 3

	Total cohort ($n = 284$)			Histological grade 3 ($n = 118$)		
	HR	95 %CI	*P*	HR	95 %CI	*P*
Age, per 10 yrs of age	0.94	0.79–1.12	0.49	0.98	0.76–1.25	0.85
Hypertension during observation	0.74	0.46–1.17	0.20	0.85	0.43–1.69	0.65
eGFR, per 10 ml/min/1.73 m^2	1.00	0.93–1.07	0.99	0.95	0.85–1.06	0.36
Urinary protein score, per one score	0.90	0.74–1.10	0.29	0.77	0.54–1.12	0.17
RAAS-I, vs absence of RAAS-I	0.96	0.64–1.44	0.86	0.80	0.42–1.51	0.50
TSP, vs CT	2.08	1.33–3.33	0.001	4.29	1.88–11.19	<0.001
CS, vs CT	1.63	0.86–3.04	0.13	4.17	1.45–12.8	0.01

HR hazard ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *TSP* tonsillectomy combined with steroid pulse therapy, *CS* corticosteroid therapy without tonsillectomy, *CT* conservative therapy (RAAS-I and/or tonsillectomy antiplatelet agents or observation)

Table 4 Multivariate Cox regression model predicting clinical remission in relation to mesangial hypercellularity (panel a), endocapillary hypercellularity (panel b), segmental glomerulosclerosis (panel c), and tubular atrophy/interstitial fibrosis (panel d)

a. Mesangial hypercellularity (M0, ≤0.5 of mesangial hypercellularity score; M1, >0.5 of mesangial hypercellularity score)

	M0 ($n = 80$)			M1 ($n = 204$)		
	HR	95 %CI	*P*	HR	95 %CI	*P*
Age, per 10 yrs of age	0.64	0.44–0.90	0.01	1.06	0.86–1.29	0.60
Hypertension during observation	1.59	0.61–4.03	0.34	0.62	0.35–1.06	0.08
eGFR, per 10 ml/min/1.73 m^2	0.99	0.86–1.12	0.83	1.00	0.91–1.08	0.93
Urinary protein score, per one score	1.01	0.68–1.50	0.96	0.93	0.72–1.19	0.54
RAAS-I, vs absence of RAAS-I	0.68	0.29–1.53	0.35	1.00	0.62–1.59	0.99
TSP, vs CT	1.72	0.84–3.58	0.14	2.54	1.38–5.08	0.002
CS, vs CT	1.64	0.49–4.83	0.40	1.72	0.76–3.98	0.20

b. Endocapillary hypercellularity (E0 absent; E1 present)

	E0 ($n = 194$)			E1 ($n = 90$)		
	HR	95 %CI	P	HR	95 %CI	P
Age, per 10 yrs of age	0.90	0.72–1.12	0.34	1.06	0.76–1.46	0.74
Hypertension during observation	0.72	0.40–1.27	0.26	0.76	0.32–1.78	0.52
eGFR, per 10 ml/min/1.73 m^2	0.97	0.89–1.06	0.56	1.08	0.93–1.25	0.29
Urinary protein score, per one score	0.91	0.71–1.15	0.42	0.86	0.60–1.24	0.41
RAAS-I, vs absence of RAAS-I	0.93	0.57–1.51	0.78	1.18	0.55–2.48	0.67
TSP, vs CT	2.01	1.18–3.55	0.01	2.43	1.06–6.15	0.04
CS, vs CT	1.55	0.72–3.25	0.26	2.02	0.59–6.66	0.26

c. Segmental glomerulosclerosis (S0, absent; S1, present)

	S0 ($n = 146$)			S1 ($n = 137$)		
	HR	95 %CI	*P*	HR	95 %CI	*P*
Age, per 10 yrs of age	0.90	0.71–1.14	0.37	0.96	0.74–1.24	0.76
Hypertension during observation	1.01	0.53–1.92	0.97	0.44	0.20–0.91	0.03
eGFR, per 10 ml/min/1.73 m^2	1.01	0.90–1.11	0.91	0.99	0.89–1.09	0.81
Urinary protein score, per one score	0.98	0.73–1.30	0.88	0.77	0.57–1.05	0.10
RAAS-I, vs absence of RAAS-I	0.86	0.49–1.48	0.58	1.19	0.62–2.28	0.60
TSP, vs CT	1.57	0.91–2.83	0.11	3.60	1.68–8.66	<0.001
CS, vs CT	1.09	0.37–2.79	0.87	2.89	1.14–7.78	0.03

d. Tubular atrophy/interstitial fibrosis (T0, ≤25 %; T1, 2, >25 %)

	T0 ($n = 215$)			T1, 2 ($n = 69$)		
	HR	95 %CI	P	HR	95 %CI	P
Age, per 10 yrs of age	0.91	0.75–1.09	0.31	1.05	0.68–1.64	0.84
Hypertension during observation	0.75	0.43–1.27	0.28	0.71	0.24–1.98	0.51
eGFR, per 10 ml/min/1.73 m^2	0.98	0.90–1.06	0.65	1.02	0.83–1.28	0.84
Urinary protein score, per one score	0.96	0.77–1.21	0.73	0.67	0.44–1.02	0.06
RAAS-I, vs absence of RAAS-I	1.07	0.67–1.68	0.77	0.66	0.24–1.83	0.41
TSP, vs CT	1.81	1.10–3.10	0.02	3.30	1.21–10.00	0.02
CS, vs CT	1.57	0.73–3.23	0.24	2.37	0.66–8.63	0.18

to directly bind to receptors expressed on mesangial cells, which triggers mesangial cell activation and mesangial hypercellularity [24]. A repeat biopsy study showed that mesangial cell proliferation in IgAN was reversible if TSP was initiated at a relatively early stage [25]. Komatsu et al. reported consecutive biopsy data showing that the extent of mesangial proliferation significantly improved after treatment compared with before treatment in the TSP group, but

not in the group who received steroid pulse monotherapy [16]. The remarkable effect of TSP noticed in the present study for patients with obvious mesangial hypercellularity may suggest that both removal of potential antigenic stimuli by tonsillectomy and suppression of the abnormal immune response by corticosteroid therapy could lead to an improvement in histological lesions including mesangial proliferation.

In the present study, a difference in the effect of TSP or CS on the clinical course was observed between the patients with segmental sclerosis and patients without segmental sclerosis. Specifically, the superiority of TSP or CS was significant in the patient group with segmental sclerosis. It is a matter of debate whether segmental sclerosis, which is considered to be mainly chronic lesions, could be reversed by treatment [26]. This result appears to suggest that segmental sclerotic lesions may include reversible factors which could be ameliorated by TSP or CS.

Several limitations of the present study should be recognized. First, it was a retrospective observational review. Due to the retrospective nature of this study, each treatment group was unique in terms of the number of patients and the steroid pulse protocol used; therefore, it is difficult to claim the additional benefit of TSP over steroid monotherapy. Second, we set the primary outcome on the basis of remission of proteinuria and hematuria, not on the renal survival rate after long time periods. Third, this study did not examine recurrence.

In conclusion, TSP may have a beneficial impact on the clinical course of IgAN patients with mild to moderate glomerular and interstitial lesions, particularly with prominent mesangial cell proliferation. Further studies are required to clarify which patient groups experience superior outcomes from TSP compared with other treatment modalities.

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Conflict of interest All of the authors declare that they have no competing interests.

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