Use of Corticosteroids, Other Immunosuppressive Therapies, and Tonsillectomy in the Treatment of IgA Nephropathy

By Osamu Hotta

Because IgA nephropathy (IgAN) was originally regarded as a benign condition, the indication of corticosteroids or other immunosuppressive therapies have been highly restricted because of potential side effects, and such drugs have been used for a specific subgroup of patients with IgAN, taking the risk/benefit ratio into consideration. During the last decade, however, with the recognition that the overall long-term prognosis of IgAN is a nonbenign condition, more aggressive treatments, including high-dose corticosteroids, various immunosuppressive agents, and tonsillectomy, have been used for wider subgroups of patients with IgAN. Moreover, recent studies have suggested that clinical remission as well as histopathologic regression of the nephropathy could be obtained by such treatments if treatment is initiated in its relatively early stage. Thus, the possibility has now been raised that the goal of treatment for patients with IgAN will shift from “slowing the progression of nephropathy” to “remission of nephropathy.”

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IgA NEPHROPATHY (IgAN) is the most common primary glomerulonephritis worldwide. IgAN was originally equated with benign recurrent hematuria. However, subsequent accumulated evidence over 30 years have clarified that the overall long-term outcome of IgAN is nonbenign. The incidence of end-stage renal disease (ESRD) has been shown to increase with the length of follow up; 10% to 20% of cases after 10 years, 30% to 40% after 20 years,4,5 and a presumably higher rate (>50%) of ESRD is expected after a follow up of over 30 years.6

During the last 2 decades, a body of evidence, mostly from anecdotal reports but some from prospective, randomized, controlled trials (RCT), has revealed the efficacy as well as the limitation of corticosteroids and immunosuppressive agents for the treatment of IgAN.7-10

Therapy for IgAN has been aimed at ameliorating the progression to ESRD so that methods preventing the progressive fall of renal function have been the main issue. In this setting, candidates for therapy were restricted to only a subset of the universe of patients with IgAN, namely those having an extremely high likelihood of progression to ESRD during a relatively short follow-up period (less than 10 years).

Once developed, IgAN has a very variable course. Elevated creatinine level at diagnosis and severe proteinuria were found to be powerful independent predictors of poor outcome in a relative short duration; however, it is now recognized that even patients with minimal proteinuria and hematuria can usually end up with a progressive disease in the long run.11 IgAN disproportionately affects younger people compared with other common causes of ESRD. Therefore, it is difficult to give any patient with IgAN the guarantee of a nonprogressive course in the very long-term follow up, e.g., over 30 years. Until recently, remission of nephropathy by treatment intervention has not been addressed. However, it is now clear that a high proportion of patients with IgAN, especially in the relatively early stage, enter clinical remission (disappearance of hematuria and proteinuria) after intensive treatment.12,13

Although the underlying pathogenesis of IgAN remains incompletely understood, one of the characteristic features of the glomerular pathology of IgAN is the coexistence of acute inflammatory lesions (segmental necrosis of glomerular tufts, cellular crescents, and endocapillary proliferation) and postinflammatory scar formation (adhesion of glomerular tufts to Bowman’s capsule and segmental sclerosis). This could be the result of the continuous process of glomerular capillary inflammation.14,15 This pathologic process seemingly consists of a chronic mucosal infection and a subsequent immune response, which causes glomerular inflammation, resulting in postinflammatory scar formation. It is obvious that the point of action of tonsillectomy is the initiation of immune response, whereas the point of action of corticoste-
roids and other immunosuppressive agents is the subsequent immune response, i.e., glomerular inflammation before glomerular sclerosis is established. Thus, the main point of action of tonsillectomy and corticosteroids is at the relatively early stage of glomerulonephritis.

On the other hand, concomitantly with the progress of glomerular sclerosis, there is an increase in the role of nonimmunologic mechanisms such as glomerular hypertension, protein-loading tubulointerstitial injury, and ischemia-induced tissue injury rather than immune-mediated inflammation. The major treatment options for those nonimmunologic mechanisms are not corticosteroids, immunosuppressive agents, or tonsillectomy, but such drugs as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists, fish oil, and a low protein diet.

The purpose of this article is to focus on the current status of tonsillectomy and corticosteroids or other immunosuppressive drugs in relation to specific pathologic conditions in IgAN.

PATHOGENETIC MECHANISM OF IgAN AND TREATMENT STRATEGIES

Upstream of the Mechanism

Mesangial IgA deposits and the dramatic symptom of macrohematuria coinciding with mucosal infection strongly suggest that antigenic stimuli at the mucosal site is the primary event of the pathogenesis of IgAN (Fig 1).

IgAN often recurs in renal allografts, whereas IgA deposits disappear from kidneys that are already affected by IgAN and which have inadvertently been transplanted into patients without IgAN. These observations indicate that persistent or recurrent antigenic stimuli is an essential pathogenic factor, which is responsible for the initiation and perpetuation of the disease. Bacterial, viral, food and autoantigenic factors have all been implicated as the pathogenic antigens, but none is ubiquitous, and the finding of such antigens in the glomerular deposits has not been established. Thus, it is likely the site of the immune response, but not the antigen responsible for it, is important.

Secondary lymphoid organs, including mucosal lymphoid tissues such as tonsils, provide the proper environment for antigen-presenting cells to interact with and activate naive T and B lymphocytes. The poorly developed lymphoepithelial symbiosis of the palatine tonsils was demonstrated in patients with IgAN, which could induce an unusual immunity against microbial antigens.

Patients with IgA nephropathy have been shown to exhibit a deficient primary mucosal immune response to the IgA subclass. Therefore, it is
postulated that because of deficient mucosal immunity, antigens persist for long periods, enable a high level of antibody production, and adequate mucosal immunity is achieved only after long and numerous exposure to recall antigens.

Thus, it seems most likely that the elevated serum IgA concentration in IgAN is the result of a selective increase in bone marrow production of IgA1 in response to repeated or prolonged exposure to antigens at the mucosal surface. Overproduction of IgA1 caused by relentless mucosal stimuli could predispose the patient to abnormal IgA1 glycosylation, which is considered to play a crucial role in mesangial IgA1 deposition.48-50

To modulate the upstream events of IgAN pathogenetic mechanisms, the elimination of antigenic stimuli is expected to be effective.51,52 Among appropriate treatments, however, antibiotics, antiviral agents, and low-antigen diets do not seem very effective because it is highly unlikely that any specific pathogenetic microorganism or antigen exists.52,53 On the other hand, removal of the palatine tonsils has been proved to be effective under certain circumstances12,54,55 together with reducing serum IgA levels and circulating IgA immune complexes,56 although other tonsils (pharyngeal, tubal, and lingual tonsils) still remain in an unremoved condition. Moreover, an improvement of underglycosylation of the IgA1 hinge region was observed after tonsillectomy.57

In addition, a recent study using mutant mice in which secondary lymphoid organs are absent demonstrated that an immunologic ignorance occurs in the absence of secondary lymphoid tissue,58 which is mediated by naive T lymphocytes but not by memory T lymphocytes.59 This phenomenon could be implicated in the effects of tonsillectomy in patients with IgAN in a similar manner to the protective effects of appendectomy against ulcerative colitis.60

Downstream of the Mechanism

Two major glomerular lesions related with the downstream of the pathogenic mechanism are mesangial IgA deposition, a pathologic hallmark of IgAN, and glomerular capillaritis, presumably the lesion responsible for hematuria, a clinical hallmark of IgAN. In contrast to diffuse glomerular IgA deposition, because glomerular capillaritis distributes in a focal and segmental manner, this lesion is likely to be overlooked by needle biopsy examination.51

It is now clear that mesangial IgA deposition is one of the necessary but not the only condition responsible for clinical IgAN. IgA deposits have been observed in the mesangium in individuals without urinary abnormalities. A biopsy of a donor kidney performed at the time of transplantation revealed the presence of widespread IgA deposits in the glomerular mesangial regions, indicating the presence of clinically silent IgAN in an otherwise healthy donor.62 In an autopsy study by Sinniah, 4% of the examined kidneys showed IgA deposits in the glomerular mesangial regions, despite the absence of clinically evident renal disease.63 These observations suggest that those individuals having so-called “silent mesangial IgA deposition” could exist with a higher incidence than we have expected.

A general consensus regarding the etiology of hematuria in patients with IgAN has not yet been achieved.64,65 Episodes of macroscopic hematuria, particularly if the hematuria lasts for more than 3 to 4 days, are frequently associated with glomerular crescent formation66,67 and occasionally acute renal failure. In addition, we have demonstrated that glomerular crescents or glomerular capillaritis were no longer present in the repeat biopsies of any of 35 patients in whom the disappearance of hematuria was obtained after the combination therapy of tonsillectomy and steroid pulse therapy, whereas glomerular crescents were present in 32 of 35 patients in the first biopsies.13 These observations strongly suggest that glomerular capillaritis, resulting in the rupture of glomerular basement membrane, is responsible for hematuria.

Thus, we assume that in addition to mesangial IgA deposition, the so-called “smoldering glomerular capillaritis” is a key condition responsible for clinical IgAN. The percentage of crescentic glomeruli of IgAN is generally low (less than 30% of glomeruli), but the similarity with the necrotizing form of Henoch-Schönlein purpura allows us to suggest the idea that IgAN can be defined as “smoldering glomerular capillaritis with mesangial IgA deposition.”

Moreover, inflammatory lesions (segmental tuft necrosis and crescents) are followed by segmental glomerular scar formation such as segmental glomerular sclerosis and adhesion of glomerular tufts to Bowman’s capsules. Repeated formations and
accumulations of glomerular scar lesions play a crucial role in the progression of IgAN, resulting in the impairment of renal function.\textsuperscript{14,15,68} Corticosteroids and other immunosuppressive agents are possible candidates to modulate inflammation of glomerular capillaritis. A marked decrease in urinary macrophage counts and disappearance of FcR\textsubscript{y}II\textsuperscript{+} macrophages, markers of disease activity of inflammatory glomerular diseases, were observed in response to steroid therapy.\textsuperscript{69,70}

TONSILLECTOMY

Although the efficacy of tonsillectomy in IgAN remains controversial,\textsuperscript{54-56,71-78} the results of previous reports can be summarized with two seemingly conflicting conclusions. First, “tonsillectomy is effective for achieving clinical remission”; but second, “tonsillectomy is ineffective for preventing the decline of renal function” (Table 1). The reason for these apparently conflicting conclusions could be the result of the differences in the stage of nephropathy of selected patient populations and the shortness of the observation period. The studies supporting the first concept were mostly from Japanese groups.\textsuperscript{55,72-75} In Japan, because of a well-developed system of annual health examinations, IgAN is likely to be found in the relatively early stage. Indeed, the patient population of those studies showing positive results included patients with early-stage IgAN. When the study population includes early-stage patients, a positive result regarding the prognosis of renal function is difficult to obtain, especially when the duration of follow up is relatively short.\textsuperscript{11}

On the other hand, Rasche et al.\textsuperscript{76} demonstrated that tonsillectomy did not reduce the risk factor of developing renal failure. In their study, as many as five of 16 patients in the tonsillectomy group and nine of 39 patients in the nontonsillectomy group reached ESRD in a short follow-up period (3.4 ± 4 years). Because the percentage of ESRD is apparently higher than the entire IgAN population, it is assumed that a considerable proportion of patients in their study were at an advanced stage of IgAN at the time of tonsillectomy. It is obvious that it is difficult to obtain remission of urinary abnormalities in patients with advanced IgAN. Because nonimmunologic mechanisms play a major role in the progression of renal disease in the advanced stage of IgAN, a negative result after tonsillectomy is quite conceivable.

Regarding this issue, Xie et al.\textsuperscript{54} recently reported interesting results. They followed 118 patients with IgAN, 48 of whom had undergone tonsillectomy, for 192.9 ± 74.8 months, and obtained positive results regarding the renal survival rate as assessed by Kaplan-Meier analysis. The estimated renal survival rates were 89.9\% and 63.7\% at 240 months in the patients with and without tonsillectomy, respectively, which seems to be in accordance with the renal survival rate of the entire population of patients with IgAN. Thus, it is likely that tonsillectomy has a favorable effect even on long-term survival in patients with IgAN, if performed during the early stage of the disease.

Unfortunately, no RCT on tonsillectomy in patients with IgAN has been conducted so far. In fact, any RCT on surgical operations such as tonsillectomy is hard to perform partly because of ethical

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Follow Up (months, mean)</th>
<th>Remission (%)</th>
<th>Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masuda\textsuperscript{55}</td>
<td>NCT</td>
<td>(36)</td>
<td>56.3%*</td>
<td>NM</td>
</tr>
<tr>
<td>Sugiyama\textsuperscript{72}</td>
<td>NCT</td>
<td>(61)</td>
<td>32.1%</td>
<td>NM</td>
</tr>
<tr>
<td>Iino\textsuperscript{73}</td>
<td>NRCT</td>
<td>(36)</td>
<td>25.8%</td>
<td>No benefit</td>
</tr>
<tr>
<td>Tamura\textsuperscript{74}</td>
<td>NCT</td>
<td>24</td>
<td>7.6%</td>
<td>NM</td>
</tr>
<tr>
<td>Bene\textsuperscript{56}</td>
<td>NCT</td>
<td>48</td>
<td>NM</td>
<td>No benefit</td>
</tr>
<tr>
<td>Akagi\textsuperscript{75}</td>
<td>NCT</td>
<td>24</td>
<td>50%*</td>
<td>NM</td>
</tr>
<tr>
<td>Rasche\textsuperscript{76}</td>
<td>NRCT</td>
<td>(41)</td>
<td>NM</td>
<td>No benefit</td>
</tr>
<tr>
<td>Xie\textsuperscript{54}</td>
<td>NRCT</td>
<td>(193)</td>
<td>NM</td>
<td>Benefit</td>
</tr>
</tbody>
</table>

Abbreviations: NCT, noncontrolled trial; NRCT, nonrandomized, controlled trial; NM, not mentioned.\n\n* Remission of proteinuria (hematuria is not mentioned).
reasons. Likewise, to our knowledge, the efficacy of tonsillectomy has also not been tested by RCT in patients with pustulosis palmaris et plantaris, in which tonsillectomy has been more extensively performed to improve skin lesions.77,78

Indication for tonsillectomy in patients with IgAN is another conflicting issue. Because there has been no compelling proof of efficacy in improving renal survival, tonsillectomy generally has been strictly limited to minor populations of patients with IgAN who have recurrent tonsillitis along with macrohematuria.8 On the other hand, in some nephrology institutes, mainly in Japan, tonsillectomy is extensively performed as a treatment of IgAN on a routine basis.

The tonsillar provocation test does not seem very useful to predict the efficacy of tonsillectomy. Akagi et al.75 performed tonsillectomy in 24 patients with IgAN on a routine basis after the tonsillar provocation test, and 50% of the patients obtained remission of their proteinuria 2 years after tonsillectomy. There was, however, no statistically significant difference between positive and negative patients as far as the rate of remission of proteinuria based on any parameter of the tonsillar provocation test at any time after surgery.

We have also performed tonsillectomy on a routine basis since 1988. A transient worsening of hematuria was observed in approximately 70% of patients with IgAN after tonsillectomy,79 which could be caused by the overexposure to antigenic stimuli during surgery, resulting in a transient exacerbation of glomerular capillaritis. This phenomenon was observed irrespective of the gross appearance of tonsils, or episodes of habitual tonsillitis or synpharyngitic gross hematuria. Moreover, histopathologically chronic inflammation has been always present in the removed tonsils, even when they were asymptomatic and had an apparently normal gross appearance before the operation.

Table 2. Effects of Corticosteroids With or Without Cytotoxics in IgA Nephropathy

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Treatment</th>
<th>Follow Up (month, mean)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional steroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai83</td>
<td>RCT</td>
<td>Daily, 4 months</td>
<td>(38)</td>
<td>No benefit</td>
</tr>
<tr>
<td>Welch84</td>
<td>RCT</td>
<td>Daily, 3 months</td>
<td>12</td>
<td>No benefit</td>
</tr>
<tr>
<td>Kobayashi80</td>
<td>NCT</td>
<td>Daily, 1–3 years</td>
<td>(61)</td>
<td>Benefit†</td>
</tr>
<tr>
<td>Kobayashi81</td>
<td>NRCT</td>
<td>Daily, 18 months</td>
<td>120</td>
<td>Benefit</td>
</tr>
<tr>
<td>Shoji82</td>
<td>RCT</td>
<td>Daily → alternate-day, 1 year</td>
<td>12</td>
<td>Benefit†</td>
</tr>
<tr>
<td>Waldo85</td>
<td>NRCT</td>
<td>Alternate-day, 2–4 years</td>
<td>(67)</td>
<td>Benefit</td>
</tr>
<tr>
<td>Katafuchi85</td>
<td>RCT</td>
<td>Daily, 2 years</td>
<td>(65)</td>
<td>Benefit†</td>
</tr>
<tr>
<td><strong>Steroid pulse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pozzi80</td>
<td>RCT</td>
<td>Pulse + alternate-day, 6 months</td>
<td>60</td>
<td>Benefit</td>
</tr>
<tr>
<td>Tamura84</td>
<td>NCT</td>
<td>Pulse + daily, 1 year</td>
<td>12</td>
<td>Benefit</td>
</tr>
<tr>
<td><strong>Steroids + cytotoxics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshikawa85</td>
<td>RCT</td>
<td>Daily → alternate day, 2 years + azathioprine</td>
<td>24</td>
<td>Benefit</td>
</tr>
<tr>
<td>Ballardie85</td>
<td>RCT</td>
<td>Daily, 2 years + cyclophosphamide → azathioprine</td>
<td>60</td>
<td>Benefit</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomized, controlled trial; NCT, noncontrolled trial; NRCT, nonrandomized, controlled trial.
* Benefit in patients with CrCl ≥70 mL/min.
† Benefit in proteinuria, but no change in renal function.

CORTICOSTEROIDS AND OTHER IMMUNOSUPPRESSIVE DRUGS

Corticosteroids are potent antiinflammatory agents that have been used in the treatment of IgAN for 30 years. The results of clinical trials published before 2003 assessing the efficacy of treatment with corticosteroids, alone or combination with cytotoxic agents, is summarized in Table 2.

Conventional Corticosteroids

Corticosteroids, when administered on a daily or alternate-day basis, have had variable success in patients with IgAN. In 1988, Kobayashi et al. reported a retrospective study of 29 patients with proteinuria over 2 g per day who were given daily
prednisolone for 12 to 36 months. Steroids stabilized kidney function in a subgroup with preserved initial creatinine clearance (over 70 mL/min).80

The same authors published a nonrandomized, controlled study in 1996 in which a subgroup of the 1988 study was compared with an untreated group. Daily steroids for 18 months showed a protective effect on renal function and a reduction in proteinuria 10 years after therapy.81

In a RCT, Shoji et al. examined two treatment protocols, a corticosteroid group and an antiplatelet group, for early-stage diffuse proliferative IgAN in adults with a 1-year course of prednisolone (0.8 mg/kg per day at initial dosage and gradually tapered to 10 mg every other day over 1 year). They determined that early corticosteroids were effective for reducing renal injury, which was confirmed by repeated biopsies after 1 year. In the corticosteroid group, proteinuria decreased, expression of α-smooth muscle actin in glomeruli was suppressed, and histologic findings (e.g., mesangial cell proliferation, mesangial matrix accumulation, cellular crescents) were improved.82

On the other hand, Lai’s prospective, randomized trial failed to show a benefit of prednisolone (1 mg/kg per day for 2 months and a tapered dosage for another 2 months). During the mean study period of 38 months, no significant difference in creatinine clearance was demonstrated between 17 steroid-treated patients and 17 control patients. Corticosteroid treatment resulted in a high rate of remission of nephrotic syndrome among patients with mild glomerular histopathologic changes, but many experienced side effects.83

Welch’s RCT of short-term prednisolone also showed negative results in terms of urinary protein and erythrocyte excretion.84

Using alternate-day prednisolone (60 mg/m²) for 2 to 4 years in a controlled study, Waldo et al. showed disappearance of proteinuria, preservation of renal function, and a decrease in the activity score in repeated renal biopsies.85

Taken together, the available data suggest that the short-term (less than 6 months) use of conventional corticosteroids is less likely to have significant beneficial effects. In a recent RCT, Katafuchi et al. reported the limitation of the low-dose prednisolone, with an initial dose of 20 mg daily, to prevent the progression of IgAN.86

Steroid Pulse

Several factors influence the magnitude of corticosteroid effects, including the dose and route of administration of the corticosteroids. The mechanism of action of conventional corticosteroid therapy is mainly regulated by genomic mechanisms, beginning with the binding to the intracellular glucocorticoid receptor, which relate to immune cell function and production of inflammatory mediators.87

In addition to the genomic action, steroid pulse induces nongenomic actions such as membrane-bound receptors or physicochemical interaction with cellular membranes.88 For example, apoptosis of inflammatory cells, especially CD4+ lymphocytes, can occur only at pulse doses of corticosteroids.89

Moreover, with prolonged clinical corticosteroid use, the intracellular glucocorticoid receptor is downregulated, making corticosteroids less effective.90 This glucocorticoid receptor downregulation could be one factor that explains why aggressive treatment early on is effective as opposed to a gradual increment in corticosteroid dose, which results in more toxicity and less beneficial effects.91 Thus, although there has been no RCT comparing steroid pulse with conventional steroid therapy, rather pronounced effects might be expected with steroid pulse therapy.

A multicenter RCT in Italy demonstrated compelling evidence favoring the use of corticosteroids, including steroid pulse therapy, for 6 months. After 5 years of follow-up, a significant higher number of control patients had a 50% rise in serum creatinine than treated patients, who also had significantly less proteinuria.92

In that study, however, although the difference in renal survival was particularly striking until the third year, the subsequent risk of renal function deterioration was quite similar in the treated and untreated patients. Therefore, they concluded that corticosteroids alone are not sufficient to ensure stable remission, and thereafter they have initiated a new RCT to study the additional role of azathioprine comparing a group of patients treated with 6-month course of steroids alone with a group receiving steroids plus low-dose azathioprine.93

The efficacy of corticosteroids, even if a high dose of steroids is used, would seem less likely in patients with already impaired renal function. A
small-sized retrospective, uncontrolled study, however, showed a positive result for steroid pulse therapy in terms of the speed of decline of renal function and magnitude of proteinuria in patients with impaired renal function.94

Corticosteroids With Cytotoxic Agents

Despite significant potential toxicity, cytotoxic agents such as cyclophosphamide and azathioprine could have a therapeutic role in the subset of patients with focal necrotizing glomerular lesions, often accompanied by crescents. As far as the pathologic aspect of “smoldering glomerular capillaritis” in IgAN is concerned, cytotoxic agents could have a role in the treatment of IgAN, especially for patients who have necrotizing lesions.

Yoshikawa et al.95 reported good results in a multicenter, prospective RCT that evaluated in 40 newly diagnosed Japanese children the efficacy of treatment with prednisolone and azathioprine in a five-drug regimen over 2 years compared with control patients receiving only the other three agents, heparin–warfarin and dipyridamole. All patients had diffuse mesangial proliferation by biopsy at diagnosis. The five-drug regimen led to a significant reduction in proteinuria and serum IgA. Posttreatment repeat renal biopsy showed that mesangial IgA staining decreased in the five-drug group with disappearance in seven patients but not in the control subjects, whereas segmental or global glomerular sclerosis worsened only in the control group.

Recently, Ballardie and Roberts96 reported a randomized, prospective controlled trial with prednisolone combined with a corticosteroid showing a significant improvement of outcome in progressive IgAN. A total of 38 patients with progressive IgAN were randomized to treatment with prednisolone and cytotoxic agents, to therapy with low-dose cyclophosphamide then azathioprine, and to control groups. The follow-up period lasted 2 to 6 years. Renal survival, as assessed by Kaplan-Meier analysis annually to 5 years, showed significant preservation of function from 3 years in the treatment group and 82%, 82%, 72%, and 72% for 2, 3, 4, and 5 years, respectively, compared with 68%, 47%, 26%, and 6% in control subjects.

The above positive results obtained from rather short-term follow-up studies indicate the benefits of the combination therapy in the severe form of IgAN. On the other hand, Oshima et al.97 reported the results of a longer follow-up period (6.6 ± 3.8 years). In their study, 21 patients were treated with 100 mg cyclophosphamide and 40 mg prednisolone for 10 weeks, followed by tapered-off prednisolone over 8 weeks. Initially, disappearance of proteinuria was obtained in 13 patients; however, relapse of proteinuria was observed in five patients during the long follow-up period. Moreover, two patients developed malignancy (renal cell carcinoma after 8 years and carcinoma in rectal adenoma in 6 years). Through their experiences, the authors warned their readers that long-term follow-up study was necessary to assess the efficacy and safety of treatment in patients with IgAN.

Other Immunosuppressive Drugs

Mycophenolate mofetil inhibits proliferation of B and T lymphocytes, reduces antibody synthesis, and decreases glycosylation of cell-surface adhesion molecules by slowing the addition of fucose and mannose residues.98 A few case reports and a small uncontrolled trial have described that administration of mycophenolate mofetil alone or combined with a corticosteroid for several months decreased proteinuria and stabilized serum creatinine in patients with IgAN.99,100

More recently, a RCT reported the effectiveness of mycophenolate mofetil as being superior to prednisolone in reducing proteinuria in patients with IgAN with severe proteinuria (>2.0 g per day).101

Mizoribine, having a similar immunosuppressive mechanism to mycophenolate mofetil, was used in childhood IgA nephropathy for 20.5 months and resulted in a significant reduction of proteinuria and hematuria with histologic improvement.102 Because mizoribine is a relatively safe and well-tolerated drug when compared with other immunosuppressants such as cyclophosphamide and azathioprine, administration of this drug could have an advantage, especially for children. A multicenter RCT of mizoribine combined with steroids versus steroids alone for severe childhood IgAN is now underway in Japan.

The information on the use of cyclosporine in IgAN is limited. A small randomized, controlled study compared cyclosporine at a dosage of 5 mg/kg per day for 12 weeks with a placebo. In patients with 1.5 g or more per day of proteinuria, a significant decrease in proteinuria was observed in the treated group. There was, however, a signif-
significant worsening in renal function, which was probably a result of the drug’s renal toxicity.103 Given the frequent recurrence of IgAN in allografts despite immunosuppression, I think the long-lasting termination of IgAN by short-term immunosuppressive treatments is rather unlikely unless the pathogenic stimulus is eliminated.

**STEROID PULSE THERAPY WITH TONSILLECTOMY**

In 1988, we treated a 29-year-old man with active IgAN with necrotizing glomerular lesions, having 1.2 g per day proteinuria and 67 mL/min creatinine clearance, with a combination therapy consisting of tonsillectomy and steroid pulse on a trial basis. He obtained disappearance of proteinuria and hematuria 4 months after the initiation of treatment. This experience has prompted us to apply this combination therapy for wider subsets of patients with IgAN in whom an adequate informed consent was obtained.

We examined the results of a variety of treatment interventions on long-term outcomes of 329 patients in our renal unit between 1977 and 1995. Forty-eight percent of the patients cleared all urinary findings, and none of these patients developed renal failure. In contrast, patients who did not have a clinical remission had a 21% chance of a 50% rise in serum creatinine at 10 years. Positive predictors for remission included lower creatinine level at entry, lower histologic score, tonsillectomy and steroid pulse therapy, but not conventional steroid, ACEI, and cyclophosphamide.12

To date, over 500 patients with IgAN in various stages have been treated with the combination of tonsillectomy and steroid pulse therapy. A summary of the clinical remission rate by histologic score in 372 patients who underwent tonsillectomy and steroid pulse therapy and in whom the follow-up period was 3 years and more is shown in Table 3. Disappearance of the hematuria was obtained in more than 80% of patients regardless of the degree of the histologic score. On the other hand, the disappearance rate of the proteinuria decreased in tandem with an increasing histologic score.

After a treatment protocol involving tonsillectomy and steroid pulse, a repeat biopsy study in 35 patients with IgAN in whom hematuria had disappeared, and in 23 of whom proteinuria had also disappeared, showed the regression of established IgAN.12 Although acute inflammatory lesions such as crescents and necrotizing lesions were no longer present and significant regression of mesangial proliferation was observed in the second biopsies, the disappearance of mesangial IgA deposition was obtained in only eight of 35 patients despite the long follow-up period with a mean of 77.1 months.

From these findings we think that “smoldering glomerular capillaritis,” an important pathologic characteristic of clinical IgAN, is a curable condition, but resolution of mesangial IgA depositions, another essential element of IgAN, could be inducible in only a small subsets of patients with IgAN by the combination therapy of tonsillectomy and steroid pulse.

In cases of IgAN with impaired renal function, it is obvious that clinical remission is realistically difficult. However, with respect to renal survival

### Table 3. Clinical Remission Rate 3 Years After the Combination Therapy of Tonsillectomy and Steroid Pulse in 372 Patients With IgA Nephropathy

<table>
<thead>
<tr>
<th>Histological Score</th>
<th>No. of Patients</th>
<th>No. of Remission Patients</th>
<th>Hematuria (%)</th>
<th>Proteinuria (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGL*≤1.5</td>
<td>161</td>
<td>140 (87.0%)</td>
<td>139 (86.3%)</td>
<td></td>
</tr>
<tr>
<td>1.5&lt;IGL≤2.0</td>
<td>99</td>
<td>83 (83.8%)</td>
<td>69 (69.7%)</td>
<td></td>
</tr>
<tr>
<td>2.0&lt;IGL≤2.5</td>
<td>63</td>
<td>59 (93.7%)</td>
<td>30 (47.6%)</td>
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</tr>
<tr>
<td>2.5&lt;IGL</td>
<td>49</td>
<td>42 (85.7%)</td>
<td>12 (24.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* IGL = index of glomerular lesion.

\[
\text{IGL} = \frac{(0 \times N_0) + (1 \times N_1) + (2 \times N_2) + (3 \times N_3) + (4 \times N_4)}{N_0 + N_1 + N_2 + N_3 + N_4}
\]

The degree of morphologic damage of each glomerulus was graded 0 to 4 according to the percentage of injured lobules as the result of mesangial proliferation and sclerosis. The average of the degree for all glomeruli was calculated and registered as the IGL.12
rates, steroid pulse with tonsillectomy might have beneficial effects even in patients with impaired renal function (serum creatinine ≥1.5 mg/dL) under a serum creatinine level of 2.0 mg/dL.104 On the other hand, we failed to demonstrate statistical benefits in those patients with more advanced IgAN (serum creatinine >2.0 mg/dL). However, an anecdotal report by Pozzi et al. described a female patient with IgAN with impaired renal function whose renal function had been progressively declining despite the use of ACEI. She underwent tonsillectomy at a serum creatinine level of 3.1 mg/dL. Five months after tonsillectomy, she was treated with a 6-month steroid course. Thereafter, she experienced long-lasting stabilization of her renal function and decrease in proteinuria.

Because the previously mentioned results have been obtained based on accumulated experiences, but not through RCTs which are the most reliable study design in evidence-based medicine, one might be skeptical regarding the efficacy of the combination of tonsillectomy and steroid pulse therapy. However, no treatment protocol that includes a surgical operation on asymptomatic organs such as the tonsils is suitable for an RCT. Thus, we believe that not only the results from RCTs, but also an appropriate analysis of accumulated mass experiences will be very important to assess the efficacy of tonsillectomy or the combination therapy of tonsillectomy with corticosteroids.

CONCLUSION

Corticosteroid therapy, especially steroid pulse, alone or in combination with azathioprine is effective in stabilizing renal function and decreasing proteinuria at least in a relatively short observation period, but the very longlasting effects following these treatments is still open to question. To avoid reaching ESRD in a normal lifespan, very longlasting effects (over 30 or 40 years) are needed, especially in young patients with IgAN.

On the other hand, once the disappearance of urinary abnormality has been obtained and can be maintained over the long-term, a subsequent fall of renal function is highly unlikely, even in patients with impaired renal function. In contrast, in the absence of clinical remission, nephropathy could show an essentially progressive course, although the speed of the progression varies among patients.12,106

There is no longer any doubt that clinical remission can be obtained by aggressive treatments such as tonsillectomy with steroid pulse, especially in the relatively early stage of IgAN. Therefore, if we look at IgAN from the patients’ point of view, “remission of nephropathy” must be a more acceptable concept than “slowing the progression of nephropathy” and should be our earnest goal in the treatment of IgAN.

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REFERENCES

94. Tamura S, Ueki K, Ideura H, et al: Corticosteroid ther-
apy in patients with IgA nephropathy and impaired renal func-
96. Ballardie FW, Roberts ISD: Controlled prospective trial
follow-up of prednisolone and cyclophosphamide therapy in
IgA nephropathy. Nephrology 5:A20-A21, 1999 (suppl)
98. Allison AC, Kowalski WJ, Muller CJ, et al: Mycope-
nolic acid and brequinar, inhibitors of purine and pyrimidine
synthesis, block the glycosylation of adhesion molecules. Transplant Proc 25:67-70, 1993
mofetil for systemic vasculitis and IgA nephropathy. Lancet
349:774, 1997
100. Chen XM, Zhang YP, Qui Q, et al: Short-term effects
of mycophenolate mofetil on IgA nephropathy [Abstract]. J Am
102. Nagaoka R, Kaneko K, Ohtani Y: Mizoribine treatment
IgA nephropathy: A short term controlled trial. BMJ 295:1165-
1168, 1987
advanced IgA nephropathy. Efficacy and limitations of cortico-
105. Pozzi C, Vecchio LD, Locatelli F: Can immunosup-
pressive therapy be useful in IgA nephropathy when the “point
of no return” has already been exceeded? Nephron 92:699-701,
2002
106. Chauveau D, Droz D: Follow-up evaluation of the first
patients with IgA nephropathy described at Necker Hospital.
Contrib Nephrol 104:1-5, 1993