Tonsillectomy and Steroid Pulse Therapy for IgA Nephropathy

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IgA nephropathy (IgAN) is the common cause of primary glomerulonephritis worldwide. The clinical course of IgAN is extremely variable and ranges from asymptomatic microscopic hematuria to rapidly progressive renal failure. The pathogenetic mechanisms of IgAN are still unclear, but a hypothesis consisting of two pathways has been proposed. The first pathway is continuous antigenic stimulation of the innate immune system by the tonsillar mucosa via the mucosa-bone marrow axis. In the second pathway, the anomalous stimulated immune response in the bone marrow results in the production of aberrantly glycosylated IgA1 and its subsequent deposition within the mesangial area. Based on the hypothesis, tonsillectomy plus steroid pulse therapy were introduced. A recent meta-analysis showed that tonsillectomy with or without steroid pulse therapy resulted in clinical remission with favorable long-term efficacy in IgAN patients. Tonsillectomy plus steroid pulse therapy now seems to be an effective treatment for IgAN patients with hematuria and minimal proteinuria, and it is more effective in patients with less severe histological findings. The efficacy of the combination therapy depends on the duration of the IgAN. Randomized, controlled trials are needed to examine the efficacy of tonsillectomy plus steroid pulse therapy in different clinical stages of IgAN.

Keywords: IgA nephropathy; prognosis; remission; steroid pulse therapy; tonsillectomy


Clinical presentation and natural history of IgAN

Asymptomatic urinary abnormalities, including microscopic hematuria with or without proteinuria, are common presenting findings, and with increasing age they are more likely to be accompanied by renal impairment and hypertension (Koyama et al. 1997). The most common presentation of microscopic hematuria following an upper respiratory tract infection is most common in the second and third decades of life and is rarely seen after the age of 40 years of age. Nephrotic syndrome occurs in around 5% of cases. Spontaneous remission of the urinary abnormalities occurs in less than 10% of all patients. More frequently, IgAN is associated with slowly progressive impairment of renal function, and 25% to 30% of IgAN patients have been found to develop ESRD within 20-25 years of presentation (D’Amico 2004). Local variations in the perceived risk of ESRD in IgAN are primarily attributable to the different diagnostic approaches adopted internationally. In countries with active urinary screening programs, renal biopsy of IgAN patients with mild urinary abnormalities may lead to the diagnosis of mild disease with a good prognosis and favorably affecting the overall outcome of the cohort. Recurrence of IgAN after renal transplantation has assumed increasing importance because of preventing graft

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failure from acute rejection. The diagnosis and management of recurrence have recently been reviewed in detail (Floege 2004). Glomerular crescent formation is associated with a poor outcome (Kowalewska et al. 2005). Our previous study showed that latent IgA deposition derived from donor kidney was a risk factor for recurrence and progression of renal dysfunction (Moriyama et al. 2005), the presence of segmental sclerosis in hypertrophied glomeruli has been found to be related to proteinuria and hematuria in post-transplant IgAN. Postoperative treatment with immunosuppressive agents is expected to suppress the progression of recurrent IgAN after renal transplantation (Ponticelli et al. 2001). However, because the waiting period for renal transplantation has continued to increase, it has been essential to promote the maintenance of graft function for as long as possible.

**Tonsils of IgAN patients**

The tonsils are located at the gateway of the respiratory and alimentary tract and are mucosa-associated lymphoid tissues. The generation of B cells in the germinal centers of the tonsils is one of their most essential functions. Secretory dimeric IgA produced by B cells has particular hydrophilic properties and is capable of preventing adsorption and penetration of bacteria and/or viruses into the upper respiratory tract mucosa (Bernstein 1992). Antigen uptake by microfold cells present in the crypt-epithelium initiates a process that ultimately results in the generation and dissemination of antigen-specific memory cells including dimeric IgA-producing effector B cells. This process requires successful cognate interactions between antigen-presenting cells and lymphocytes that depend not only on antigen-specific signals but on the expression of various complementary adhesion and costimulatory molecules as well (van Kempen et al. 2000).

There are significant differences between the histological structure and cell adhesion molecules in the tonsils of healthy subjects and IgAN. Enlarged primary T nodules are a characteristic feature of the tonsils of IgAN patients. A few T nodules in IgAN contain high endothelial venules and non-lymphoid cells. By contrast, the T nodules of patients with habitual tonsillitis do not expand, and non-lymphoid cells and many endothelial venules are distributed peripherally around the nodules (Kawaguchi et al. 1993). The basic structure and functional unit of reactive lymphoid tissues is composed of two separate T nodules and B-lymphoid follicles. These composite nodules play a major role in the triggering for helper T-cell–dependent stimulation and subsequent maturation of antigen-responsive B cells into antibody-secreting plasma cells. With regard to this relationship between T-cell and B-cell domains, the enlarged primary T nodules remind us that extra-follicular maturation of stimulated B lymphocytes into plasma cells may occur more frequently in the tonsils of IgAN patients than of habitual tonsillitis patients. The tonsils of control patients with recurrent tonsillitis or tonsillar hypertrophy showed well-developed reticular crypt epithelium with lymphoepithelial symbiosis, and the non-reticulated area accounted for less than 7% of the total crypt epithelium. However, non-reticulated crypt epithelium is frequently observed in the tonsils of IgAN patients, and it exceeds 50% of the total crypt epithelium in the advanced stage of IgAN (Sato et al. 1996).

**Effect of tonsillectomy for IgAN**

Table 1 summarizes the effects of tonsillectomy for IgAN. Bene et al. (1993) reported that the urinary protein level and microhematuria of 34 IgAN patients decreased significantly 6 months after tonsillectomy and that there were no significant changes in their serum creatinine (Cr) levels. Tamura et al. (1993) found that 46% of IgAN patients with chronic tonsillitis showed a distinct improvement in their urinary findings after tonsillectomy. Akagi et al. (1999) reported that remission of proteinuria in 50.0% of a group of patients 2 years after tonsillectomy. Hotta et al. (2002) performed a repeat biopsy, and found that the clinical remission rate of the urinary findings and the stable renal function in 35 patients with IgAN after tonsillectomy. The intervals between the first and second biopsy ranged from 18 to 138 months. Mesangial proliferation and interstitial mononuclear cell infiltration were significantly reduced in the second biopsy specimens. Acute inflamma-

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<th>Author (year)</th>
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<tr>
<td>Bene et al. (1993)</td>
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<td>48</td>
<td>NM</td>
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<td>Tamura et al. (1993)</td>
<td>NCT</td>
<td>24</td>
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<td>Akagi et al. (1999)</td>
<td>NCT</td>
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<td>50%*</td>
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<td>Rasche et al. (1999)</td>
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<td>55</td>
<td>NM</td>
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<td>Akagi et al. (2003)</td>
<td>CT</td>
<td>71</td>
<td>24.4%</td>
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<td>Xie et al. (2003)</td>
<td>NRCT</td>
<td>193</td>
<td>NM</td>
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<td>Chen et al. (2007)</td>
<td>CT</td>
<td>112</td>
<td>46.3%</td>
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Abbreviations: CT, controlled trial; NCT, non-controlled trial; NRCT, non-randomized, controlled trial; NM, not mentioned. *Remission of proteinuria (hematuria is not mentioned)
tory glomerular lesions, such as endocapillary proliferations, glomerular tuft necrosis, and cellular crescents, were present in the first biopsy specimens of 32 patients, but were not detected in any of the second biopsy specimens. Akagi et al. (2004) investigated the long-term results of tonsillectomy as a treatment for IgAN and reported that clinical remission rate was 24.4% in tonsillectomy group and 13.3% in non-tonsillectomy group.

Rasche et al. (1999) reported that there was no significant correlation between tonsillectomy and ESRD in 16 IgAN patients who underwent tonsillectomy and 39 patients who did not undergo tonsillectomy, and they concluded that tonsillectomy did not reduce the risk of renal failure during a mean follow-up period of 3.4 years. Chen et al. (2007) reported that there was no significant difference in survival rate between 54 IgAN patients who underwent tonsillectomy and 58 IgAN patients who did not undergo tonsillectomy during a mean observation period of 130 months, although the proportion of cases that achieved a clinical remission was significantly higher in the tonsillectomy group. However, tonsillectomy was not an independent factor related to clinical remission according to the results of a Cox regression analysis. In a recent retrospective study, Piccoli et al. (2010) have reported that tonsillectomy was not associated with a different progression rate of IgAN after 20 years of follow-up.

Xie et al. (2003) followed up 118 IgAN patients, consisting of 48 tonsillectomy patients and 70 non-tonsillectomy patients, for 192.9 ± 74.8 months. After a mean period of 15 years after the diagnostic biopsy, only five (10.4%) of the 48 tonsillectomy patients were on dialysis, whereas 18 (25.7%) of the 70 non-tonsillectomy patients required dialysis. A Kaplan-Meier analysis showed that the renal survival rate of the tonsillectomy group was significantly higher than in the non-tonsillectomy group, and a Cox regression analysis showed that the relative risk of terminal renal failure in the tonsillectomy group was lower than in the non-tonsillectomy group. Kennoki et al. (2009) reported that in patients receiving oral immunosuppressive therapy for recurrence of IgAN after kidney transplantation, reducing of urinary protein excretion can be expected with tonsillectomy alone, without accompanying pulse steroid therapy.

Wang et al. (2010) recently published a meta-analysis of the clinical remission rates and long-term efficacy of tonsillectomy in IgAN patients. Seven retrospective studies with a total of 858 IgAN patients, in which 534 underwent tonsillectomy and 324 did not, were included. The total clinical remission rate was higher in the tonsillectomy group, while the ESRD rate was higher in non-tonsillectomy group. The clinical remission rate in patients who underwent tonsillectomy remained higher than in the non-tonsillectomy group at both 5- and 10-year follow-up. The clinical remission rate in patients who underwent tonsillectomy plus steroid pulse was higher than in those treated with steroid pulse alone, normal-dose steroids or general treatment alone. However, the clinical remission rate of simple tonsillectomy was not higher than that of general treatment. The Funnel plot suggested publication bias. They concluded that whereas neither tonsillectomy nor steroid treatment alone increased the remission rate of the IgAN patients, tonsillectomy combined with either conventional steroid therapy or steroid pulse therapy resulted in higher remission rates and more favorable long-term efficacy (Fig. 2).

Taken together, tonsillectomy is effective in achieving a clinical remission, but is ineffective in preventing the decline of renal function. The reason for these apparently conflicting conclusions may be attributable to differences in the stage of nephropathy of selected patient populations and

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**Fig. 1.** Possible pathogenesis of IgA nephropathy and treatment strategies.
the shortness of the observation period. According to the report by Coppo (2010), tonsillectomy was unlikely to affect IgA-mediated diseases, since the tonsils are such a small fraction of the gut-associated mucosal tissue. Because of the well-developed system of annual health examinations in Japan, IgAN is likely to be diagnosed in a relatively early stage. Indeed, the patient populations in the studies that reported positive results included patients with early-stage IgAN. When the study population includes early-stage patients, positive results regarding the outcome of renal function are difficult to obtain, especially when the follow-up period is relatively short. So far as I know no International Practice Guidelines currently recommend or suggest tonsillectomy for treatment of IgAN.

### Oral steroid and steroid pulse therapy for IgAN

Table 2 summarizes the effects of oral steroid and steroid pulse therapy for IgAN.

#### 1) Oral steroid therapy

Steroid therapy administered on a daily or alternate-day basis has had variable success in IgAN patients. Kobayashi et al. (1988) reported a retrospective study of 29 patients with proteinuria over 2 g/day who were given prednisolone (PSL) daily for 12 to 36 months, stabilized the kidney function of a subgroup with preserved initial Cr clearance of over 70 mL/min. Kobayashi et al. (1996) also published a non-randomized, controlled study in which they compared a subgroup of the 1988 study with an untreated group in that study. PSL therapy daily for 18 months had a
protective effect on renal function and resulted in a reduction in proteinuria after 10 years of therapy. A retrospective cohort analysis in our previous study indicated that oral PSL therapy at a dose of 0.8 mg/kg daily decreased proteinuria and prevented progression to ESRD in IgAN patients with advanced stage and deteriorated renal function (Moriyama et al. 2004).

In a randomized, controlled trial (RCT), Shoji et al. (2000) compared two treatment groups that consisted of a steroid group and an anti-platelet group. Early-stage diffuse proliferative IgAN in adults underwent a 1-year treatment of PSL (0.8 mg/kg/day at initial dosage and gradually tapered to 10 mg every other day over 1 year). They concluded that early steroid therapy was effective in reducing renal injury, and their conclusion was confirmed by a repeat biopsy 1 year later. Proteinuria decreased and expression of α-smooth muscle actin in glomeruli was suppressed in the PSL group, and the histological findings, including mesangial cell proliferation, mesangial matrix accumulation, and cellular crescents, had improved.

On the other hand, Lai et al. (1986) reported a prospective, randomized trial that failed to show a benefit of PSL (1 mg/kg/day for 2 months followed by a tapered dosage for another 2 months). During the mean study period of 38 months, no significant difference in renal function was demonstrated between 17 steroid-treated patients and 17 control patients. Steroid treatment resulted in a high rate of remission of nephrotic syndrome among patients with mild glomerular histopathological changes, but many experienced side effects.

A controlled study of alternate-day PSL (60 mg/m²) for 2 to 4 years in a controlled study by Waldo et al. (1993) showed disappearance of proteinuria, preservation of renal function, and a decrease in activity score in repeated renal biopsies. In a Japanese RCT, Katafuchi et al. (2003) reported the limitation of the low-dose PSL therapy, with an initial dose of 20 mg daily, to prevent the progression of IgAN. We have reported finding that low-dose PSL was effective in decreasing proteinuria during 2-year treatment period (Koike et al. 2008). Six trials (341 patients) were considered to have been of sufficient quality to be included in a meta-analysis of immunosuppressive therapy for IgAN (Samuels et al. 2004). Cheng et al. (2009) reported a meta-analysis of RCTs that had been performed to evaluate steroid therapy and concluded that steroid therapy has statistically significant effects on protecting renal function and reducing proteinuria. The results of these analyses suggest that steroid therapy is effective in ameliorating proteinuria and reducing the risk of ESRD.

2) Steroid pulse therapy

Several factors, including the dose and route of administration, affect the efficacy of steroid therapy. The response to conventional steroid therapy is mainly regulated by genomic mechanisms, beginning with binding to the intracellular glucocorticoid receptor (GCR), which is related to immune cell function and production of inflammatory mediators (Baldwin 1996). In addition to the genomic action, steroid pulse therapy induces non-genomic actions, via membrane-bound receptors or physicochemical interaction with cellular membranes (Buttgereit et al. 1998).

Moreover, prolonged clinical steroid therapy results in down-regulation of intracellular GCRs, which causes steroids to be effective. The GCR down-regulation may be one factor in explaining why early aggressive treatment is more effective than gradual steroid dose escalation, which results in greater toxicity and less beneficial effects. Thus, greater efficacy can be expected with steroid pulse therapy.

A multicenter RCT in Italy yielded compelling evidence for treatment with steroids, including steroid pulse therapy, for 6 months. After 1 year of treatment, in 72% of the cases, proteinuria had decreased to < 1 g/day, although 30% in control group. The 10-year survival rate until doubling of the serum Cr from baseline was significantly higher than in the control group (97% vs. 53%, log-rank test; p = 0.0003). Steroid pulse therapy improved the outcome of IgAN even in the cases with severe histological damage.

Taken together, there is strong evidence that steroid pulse therapy decreases proteinuria and improves the renal outcome.

3) Tonsillectomy plus steroid pulse therapy (Fig. 2)

The pathogenetic mechanisms of IgAN are still unclear, but a hypothesis consisting of two main pathways such as upstream and downstream, has been proposed by Hotta (2004). As shown in Fig. 1, the upstream pathway is continuous antigenic stimulation of the innate immune system by the tonsillar mucosa via the mucosa–bone marrow axis. In the downstream pathway, the anomalous stimulated immune response in the bone marrow results in the production of aberrantly glycosylated IgA1, and its subsequent deposition within the mesangial area. From this hypothesis, tonsillectomy may affect the upstream pathway of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa. Also, steroid pulse therapy may influence the downstream pathway of the immunological mechanism by suppressing the abnormal immune response in the bone marrow that leads to subsequent inflammation in renal glomeruli.

Hotta et al. (2001) examined the results of a variety of treatment interventions on long-term outcome of 329 patients. They found that 48% of the patients, all of the abnormal urinary findings resolved in, and that none of these patients developed renal failure. By contrast, the patients who did not experience a clinical remission had a 21% change of a 50% rise in serum Cr levels at 10 years. Positive predictors for remission were a lower serum Cr level at entry, lower histological score, and tonsillectomy plus steroid pulse therapy, but conventional steroid, angiotensin-converting enzyme inhibitor, and cyclophosphamide were not. Resolution of the hematuria was achieved in
more than 80% of the IgAN patients regardless of their histological score at entry. On the other hand, the rate of resolution of the proteinuria decreased as the histological score rose. The clinical remission rate of the patients with a serum Cr value under 1.4 mg/dl was significantly higher in the group that that underwent tonsillectomy plus steroid therapy (steroid pulse therapy, 153 patients; conventional steroid therapy, 22 patients) (59.7% vs. 35.3%, \( p < 0.01 \)). However, the investigators did not report the details regarding the clinical remission rate or outcome in the cases treated by tonsillectomy plus steroid pulse therapy.

Miyazaki et al. (2007) conducted a multicenter prospective cohort study of combined treatment by tonsillectomy and steroid pulse therapy, in which 101 patients were followed up for 5 years. The subjects were classified according to their daily proteinuria (UP) and serum Cr levels. Both tonsillectomy and high-dose steroid therapy were performed in 75 patients. The clinical remission rate treated in the combination therapy group was 86.2% in stage 1 (UP < 0.5 g/day), 73.1% in stage 2 (UP = 0.5-1.0 g/day), and 43.8% in stage 3 (1.0 g/day < UP and Cr >1.2 mg/dL in female or > 1.4 mg/dl in male), as opposed to 71.4% in stage 2, and 11.1% in stage 3 in the steroid monotherapy group.

Komatsu et al. (2008) performed a prospective, controlled study to compare the effects of combination therapy and steroid pulse alone in IgAN patients. Fifty-five patients were followed up for 54 months, i.e., 35 who had undergone tonsillectomy and steroid pulse therapy and 20 who had received steroid pulse monotherapy. None of the patients in the combination therapy group experienced a 100% increase in serum Cr from the baseline level. The Cox regression model analysis showed that the combination therapy was approximately six fold more effective than steroid pulse monotherapy in causing resolution of UP. Their findings were confirmed by Miura et al. (2009) in a nationwide survey of IgAN patients who had been treated by tonsillectomy plus steroid pulse therapy in Japan. However, the clinical remission rate of urinary abnormalities varied from less than 10% to more than 90% among the institutions according to differences in the clinical and histological background of the patient populations.

Clinical remission is difficult to achieve in IgAN patients with impaired renal function. However, tonsillectomy plus steroid pulse therapy may have a beneficial effect on the renal survival rate, even in patients with impaired renal function (serum Cr \( \geq 1.5 \) mg/dL) under a serum Cr level of 2.0 mg/dL (Sato et al. 2003). On the other hand, they failed to demonstrate statistically significant benefit in patients with more advanced IgAN (serum Cr > 2.0 mg/dL).

Kawaguchi et al. (2010) studied the effectiveness of combination therapy consisting of tonsillectomy plus steroid pulse therapy in IgAN patients with minor urinary abnormalities. Data from 388 IgAN cases were analyzed, and during a median follow-up of 24 months 170 clinical remissions were observed. The patients who received combination therapy were younger and had a significantly higher clinical remission rate than the patients who had not undergone tonsillectomy or received steroid pulse therapy. Less severe histological findings were associated with a much higher clinical remission rate in the combination therapy group. These results indicate that a higher clinical remission rate in response to tonsillectomy plus steroid pulse therapy can be expected in IgAN patients with hematuria and minimal proteinuria.

**Conclusion**

Oral steroid therapy is effective in stabilizing renal function and decreasing proteinuria, at least during a relatively short treatment period, but the long-term effects of these treatments is still open to question. Steroid pulse therapy has been demonstrated to decrease proteinuria and to prevent progression to ESRD by very strong evidence. On the other hand, tonsillectomy plus steroid pulse therapy has the potential ability to provide a renoprotective effect that is superior to steroid pulse therapy, because it can suppress both the upstream pathway and the downstream pathway of pathogenetic mechanism of IgAN. The higher rate of clinical remission in response to tonsillectomy plus steroid pulse therapy than to steroid pulse therapy alone supports the pathogenesis. Once the urinary abnormalities have been resolved and normal values have been maintained long-term, a subsequent decline in renal function is highly unlikely, even in patients with impaired renal function. However, no RCTs have compared the long-term efficacy of tonsillectomy plus steroid pulse therapy and steroid pulse monotherapy.

RCTs are the most reliable study design in evidence-based medicine and are needed to explore the efficacy of tonsillectomy plus steroid pulse therapy in different clinical stages of IgAN. Since IgAN is a syndrome which has a lot of phenotypes, not only in clinical, but also in pathologic, it should be careful to choose the same way of treatment for all of patients with IgAN. It is necessary to have an indication of specific therapy for one of IgAN subgroups.

**Conflict of Interest**

The authors report no conflict of interest.

**References**


