Internal Medicine (2012.01) 51巻11号:1323～1328.

Retrospective Comparison of the Efficacy of Tonsillectomy with and without Steroid-pulse Therapy in IgA Nephropathy Patients.

Nakagawa Naoki, Kabara Maki, Matsuki Motoki, Chinda Junko, Fujino Takayuki, Hirayama Tomoya, Takahara Miki, Harabuchi Yasuaki, Kikuchi Kenjiro, Hasebe Naoyuki

Retrospective Comparison of the Efficacy of Tonsillectomy with and without Steroid-pulse Therapy in IgA Nephropathy Patients

Naoki Nakagawa [1], Maki Kabara [1], Motoki Matsuki [1], Junko Chinda [1], Takayuki Fujino [1], Tomoya Hirayama [2], Miki Takahara [3], Yasuaki Harabuchi [3], Kenjiro Kikuchi [1] and Naoyuki Hasebe [1]

[1] Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine and [3] Department of Otolaryngology-Head and Neck Surgery, Asahikawa Medical University, Asahikawa, [2] Departments of Nephrology, Kitasaito Hospital, Asahikawa, Japan

Corresponding author: Naoki Nakagawa, M.D., Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine, Asahikawa Medical University, Asahikawa, Japan, Phone：+81-166-68-2442, FAX：+81-166-68-2449

E-mail：naka-nao@asahikawa-med.ac.jp

The authors report no conflicts of interest.

Abstract

Objective: Tonsillectomy and steroid-pulse (TSP) therapy have been proposed as a curative treatment for immunoglobulin A nephropathy (IgAN) in Japan. However, we sometimes encounter patients who reject steroid-pulse therapy because of concerns about the side effects of corticosteroids. Here, we examined the efficacy of TSP therapy and tonsillectomy alone for IgAN with urinary abnormalities.

Methods and Patients: Data on 40 IgAN patients diagnosed by renal biopsies, who presented glomerular hematuria and proteinuria at baseline and underwent bilateral palatine tonsillectomy, were analyzed retrospectively. Twenty of them underwent TSP therapy (TSP group), and 20 underwent tonsillectomy alone (T group). We examined associations between therapies, changes in urinary findings and renal function, and subsequent clinical remission (CR), defined as negative proteinuria and urinary erythrocytes of less than 5/high-power field.

Results: TSP group showed a significant decrease in proteinuria and hematuria earlier than T group. The rates of CR were significantly higher in TSP group compared with T group on the final observation period (75% vs. 45%, $P<0.05$). There was a significant difference between CR group and non-CR group only in the rate of receiving TSP therapy.

Conclusion: TSP therapy significantly increased the probability of CR compared with tonsillectomy alone in IgAN patients with urinary abnormalities.

Keywords: clinical remission, IgA nephropathy, methylprednisolone pulse, tonsillectomy

Introduction

Immunoglobulin A nephropathy (IgAN), which is one of the most common types of primary glomerulonephritis, is an underlying disease that typically necessitates dialysis. Approximately 40% of IgAN patients develop renal failure within 20 years of diagnosis, and the long-term prognosis is poor (1, 2). Pozzi et al reported that corticosteroid therapy for IgAN exerted a renoprotective effect but that a relapse of proteinuria was observed in a relatively large number of patients after treatment (3). This report also suggested that complete remission (CR) cannot be achieved without preventing continuous tissue deposition of IgA. Focal infection of the palatine tonsils or other mucosal sites causes immune abnormalities, leading to sugar-chain incompleteness in the production of IgA1, which is then overproduced and deposited in renal glomeruli (4). In Japan, a combination of bilateral palatine tonsillectomy and steroid pulse (TSP) therapy has been reported to be effective in the treatment of IgAN (5-7), although in Western countries, evidence of the efficacy of this combination is considered to be low (8, 9). In some patients, steroid-associated adverse events have occurred in a dose-dependent manner, necessitating dose reduction, but few studies have compared the differing efficacy between the TSP therapy and tonsillectomy alone. In this study, we compared the therapeutic efficacy of TSP therapy and tonsillectomy alone in 40 patients with IgAN who were followed up for at least 12 months, in terms of changes in their urinary findings and the rate of CR.

Methods

Subjects

Among 154 patients who underwent renal biopsy in our hospital between April 2003 and December 2010, we identified 51 patients who had histologically proven IgAN. All 51 IgAN patients, including 19 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/or pus in the tonsillar crypts), and 48 patients had fulfilled the indication. We could obtain sufficient informed consent from 46 patients, and they underwent tonsillectomy. We explained

TSP therapy to all of them, and then 24 patients underwent TSP therapy. Meanwhile, 8 patients did not undergo steroid-pulse therapy due to the doctor's decision and 14 patients rejected it because of the possibility of steroid-associated adverse events such as acne, moon face, osteoporosis, worsening of diabetic mellitus, and so on. Then, the inclusion criteria for this study comprised 1) IgAN patients who underwent bilateral palatine tonsillectomy and were followed up for at least 12 months; 2) persistent microscopic hematuria and proteinuria more than 0.1 (g/g Cr); 3) a serum creatinine level of <2.0 mg/dl; 4) an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2 or higher; 5) age <70 years; and 6) willingness to provide written informed consent in accordance with the ethical standards laid down in the Declaration of Helsinki. We excluded patients for whom steroids were contraindicated as well as those in whom the renal disease was associated with systemic lupus erythematosus or other systemic diseases. As a result, 40 IgAN patients who underwent bilateral palatine tonsillectomy were included in this retrospective study. There were 20 patients treated with TSP therapy (TSP group) and 20 patients treated with tonsillectomy alone (T group). 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, (3+) to 3, and (4+) to 4, as described previously (6). Hypertension was defined as systolic BP >140 mmHg and/or diastolic BP >90 mmHg or the use of antihypertensive medication.

Assessment of Histological Severity

We assessed the histological 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 (10).

The extent of glomerular mesangial proliferation, interstitial lesions and arteriosclerosis were scored as follows: mild, 1; moderate, 2; and severe, 3. Lesions of global sclerosis of glomeruli, crescent formation, and adhesion to Bowman’s capsule are indicated as ratios (%) of diseased glomeruli, as described previously (6, 11).

Therapeutic intervention

After each patient had provided informed consent, bilateral palatine tonsillectomy was performed in all patients as described above. In the TSP group, one month after surgery,

intravenous methylprednisolone (mPSL) pulse therapy (500 mg/day) was administered as three installations over the course of 3 days, followed by 30 mg of PSL on alternate days for 8 weeks, as reported by Hotta et al (5) The dose of PSL was then decreased by 5 mg every 8 weeks and discontinued in the 12th month. Supportive therapies were administered, if necessary, by doctors in each treatment group, which included oral treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), antiplatelet drugs, anticoagulant drugs and antiulcer drugs.

Efficacy assessment

The primary endpoint was the rate of CR (assessed by urinalysis at 6 months and 12 months, and at the end of the follow-up period for proteinuria and hematuria). CR was defined as remission of both proteinuria and hematuria, specifically, (1) qualitative urinary protein of < (±) and (2) <5 red blood cells per high-power field on microscopic evaluation of the urinary sediment for at least 3 months. The secondary endpoint was the efficacy of our treatment in preventing progressive deterioration of IgAN, which was assessed through the evaluation of renal function. The eGFR was calculated using the equation recommended by the Japanese Society of Nephrology: eGFR = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 for females) (12). The presence or absence of adverse events was examined during the follow-up period through the periodic determination of clinical symptoms, blood pressure, hematological and biochemical parameters, urinalysis, and infection markers. Finally, we analyzed the parameters between the CR group and the non-CR group at the end of the follow-up period.

Statistical analysis

We compared the demographics of patients in the TSP group and the T group by an analysis of categorical variables using the $\chi 2$ test and Fisher's exact test and by an analysis of continuous variables using Student's *t*-test or the Wilcoxon rank-sum test. Changes in proteinuria, hematuria and eGFR in each group were analyzed using a linear mixed model with Bonferroni correction. In addition, differences between groups at each time of measurement were evaluated using the Wilcoxon rank-sum test. Values are expressed as the mean ± SD or SEM. The statistical significance level was set at $P<0.05$ (for a two-tailed test). All statistical analyses were performed with the SPSS software

package Version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the baseline characteristics of the 40 subjects according to therapy. There were more women than men in the T group, because some young female patients were concerned about steroid-associated adverse events and refused TSP therapy. The serum creatinine in the TSP group was higher than in the T group, while eGFR was not significantly different between the two group. Based on the criteria for determining the prognosis of IgAN, the TSP group displayed a greater frequency for severe histological changes. In the histological findings at the time of renal biopsy, the degree of mesangial proliferation was only significantly higher in the TSP group than in the T group. The duration of follow-up period was significantly longer in the T group than in the TSP group, suggesting that many of the recent cases underwent TSP therapy. The other parameters were not significantly different between the two groups.

Changes in UP score and the urinary red blood cell count from baseline to the end of the observation period in the two groups are shown in Fig. 1. Compared with the baseline value, significant decreases in the UP score were observed at 12 months and upon final observation in the T group (Fig. 1A). On the other hand, significant decreases were seen at 6 months, 12 months and at the final observation in the TSP group, suggesting that TSP therapy has an earlier effect that decreases proteinuria. Meanwhile, compared with the baseline values, significant decreases were seen at 6 months, 12 months and at the final observation in both the T group and the TSP group (Fig. 1B). Changes in eGFR from baseline to the end of the observation period are shown in Table 2. No significant changes were seen in both groups between baseline and the end of the observation period.

Table 3 shows the rates of CR of the 40 subjects according to therapy. The rates of CR were significantly higher in the TSP group compared with the T group at 6 months after treatment (45% vs. 25%; $P<0.05$) and at the final observation period (75% vs. 45%; $P<0.05$). No patient in either group developed end-stage renal failure. Except for pain, there were no other tonsillectomy-related complications. During the follow-up period, steroid-induced acne occurred in three patients in the TSP group as an adverse event and required treatment, although this was transient. None of the patients

developed severe immunosuppression or other severe adverse events.

Table 4 shows the parameters of the 40 subjects as categorized according to the CR group (n=24) and the non-CR group (n=16). In comparing data from patients in the CR and non-CR groups, a significant difference was observed only in those receiving TSP therapy [15 of 24 (63%) vs. 5 of 16 (31%); $P<0.05$].

Discussion

This retrospective study identified that TSP therapy was superior to tonsillectomy alone in inducing clinical remission and that the therapeutic effect persisted for approximately 3 years after the initial treatment. None of the patients developed severe immunosuppression or other severe adverse events in the patients who underwent TSP therapy.

Many patients with IgAN show episodic macroscopic hematuria, which coincides with mucosal infection, often of the upper respiratory tract (13), and there is evidence that tonsillectomy has a favorable effect on the long-term renal survival in IgAN patients (14, 15). Focal infection of the palatine tonsils or other mucosal sites causes immune abnormalities, leading to incomplete sugar-chain production of IgA1, which is subsequently overproduced, predominantly in tonsillar lymphocytes (14, 16), and deposited in renal glomeruli (4). Recently, we reported on the selective expansion of T-cell receptor (TCR) Vβ6 in tonsillar and peripheral blood T cells (17), as well as on the increase in B cell activation factor (BAFF), upregulated by interferon-γ in tonsillar mononuclear cells in patients with IgAN (18). These data suggest that tonsillar lymphocytes may play an important role in the pathogenesis of IgAN, and that tonsillectomy may act upstream of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa via the mucosa–bone marrow axis (19). Additionally, steroid-pulse therapy can act downstream of the immunological mechanism by suppressing the abnormal immune response in bone marrow, leading to subsequent inflammation in renal glomeruli.

The TSP group showed a significant decrease in proteinuria and hematuria earlier than did the T group, although the degrees of proteinuria and hematuria were higher compared with the T group. The rates of CR were significantly higher in the TSP group (75%) compared with the T group (45%) on the final observation period. Furthermore,

in comparing data from patients in the CR and non-CR groups, a significant difference was observed only in those receiving TSP therapy. Wang et al most recently reported that whereas neither tonsillectomy nor steroid treatment alone increased remission rates in patients with IgAN, tonsillectomy combined with either normal steroid or steroid pulse treatment resulted in higher remission rates with favorable long-term efficacy (20). Therefore, as well as our results, TSP therapy, an intervention against both pathogenic and immunological mechanisms, can have an improved therapeutic effect on IgAN compared with tonsillectomy alone. Meanwhile, CR was observed, at least, in 45% of tonsillectomy alone patients, indicating that we need a useful tool or biomarker to more precisely predict the therapeutic effect of TSP therapy and tonsillectomy alone.

The present study has several limitations. First, this study targeted patients with less severe IgAN. Although IgAN that presents hematuria and minimal proteinuria can be progressive, urinary remission may be seen spontaneously in some patients with mild IgAN (1, 2). Our study has shown that TSP therapy was effective for CR in comparison with tonsillectomy alone, but further analyses may be necessary to identify the IgAN patients who will show CR spontaneously and to precisely identify those targeted patients who would potentially benefit from TSP therapy. Second, we could not control the selection bias related to treatment because this study was a retrospective observational study and it was not designed as a randomized, controlled trial. Residual confounding by imperfectly measured or unknown confounders may still be present. Thus, further prospective randomized controlled trials in which the primary endpoint is the renal survival rate at 20 years or cohort studies with large numbers of patients are needed to clarify the efficacy of tonsillectomy alone and TSP therapy.

In conclusion, TSP therapy was more effective than tonsillectomy alone in IgAN patients with urinary abnormalities and is recommended for IgAN patients, even for those with mild to moderate renal dysfunction.

Acknowledgement

The authors thank all colleagues in Asahikawa Medical University Hospital who performed renal biopsies, treated patients, assisted with their follow-up and took medical records. This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, from the Ministry of Health, Labour and Welfare of Japan.

No author has any potential conflicts of interest to declare.

References

1. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis **29**: 526-532, 1997.
2. Berthoux FC, Mohey H, Afiani A. Natural history of primary IgA nephropathy. Semin Nephrol **28**: 4-9, 2008.
3. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol **15**: 157-163, 2004.
4. Hiki Y, Odani H, Takahashi M, et al. Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int **59**: 1077-1085, 2001.
5. Hotta O, Miyazaki M, Furuta T, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis **38**: 736-743, 2001.
6. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Kitamura K. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: A controlled study. Clin J Am Soc Nephrol **3**: 1301-1307, 2008.
7. Miura N, Imai H, Kikuchi S, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol **13**: 460-466, 2009.
8. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. Kidney Int **69**: 1939-1944, 2006.
9. Locatelli F, Del Vecchio L, Pozzi C. IgA glomerulonephritis: beyond angiotensin-converting enzyme inhibitors. Nat Clin Pract Nephrol **2**: 24-31, 2006.
10. Tomino Y, Sakai H. Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. Clin Exp Nephrol **7**: 93-97, 2003.
11. Asaba K, Tojo A, Onozato ML, et al. Long-term Renal Prognosis of IgA Nephropathy with Therapeutic Trend Shifts. Intern Med **48**: 883-890, 2009.
12. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from

serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.

13. Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P. The clinical course of mesangial IgA associated nephropathy in adults. Q J Med **53**: 227-250, 1984.

14. Bene MC, Hurault de Ligny B, Kessler M, Foliguet B, Faure GC. Tonsils in IgA nephropathy. Contrib Nephrol **104**: 153-161, 1993.

15. Xie YS, Nishi S, Ueno M, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int **63**: 1861-1867, 2003.

16. Egido J, Blasco R, Lozano L, Sancho J, Garcia-Hoyo R. Immunological abnormalities in the tonsils of patients with IgA nephropathy: inversion in the ratio of IgA: IgG bearing lymphocytes and increased polymeric IgA synthesis. Clin Exp Immunol **57**: 101-106, 1984.

17. Nozawa H, Takahara M, Yoshizaki T, Goto T, Bandoh N, Harabuchi Y. Selective expansion of T cell receptor (TCR) V beta 6 in tonsillar and peripheral blood T cells and its induction by in vitro stimulation with Haemophilus parainfluenzae in patients with IgA nephropathy. Clin Exp Immunol **151**: 25-33, 2008.

18. Goto T, Bandoh N, Yoshizaki T, et al. Increase in B-cell-activation factor (BAFF) and IFN-gamma productions by tonsillar mononuclear cells stimulated with deoxycytidyl-deoxyguanosine oligodeoxynucleotides (CpG-ODN) in patients with IgA nephropathy. Clin Immunol **126**: 260-269, 2008.

19. Suzuki Y, Tomino Y. Potential immunopathogenic role of the mucosa-bone marrow axis in IgA nephropathy: insights from animal models. Semin Nephrol **28**: 66-77, 2008.

20. Wang Y, Chen JY, Wang YE, Chen Y, Wang L, Lv YM. A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy. Nephrol Dial Transplant **26**: 1923-1931, 2011.

Figure legends

Figure 1. Change in urinary protein (UP) scores (A) and urinary red blood cells per high-power field (HPF) (B) over time after treatment in patients treated with tonsillectomy alone (T group) (filled circles) or tonsillectomy and steroid-pulse therapy (TSP group) (open circles). #$P<0.05$ vs. baseline in each group. 6 mo, 6 months after treatment; 12 mo, 12 months after treatment. Data are expressed as mean ± SEM. *$P<0.05$ vs. T group at the same points.

Table 1. Baseline characteristics

Characteristics	T group	TSP group
Number	20	20
Age, years	42.1 ± 3.4	35.7 ± 3.0
Gender, M/F	3/17	13/7 *
Duration of illness, years	7.3 ± 1.6	6.2 ± 1.4
Duration of final follow-up, years	4.8 ± 0.3	3.0 ± 0.2 *
Systolic BP, mmHg	120.8 ± 3.0	117.7 ± 3.3
Diastolic BP, mmHg	73.2 ± 2.1	72.2 ± 2.7
UP score	1.1 ± 0.2	1.3 ± 0.2
Proteinuria, g/day	0.41 ± 0.10	0.72 ± 0.14
No. of patients with UP >1.0 g/day	4 (20%)	5 (25%)
UOB score	2.9 ± 0.2	2.9 ± 0.3
Urinary red blood cells, /HPF	27.1 ± 7.3	40.7 ± 9.0
Serum creatinine, mg/dl	0.70 ± 0.05	0.97 ± 0.09 *
eGFR, ml/min/1.73 m^2	83.0 ± 5.7	76.7 ± 6.6
Serum IgA, mg/dl	375 ± 31	357 ± 25
Hypertension, n (%)	6 (30%)	7 (35%)
Usage of ACEI or ARB (%)	14 (70%)	17 (85%)
Diabetes, n (%)	1 (5%)	2 (10%)
Histological grade, n (%)		
1	4 (20%)	2 (10%)
2	7 (35%)	3 (15%)
3	5 (25%)	8 (40%)
4	4 (20%)	7 (35%)
Histological findings		
Glomerulus		
no. of glomeruli	14.4 ± 1.1	20.7 ± 3.0
mesangial proliferation	1.1 ± 0.1	1.5 ± 0.2 *
crescent formation, %	4.8 ± 2.2	11.1 ± 3.6
global sclerosis, %	9.4 ± 2.3	11.5 ± 3.7
adhesion, %	16.0 ± 4.0	9.8 ± 3.8
Tubulointerstitium		
interstitial lesion	0.7 ± 0.1	0.9 ± 0.2
arteriosclerosis	0.3 ± 0.1	0.3 ± 0.1

Variables are presented as the mean ± SEM, or number (percentage). T, tonsillectomy alone; TSP, tonsillectomy and steroid pulse; BP, blood pressure; UP, urinary protein; UOB, urinary occult blood; HPF, high-power field; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. *P<0.05 vs. T group at same category. #P<0.05 vs. eGFR≥60 group at same group.

Table 2. Changes in eGFR

	T group (N=20)	**TSP group** (N=20)
Baseline	83.0 ± 5.7	76.7 ± 6.6
6 mo	81.4 ± 5.7	75.6 ± 6.2
12 mo	76.5 ± 5.2	73.6 ± 6.3
Final	73.0 ± 4.6	73.5 ± 6.5

Variables are presented as the mean ± SEM. eGFR, estimated glomerular filtration rate; 6 mo, 6 months after treatment; 12 mo, 12 months after treatment.

Table 3. The rates of complete remission in each group

	T group (N=20)	**TSP group** (N=20)
6 mo	4 (20%)	9 (45%) *
12 mo	7 (35%)	10 (50%)
Final	9 (45%)	15 (75%) *

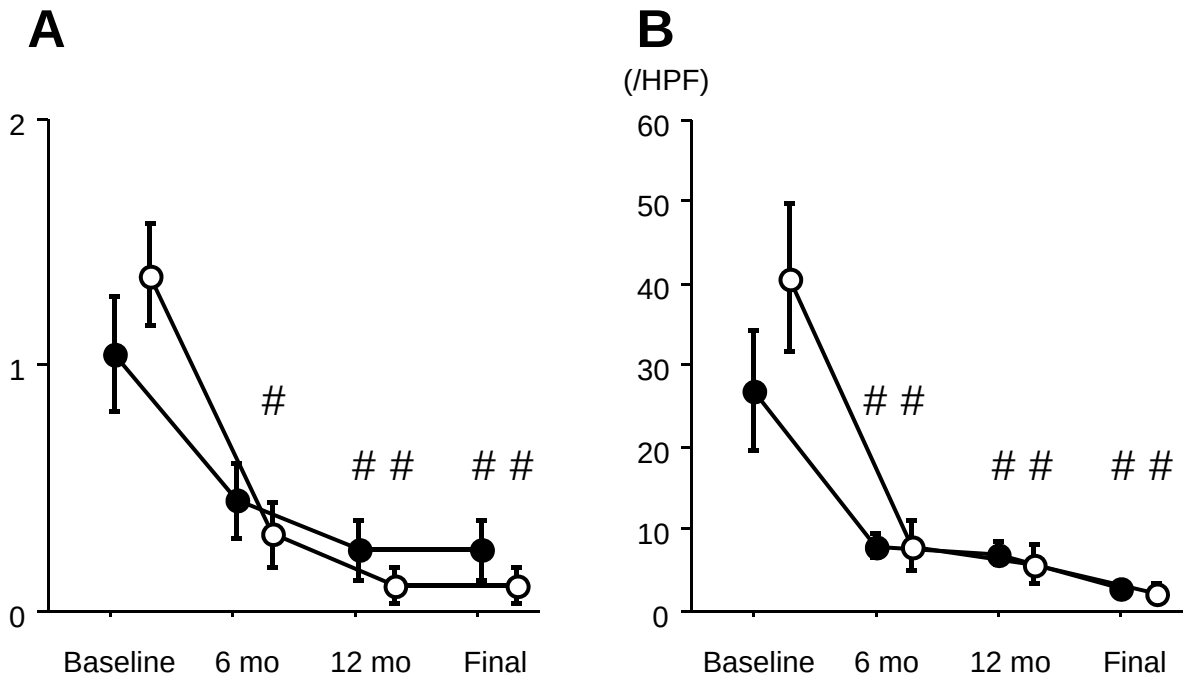
*P<0.05 vs. T group at same point. 6 mo, 6 months after treatment; 12 mo, 12 months after treatment.

Table 4. Comparison of clinical findings in CR group and non-CR group

Characteristics	**CR group**	**non-CR group**
Number	24	16
Age, years	40.0 ± 2.7	37.5 ± 4.2
Gender, M/F	11/13	5/11
Duration of illness, years	5.7 ± 1.3	8.4 ± 1.6
Duration of final follow-up, years	3.9 ± 0.7	3.9 ± 0.5
Systolic BP, mmHg	120.8 ± 2.5	116.9 ± 4.1
Diastolic BP, mmHg	73.7 ± 2.0	71.2 ± 3.1
UP score	1.1 ± 0.2	1.3 ± 0.3
Proteinuria, g/day	0.57 ± 0.11	0.55 ± 0.13
No. of patients with UP >1.0 g/day	4 (17%)	4 (25%)
Urinary red blood cells, /HPF	35.4 ± 7.4	31.1 ± 9.6
eGFR, ml/min/1.73 m^2	75.7 ± 5.0	86.7 ± 7.7
Serum IgA, mg/dl	364 ± 25	370 ± 34
Hypertension, n (%)	8 (33%)	5 (31%)
Usage of ACEI or ARB (%)	19 (79%)	12 (75%)
Diabetes, n (%)	3 (13%)	0 (0%)
TSP therapy, n (%)	15 (63%) *	5 (31%)
Histological grade, n (%)		
1	3 (12%)	3 (19%)
2	4 (17%)	6 (37%)
3	9 (38%)	4 (25%)
4	8 (33%)	3 (19%)
Histological findings		
Glomerulus		
no. of glomeruli	15.9 ± 1.3	20.8 ± 4.2
mesangial proliferation	1.3 ± 0.1	1.1 ± 0.1
crescent formation, %	10.0 ± 3.1	4.3 ± 1.9
global sclerosis, %	11.1 ± 3.1	7.6 ± 2.0
adhesion, %	10.7 ± 3.4	16.8 ± 4.8
Tubulointerstitium		
interstitial lesion	0.9 ± 0.2	0.6 ± 0.1
arteriosclerosis	0.3 ± 0.1	0.4 ± 0.1

Variables are presented as the mean ± SEM. *P<0.05 vs. non-CR group.

Figure 1



Nakagawa, N., *et al*