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REVIEW ARTICLE

A treatment dilemma in adult immunoglobulin A nephropathy: what is the appropriate target, preservation of kidney function or induction of clinical remission?

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Abstract Immunoglobulin (Ig) A nephropathy is the most common type of glomerulonephritis worldwide. Data on its natural history suggest that approximately 40% of patients progress to end-stage renal failure after 20 years. Various therapies such as antiplatelet medication, fish oil, oral prednisolone, intravenous prednisolone, tonsillectomy, and tonsillectomy plus steroid pulse (TSP) have been proposed. Japanese nephrologists face challenging issues regarding this disease, such as the usefulness of the annual urinary screening system (kenshin) and kidney biopsies, the desire of patients and their families for treatment despite insufficient clinical evidence, and the risk of overtreatment with TSP versus the loss of a 'golden period' with late intervention. We review the current literature on tonsillectomy, steroid therapy, and TSP, which was first proposed in Japan, and present some perspectives on the treatment of IgA nephropathy.

Keywords IgA nephropathy · Steroid therapy · Tonsillectomy · Tonsillectomy plus steroid pulse therapy (TSP)

Introduction

More than 40 years have passed since immunoglobulin (Ig) A nephropathy was first described by Berger and Hinglais in 1968 [1]. Various approaches such as antiplatelet medication, fish oil, oral prednisolone, intravenous prednisolone, tonsillectomy, and tonsillectomy plus steroid pulse therapy (TSP), have been proposed for treating patients with adult IgA nephropathy. Clinicians often face challenges in deciding which treatment is most suitable for each patient, while balancing the hopes of patients and their families with insufficient clinical evidence. Here we review the data from clinical trials and give a perspective on the treatment of IgA nephropathy.

What is the treatment dilemma for Japanese nephrologists?

Are the annual urinary screening system (kenshin) and kidney biopsies useful?

A Japanese law established a system of annual urinary screening (kenshin) in schools and workplaces approximately 40 years ago. About 40% of the Japanese population receive kenshin each year. Persons with detected urinary abnormalities are advised to consult local physicians. If a local physician finds >1+ proteinuria on repeat urinary testing, he refers the patient to a nephrologist. Approximately 10,000 kidney biopsies are performed each year in Japan, of which 30–40% (3,000–4,000 persons) receive a diagnosis of IgA nephropathy. Many patients with IgA nephropathy are diagnosed at an early stage in Japan. The benefit of kenshin and kidney biopsies depends on whether early intervention can improve the prognosis of IgA nephropathy. The Ministry of Health, Labour and Welfare of Japan requires the Japanese Society of Nephrology to demonstrate the efficacy of kenshin; however, Japanese nephrologists are not currently able to do so.

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The desire of patients and their families versus insufficient clinical evidence

Since TSP was first reported by Hotta et al. in 2001 [2], a recent analysis revealed that 600 patients in Japan received TSP in 2006. More than one thousand patients received TSP in 2010. One year after TSP, 50% of patients achieved clinical remission (CR), defined as no urinary abnormalities [3]. Many patients and their families, having discovered information about the efficacy of TSP through the Internet or personal communications, visit the hospital to seek TSP. Although many Japanese nephrologists know that several international guidelines do not recommend TSP for IgA nephropathy, they are challenged with making decisions on which treatment is suitable for the patient, while balancing the desire of patients and their families against insufficient clinical evidence.

A risk of overtreatment versus a lost 'golden period'

Many Japanese nephrologists feel that patients with early-stage or mild IgA nephropathy respond readily to TSP or steroid pulse therapy. On the other hand, patients with proteinuria >1.0 g/day and creatinine clearance (CCr) <70 ml/min are resistant not only to TSP but also to oral steroid therapy. The 'golden period' exists when patients have proteinuria <1.0 g/day.

Preservation of kidney function versus induction of clinical remission

The goal of many clinical studies is the preservation of renal function. However, Hotta et al. emphasized that TSP can induce CR and demonstrated that patients who respond to TSP could maintain their kidney function. Some Japanese nephrologists are shifting from a paradigm of preserving kidney function to inducing CR.

What is the overall natural history of IgA nephropathy?

Chauveau and Droz [4] studied the natural history of IgA nephropathy in 1993. In a series of 119 patients with biopsy-proven IgA nephropathy from 1968 to 1972 at Necker Hospital, 74 patients (44 men and 30 women) received no therapy. Of this subset, 22 patients (29.7%) showed spontaneous remission, defined as no urinary abnormalities and normal kidney function, 24 patients (32.4%) had urinary abnormalities without aggravation of kidney function, and 28 patients (37.8%) progressed to end-stage renal failure during a 20-year observation period (Table 1).

Table 1 A natural history of IgA nephropathy at Necker Hospital

	Chauveau and Droz
Observation period	20 years
Number of patients	74
Spontaneous remission	29.7%
Persistent urinary abnormalities without aggravation of kidney function	32.4%
End-stage renal failure	37.8%

Do patients with mild or early-stage IgA nephropathy recover or progress?

Szeto et al. reported on the natural history of mild or early-stage IgA nephropathy in patients with proteinuria <0.4 g/day over an observation period of 7 years [5]. About 40% of these patients showed a progressive course—33% had proteinuria increased to >1.0 g/day, and 7% had decreased kidney function defined as CCr <70 ml/min/1.73 m^2. Another 42% of patients had persistent proteinuria and hematuria; however, 14% of patients reached CR that the authors defined as the disappearance of hematuria (Table 2).

Shen et al. also analyzed the natural history of IgA nephropathy with isolated microscopic hematuria, defined as no detection of urinary protein by dipstick [6]. They compared patients with no proteinuria (<0.03 g/day) and microalbuminuria (0.03–0.30 g/day): the CR rate (disappearance of hematuria) was 22 versus 6% ($p = 0.005$), the incidence of increased proteinuria was 6 versus 42% ($p < 0.0001$), hypertension was 12 versus 44% ($p = 0.0001$), and impaired kidney function [glomerular filtration rate (GFR) <60 ml/min/1.73 m^2] was 4 versus 29% ($p = 0.0042$), respectively. They demonstrated that microalbuminuria was one of the prognostic factors in IgA nephropathy with isolated microscopic hematuria (Table 2).

Does oral prednisolone therapy improve the outcome of IgA nephropathy?

In 1996, Kobayashi et al. [7] evaluated the efficacy of oral steroid therapy for patients with IgA nephropathy. Their retrospective cohort study tracked the prognosis of 20 patients who received oral steroid therapy and 26 patients who did not receive steroid therapy for 10 years. All patients in both groups had persistent baseline proteinuria ranging between 1.0 and 2.0 g/day. In the steroid therapy group, 40 mg/day of prednisolone was administered for 8 weeks, which was then tapered to 30 mg/day for 8 weeks, 25 mg/day for 8 weeks, 20 mg/day for 8 weeks, and 10–15 mg/day for 80 weeks. The total duration of

Table 2 The natural history of patients with mild or early-stage IgA nephropathy

	Shen et al.			Szeto et al.
Daily proteinuria	<0.03 g	>0.03, <0.3 g	Total (<0.3 g)	<0.4 g
Observation period			92 ± 28 months	84 (14–180) months
Number of patients	50	85	135	72
Disappearance of hematuria	22%	6%	12%	14%
Increased proteinuria (>1.0 g)	6%	42%	29%	33%
Hypertension	12%	44%	32%	19%
Decreased kidney function	4%	29%	20%	7%

Table 3 Oral steroid therapy and intravenous steroid pulse therapy

	Kobayashi et al.	Pozzi et al.
Study design	Retrospective cohort study	Randomized controlled trial
Treatment groups	Oral steroid versus control	Steroid pulse versus control
Daily proteinuria	1.0–2.0 g	1.0–3.5 g
CCr	85 ± 14 versus 88 ± 13	70–111 ml/min (mean 91)
CCr (≥70 ml/min)	Renal survival rate: 100 versus 80% at 5 years (ns)	Non-progression rate: 97 versus 53% at 10 years ($p = 0.0003$)
	80 versus 34% at 10 years ($p < 0.001$)	Urinary complete remission rate: ~10% in the steroid pulse group

CCr creatinine clearance, *ns* not significant

prednisolone therapy was 2 years, after which patients were treated with only the same antiplatelet drugs that the control group received. In the control group, patients had a renal survival rate at 5 and 10 years of 84 and 34%, respectively. On the other hand, in the steroid therapy group, the renal survival rate at 5 and 10 years in patients was 100 and 80%, respectively (compared to control group: $p < 0.001$). They concluded that patients with early-stage IgA nephropathy, with proteinuria between 1.0 and 2.0 g/day and CCr >70 ml/min, had a durable response to oral steroid therapy at 10 years (Table 3).

Does methylprednisolone pulse therapy preserve kidney function?

Pozzi et al. [8] demonstrated the efficacy of steroid pulse therapy for patients with IgA nephropathy with daily proteinuria in the range of 1.0–3.5 g and serum creatinine <1.5 mg/dl. In 86 patients with biopsy-proven IgA nephropathy diagnosed between 1987 and 1995, 43 patients were randomized to steroid pulse therapy and 43 to non-steroid (antiplatelet) therapy. Patients in both groups were balanced with respect to age (38 vs. 40), the presence of hypertension (14/43 vs. 15/43), daily proteinuria (1.6–2.4 vs. 1.4–2.4 g/day), CCr (70–111 vs. 72–112 ml/min), and percentage of glomerular sclerosis (0–25 vs. 5–26%); these patients are similar to the patients in the study by Kobayashi et al. Pozzi et al. defined renal outcome as the primary endpoint, measured as the doubling of baseline serum creatinine, and the reduction of urinary protein as the secondary endpoint, but did not evaluate parameters of renal function such as CCr or GFR or the renal survival rate. The percentage of non-progressive patients at 10 years was 97% in the steroid pulse therapy group and 53% in the control group. Although they did not specifically evaluate CR, approximately 10% of patients receiving steroid pulse therapy reached CR. Pozzi et al. suggested that steroid pulse therapy is efficacious in patients with IgA nephropathy with CCr >70 ml/min (mean 90 ml/min) and proteinuria between 1.0 and 3.5 g/day (Table 3).

Does tonsillectomy stop the progression of renal failure?

Rasche et al. [9] reported that tonsillectomy showed no efficacy in a retrospective cohort study in 1999. Of 55 patients diagnosed with IgA nephropathy from 1968 to 1994, 16 patients received tonsillectomy and 39 patients did not. The patient characteristics were as follows: mean age, 32 (range 23–34) versus 33 (28–34); presence of hypertension, 14/16 versus 16/39; daily proteinuria >1.5 g, 9/16 versus 25/39; mean serum creatinine ± SD, 2.4 ± 2.8 versus 1.6 ± 0.9 mg/dl; serum creatinine >1.7 mg/dl, 4/16 versus 15/39. The CCr was estimated to be <70 ml/min, a level below which Kobayashi et al. found oral steroid therapy not to be efficacious. The renal survival rates of

Table 4 A retrospective cohort study of tonsillectomy

	Rasche et al.	Xie et al.	Chen et al.
Treatment groups	Tonsillectomy versus control	Tonsillectomy versus control	Tonsillectomy versus control
Daily proteinuria	(>1.5 g)	0.91 ± 1.12 versus 1.09 ± 1.43	0.973 ± 0.924 versus 1.17 ± 1.02
	9/16 versus 25/39		(>1.0 g) 19/54 versus 23/58
sCr	2.4 ± 2.8 versus 1.6 ± 0.9	1.07 ± 0.27 versus 1.07 ± 0.31	1.08 ± 0.33 versus 1.07 ± 0.275
CCr (≥70 ml/min)	Not available	Renal survival rate: 98 versus 89% at 10 years (ns)	CR rate: 46.3 versus 27.5% ($p = 0.04$)
		90 versus 63.8% at 20 years (efficacy at 20 years; $p < 0.05$)	Relapse rate: 38.9 versus 48.3% ($p = 0.317$)
			Not improved rate: 16.7 versus 34.5% ($p = 0.031$)
			ESRD at less than 15 years: 3.7 versus 12.1% ($p = 0.059$)
CCr (<70 ml/min)	Renal survival rate: 40% and 60% at 10 years (ns)	Not available	Not available

sCr serum creatinine, *CCr* creatinine clearance, *CR* clinical remission, *ESRD* end-stage renal disease, *ns* not significant

both groups at 5 years were between 60% and 70% and at 10 years were between 40% and 60%, with no significant differences between both groups. They concluded that tonsillectomy did not prevent a progressive course in patients with IgA nephropathy (Table 4).

On the other hand, Xie et al. [10] demonstrated the efficacy of tonsillectomy with an observation period of 20 years. They analyzed the data from a retrospective cohort study that included 48 patients who received tonsillectomy and 70 patients who did not receive tonsillectomy. The mean age ± SD was 30 ± 11 versus 34 ± 12 years, daily proteinuria 0.91 ± 1.12 versus 1.09 ± 1.43 g, and serum creatinine was 1.07 ± 0.27 versus 1.07 ± 0.31 mg/dl. These patients correspond to an earlier or milder stage than those in the study by Rasche et al. The renal survival rates of the tonsillectomy and non-tonsillectomy groups at 10 years were 98% and 89%, respectively, with no statistically significant difference; however, the renal survival rates at 20 years were 90% and 63.8%, respectively ($p < 0.05$). They summarized that tonsillectomy improved renal survival in IgA nephropathy patients 20 years later (Table 4).

In 2007, Chen et al. [11] investigated the efficacy of tonsillectomy in terms of long-term CR and renal survival in Chinese patients with IgA nephropathy. They performed a 130-month retrospective case−control study of 112 patients with idiopathic biopsy-proven IgA nephropathy from 1983 to 1999. There were 54 patients who underwent tonsillectomy and 58 patients who did not. The CR rate was 46.3% in patients with tonsillectomy and 27.6% in those without tonsillectomy during the follow-up period that lasted a mean ± SD of 130 ± 50.3 months (range 60–276 months). The Kaplan–Meier analysis showed no significant difference in renal survival rates between patients with and without tonsillectomy ($p = 0.059$). Since the p value was 0.059 with an observation period of 15 years, differences in the renal survival rate with versus without tonsillectomy may become significant if the observation period were extended to over 20 years (Table 4).

Does TSP induce CR?

In 2001, Hotta et al. [2] proposed TSP as a new approach that can induce CR in IgA nephropathy. They analyzed 329 patients with IgA nephropathy from 1977 to 1995. The patient profile was as follows: age (mean ± SD), 36.1 ± 12.8 years; daily proteinuria, 1.40 ± 1.09 g; serum creatinine, 1.14 ± 0.48 mg/dl. There was a correlation between serum creatinine levels and urinary remission rates. In patients with serum creatinine <0.8 mg/dl, the urinary complete remission rate was 55% in men and 65% in women. In patients with serum creatinine between 0.9 and 1.0 mg/dl, it was 55% in both men and women, and in patients with serum creatinine between 1.1 and 1.3 mg/dl, it was 50% in men and 30% in women. Male and female patients with serum creatinine >1.4 mg/dl had a urinary complete remission rate of approximately 20%. These results suggest that patients with serum creatinine >1.4 mg/dl are resistant to several types of therapy, including steroid therapy and TSP. In a Cox regression analysis with 13 variables, serum creatinine <1.3 mg/dl, daily proteinuria between 0.5 and 1.5 g, histological score (the index of glomerular lesion, calculated by the degree of mesangial proliferation and sclerosis) <2.00, steroid pulse therapy, and tonsillectomy were identified as prognostic factors for urinary complete remission. A comparison of the CR rate with TSP and steroid therapy found TSP to be superior (59.7 vs. 35.3%; $p < 0.01$) [8] (Table 5).

Table 5 A retrospective cohort study of tonsillectomy plus steroid pulse (TSP) therapy

	Hotta et al.	Miura et al.
Study design	Retrospective cohort study	Multicenter retrospective study
Patients' background	Daily proteinuria: mean ± SD: 1.38 ± 1.17 g sCr: 0.96 ± 0.22 mg/dl	
CCr (>70 ml/min)	TSP versus steroid: CR rate: 59.7 versus 35.3%; $p < 0.01$	CR rate: 54.1% CR versus non-CR: Years from diagnosis until TSP therapy: mean ± SD 5.3 ± 5.2 versus 6.9 ± 6.8 ($p = 0.02$) Daily proteinuria 0.8 ± 0.8 versus 1.5 ± 1.6 ($p < 0.0001$) sCr 0.87 ± 0.34 versus 0.99 ± 0.40 ($p = 0.006$)
CCr (<70 ml/min)	Sato et al. Retrospective cohort study TSP versus steroid versus control Daily proteinuria: mean ± SD: 2.2 ± 1.9 versus 1.9 ± 0.9 versus 0.9 ± 0.6 CCr: 45.0 ± 15.1 versus 44.4 ± 14.9 versus 48.6 ± 19.7 Renal survival rate at 8 years: 82.8 versus 51.0 versus 45.1%: $p = 0.017$ (No significant difference in patients with sCr >2.0 mg/dl)	Not available

sCr serum creatinine, *CCr* creatinine clearance, *CR* clinical remission

Table 6 Prospective controlled trials

	Komatsu et al.	Miyazaki et al.
Study design	Prospective controlled trial	Randomized controlled trial
Treatment groups	TSP versus steroid pulse	TSP (40 patients) versus steroid pulse (40 patients)
Daily proteinuria (mean ± SD)	1.06 ± 1.01 versus 1.41 ± 1.05	Between 1.0 and 3.5 g
sCr	0.72 ± 0.29 versus 0.84 ± 0.30	sCr <1.5 mg/dl
CCr (>70 ml/min)	CR rate: 21/34 (61.8%) versus 3/17 (17.6%) ($p < 0.001$)	Forthcoming

TSP tonsillectomy plus steroid pulse, *RCT* randomized controlled trial, *sCr* serum creatinine, *CCr* creatinine clearance, *CR* clinical remission

In 2002, Sato et al. [12] evaluated the efficacy and limitations of TSP in patients with advanced IgA nephropathy. TSP is superior to steroid therapy or anti-platelet therapy in terms of 8-year renal survival rates (82.8 vs. 51.0 vs. 45.1%, respectively); however, there was no significant difference among patients whose baseline serum creatinine was >2.0 mg/dl. They recommended initiating TSP before serum creatinine reaches 2.0 mg/dl (Table 5).

In 2010, Kawaguchi et al. [13] retrospectively analyzed 388 patients diagnosed with IgA nephropathy by renal biopsy between 1987 and 2000 who presented with hematuria and minimal proteinuria (<0.5 g/day) at baseline. Patients treated with TSP had a significantly higher rate of CR than patients who were not treated with tonsillectomy or pulsed steroids in both an unadjusted Cox model [hazard ratio (HR) 5.51; 95% confidence interval (CI) 3.33–9.12; $p < 0.001$] and one adjusted for age, sex, estimated GFR, index of glomerular lesion, systolic blood pressure, immunoglobulin A, 24-h urinary protein excretion, urinary red blood cells, comorbidities, and medication (HR 4.65; 95% CI 2.43–8.88; $p < 0.001$). TSP significantly increased the probability of CR in IgA nephropathy patients with minimal proteinuria (Table 5).

Do all patients with IgA nephropathy respond to TSP?

Miura et al. [3] evaluated the efficacy of TSP in a multicenter retrospective cohort study. After collecting data from many hospitals in Japan, they first identified groups with higher and lower CR rates and compared patient characteristics between the two groups. There was a

significant difference in age at onset ($p = 0.05$), daily proteinuria ($p = 0.02$), total protein ($p = 0.02$), and pathological grade ($p = 0.009$) between the higher CR rate group and the lower CR rate group. In the 303 patients included in their study, 164 (54.1%) patients reached CR 1 year after TSP. The comparison between patients who reached CR and those who did not achieve CR revealed significant differences in the number of years from diagnosis until TSP ($p = 0.02$), daily proteinuria ($p < 0.0001$), serum creatinine ($p = 0.006$), and pathological grade ($p = 0.0006$). Miura et al. showed that TSP was effective for patients with early-stage disease if performed within 5 years at onset, with daily proteinuria <1.1 g and serum creatinine <1.5 mg/dl (Table 5).

Do prospective controlled studies confirm the efficacy of TSP?

Komatsu et al. [14] reported the results of a prospective trial of TSP in 2008. They compared the data on patients treated with TSP ($n = 35$) and patients who received only steroid pulse therapy ($n = 20$). The mean daily proteinuria ± SD was 1.06 ± 1.01 versus 1.41 ± 1.05 g, and mean serum creatinine ± SD was 0.72 ± 0.29 versus 0.84 ± 0.30 mg/dl, respectively. The CR rate at 24 months was 61.8 versus 17.6% ($p < 0.001$). The authors concluded that TSP can induce CR in patients with IgA nephropathy with daily proteinuria of approximately 1.0 g and serum creatinine <1.1 mg/dl. However, their study was limited since it was not randomized, and the patients' baseline data differed slightly between the two treatment groups (Table 6).

Miyazaki et al. [15] performed a randomized controlled trial (RCT) of TSP in Japan, with the following inclusion criteria: daily proteinuria between 1.0 and 3.5 g, serum creatinine <1.5 mg/dl, and chronic tonsillitis. Although detailed data will be available in the near future, preliminary data from this trial suggest that TSP is a promising treatment for inducing CR of IgA nephropathy, and might become first-line treatment for IgA nephropathy (Table 6).

Perspectives on the treatment of IgA nephropathy

After the details of the RCT on TSP are released, several clinical questions will emerge. Which patients with IgA nephropathy are ideal candidates for TSP? At what level of daily urinary protein is a kidney biopsy indicated? Does early intervention really improve prognosis? Can IgA nephropathy recur after TSP? We have to answer these questions.

In order to obtain clinical evidence within a short 5-year period, we propose a clinical trial enrolling patients with daily proteinuria <1.0 g and GFR or CCr >90 ml/min whose primary endpoints are the CR rate and the proportion of patients whose GFR or CCr decrease to ≤70 ml/min (rate of decline in renal function). Patients should be divided randomly into three groups: antiplatelet drugs, steroid pulse therapy according to the protocol in Pozzi et al., and TSP according to the protocol of Hotta et al. This trial should be open to international investigators. This proposed RCT is essential for studying TSP for early stages of IgA nephropathy. Alternatively, prospective cohort studies are needed to evaluate the renal survival rate after 20 years. Finally, as the recurrence of IgA nephropathy after renal transplantation is a significant issue, RCTs involving TSP before transplantation will provide information on recurrence of IgA nephropathy. The results of the current RCT in Japan will propel us into a new era of treatment for IgA nephropathy.

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Conflict of interest None declared.

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