A clinicopathological study of IgA nephropathy in renal transplant recipients: beneficial effect of angiotensin-converting enzyme inhibitor

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Abstract

Background. Prolonging the survival of transplant kidneys is a major task of modern nephrology. It has recently been shown that deteriorating renal function and substantial graft loss were observed in 55% of renal allograft recipients with recurrent IgA nephropathy (IgAN) at long-term follow-up. To gain a useful insight into the therapeutic approach towards protecting allograft kidneys from deteriorating graft function, we compared the histological characteristics of post-transplant IgAN to primary IgAN and investigated the effects of an ACE inhibitor.

Methods. Twenty-one patients with post-transplant IgAN and 63 patients with primary IgAN were included in the histopathological study. The effectiveness of angiotensin-converting enzyme (ACE) inhibitor treatment in post-transplant IgAN was also studied in 10 patients.

Results. The prevalence of glomeruli with adhesions and/or cellular crescents in primary IgAN was significantly greater than in post-transplant IgAN (P < 0.05), but the proportion of glomeruli with segmental sclerosis was similar in both groups. The rate of global obsolescence, and the degree of interstitial fibrosis in post-transplant IgAN were significantly greater than in primary IgAN (P < 0.05). The degree of glomerular obsolescence and the severity of interstitial fibrosis correlated with the severity of glomerular lesion in primary IgAN, but not in post-transplant IgAN. In primary IgAN, glomerular diameter significantly correlated with the proportions of glomerular obsolescence, but not in post-transplant IgAN, suggesting that allograft kidneys may be in a hyperfiltration state.

Both the blood pressure and the urinary protein excretion significantly improved after ACE-inhibitor treatment (P < 0.001).

Conclusion. In post-transplant IgAN, histopathological lesions indicative of acute inflammatory insults were suppressed, and glomerular hypertrophy, which may relate to haemodynamic burden such as hyperfiltration, was prominent. Preliminary study of ACE-inhibitor treatment in 10 patients showed favourable effects. A future long-term follow-up study is required to establish the effectiveness of ACE inhibitors in treatment of post-transplant IgAN.

Keywords: ACE inhibitors; graft function loss; hyperfiltration; kidney allograft; post-transplant IgA nephropathy

Introduction

Renal transplantation is universally considered to be the treatment of choice for patients with end-stage renal disease, providing good patient survival and quality of life. Recent improvements in immunosuppressive therapy have led to a dramatic increase in short-term renal allograft survival. However, acceptable improvements in long-term allograft survival have not been achieved. After the first year, the number of functioning grafts begins to decline, to approximately 70%, and to less than 50% at 5 and 10 years after transplantation, respectively. Prolonging the survival of transplanted kidneys is, therefore, a major task of modern nephrology.

Currently, post-transplant IgA nephropathy (IgAN) is considered to include recurrence of IgAN, de novo IgAN, or transmission of IgA deposit from donor kidney [1]. Yamaguchi et al. [2] reported that the prevalence of post-transplant IgAN was 34% in renal biopsies of allografts surviving more than 5 years. Berger et al. [3] were the first to describe recurrence of IgA deposit, and subsequent studies showed 50–60% prevalence of recurrent IgAN. Graft loss due to recurrent renal diseases has been reported to be a rare event, estimated as less than 5% [4]. However, it has recently been shown that deteriorating renal function and substantial graft loss were observed in 55% of renal
allograft recipients with recurrent IgAN at long-term follow-up [5–7].

In primary IgAN, many clinicopathological studies revealed that diffuse mesangial proliferation, or severe sclerotic changes such as segmental/global glomerulosclerosis, interstitial fibrosis, and tubular atrophy, have been shown to be associated with poor prognosis of the disease [8–11]. However, little has been reported in post-transplant IgAN about the relationship between the histopathological features and the clinical course of the allograft kidneys.

Proteinuria was shown to be an important predictive parameter of long-term renal prognosis in post-transplant IgAN [12]. Hypertension after renal transplantation is an important factor in cardiovascular mortality as well as a risk factor for graft loss [13]. Multiple causes and mechanisms are considered to be responsible for post-transplant hypertension.

It appears that normal blood pressure is a good marker of graft survival and that an effective antihypertensive treatment reduces the progression of graft damage [14]. Protection of allografts from long-term functional deterioration is one of the major goals of treatment of post-transplant patients. In primary IgAN, hypertension and proteinuria (more than 1 g/day) are considered to indicate a poor prognosis [15,16].

Numerous studies have shown that angiotensin-converting enzyme (ACE) inhibitors interfere with progressive deterioration of many chronic renal diseases, including IgAN [17]. Only one report so far has shown the antiproteinuric efficacy of ACE inhibitors in patients with post-transplant glomerulonephritis [18]. The beneficial effect of ACE inhibitors still remains obscure for post-transplant IgAN, and to date there are a few in-depth studies in renal transplantation that have analysed the relationship between histological lesions and response to ACE inhibitor treatment [18,19].

In this paper, we report the histological characteristics of post-transplant IgAN compared with those of primary IgAN. To address whether ACE inhibitor treatment favourably influences disease progression in post-transplant IgAN, we investigated the effects of an ACE inhibitor on blood pressure and changes in renal graft function.

Subjects and methods

Patients

Post-transplant IgAN was found in 21 patients out of 68 renal biopsy specimens from allograft kidneys from 1997 to 1998 at Osaka University Hospital. These biopsies were performed because of the presence of proteinuria (17 cases) or as non-episode protocol biopsy (four cases). The patients consisted of 16 men and five women, with a mean age of 29±11 years at the time of biopsy. The aetiology of the end-stage renal disease was unknown in all patients. The mean interval from renal transplantation to the diagnosis of post-transplant IgAN was 2335±1346 days. Interval from the appearance of abnormal urinalysis to renal biopsy in 17 patients was more than 3 years. Three patients had experienced acute rejection in the past, which had been diagnosed by clinical manifestations and confirmed by renal biopsy. No patient had macroscopic haematuria. Sixty-three untreated patients with primary IgAN diagnosed at Osaka University Hospital during the same period (1997–1998) were analysed. The average duration of abnormal urinalysis prior to renal biopsy was 7±4 years (range 2 months to 12 years). Clinical data of the patients is shown in Table 1.

Analysis of histology

Histopathological analyses of each graft biopsy were performed based on light-microscopic findings. IgAN was diagnosed on the basis of the following immunohistological criteria: presence of predominant IgA deposition mainly in the mesangium and occasionally along some peripheral loop segments in a granular pattern. Renal biopsy samples were assessed by a semi-quantitative analysis of light-microscopic changes in the glomeruli, interstitium, and vessels. All renal biopsy samples were independently interpreted by one of the authors without knowledge of the clinical information. Glomerular changes observed with light microscopy were classified as follows [20,21]: 0, minor glomerular abnormalities; 1, diffuse mesangial proliferative glomerulonephritis (PGN) (mild); 2, diffuse mesangial PGN (moderate); and 3, diffuse mesangial PGN (severe). We also determined the proportion of glomeruli showing crescents, global obsolescence, segmental sclerosis, or adhesions. All lesions except crescents were considered as chronic lesions. Interstitial fibrosis was graded semi-quantitatively as 0, none; 1, mild changes; 2, moderate changes; and 3, severe changes.

Morphometric analysis

The method for measuring glomerular diameter (Bowman’s capsule) has been described previously [22]. The geometric mean of two diameters measured perpendicular to each other was calculated. At least five glomeruli showing juxtaglomerular apparatus or vascular pole were selected and analyzed, and means ± standard deviations were then calculated for each biopsy.

ACE inhibitor treatment and subjects

Ten patients with post-transplant IgAN, nine men and one woman aged 14–44 (34±10) years, with stable renal allograft function (serum creatinine less than 2 mg/dl), moderate to severe hypertension, and proteinuria (0.3–3.0 g/day) were treated with the ACE inhibitor trandolapril. Written informed consent was obtained from all patients. No patients revealed renal artery graft stenosis after screening by technettium-scan imaging. All patients were given immunosuppressive medications as follows: cyclosporin A (CsA)/prednisolone in six cases, tacrolimus/azathioprine/prednisolone in two cases, and azathioprine/prednisolone in two cases. All patients were treated for their hypertension with the calcium-channel blocker amlodipine (20–40 mg/day) or 2.5–5 mg/day amlodipine besilate. To assess the effectiveness of the ACE inhibitor in the treatment of hypertension, proteinuria, and renal graft function, trandolapril was added at a dose of 1 mg/day to the above regimen and these patients were followed for mean duration of 12.8 months (range 12–16 months). Trandolapril is a long-acting ACE inhibitor that is metabolized and excreted mainly in the liver. The
immunosuppressive and antihypertensive treatment regimen was kept unchanged throughout the study.

**Clinical data**

Blood pressure was monitored monthly in a seated position after 5 min rest. The effects of trandolapril on proteinuria and renal function were evaluated every 3 months by urinary protein excretion (g/day), and serum creatinine (s-Cr) level (mg/dl) respectively.

**Statistics**

Values are expressed as mean ± standard deviation. A comparison of the clinical data between before and after the ACE-inhibitor treatment was performed by Student’s paired t-test. The prevalence of the histological findings in post-transplant IgAN and primary IgAN was compared by Student’s t-test. The relationship between segmental sclerosis and urinary protein excretion in post-transplant IgAN and primary IgAN was compared by Fisher’s exact probability test. *P* < 0.05 was considered as statistically significant.

**Results**

**Comparison of adhesion, crescents, segmental sclerosis, global obsolescence, and interstitial fibrosis between post-transplant and primary IgAN**

We studied the prevalence of adhesion, crescents, segmental sclerosis, global obsolescence, and interstitial fibrosis in both post-transplant and primary IgAN (Figure 1). The prevalence of glomeruli with adhesions and cellular crescents was significantly greater in primas than in post-transplant IgAN (*P* < 0.05), while the prevalence of glomeruli with segmental sclerosis was similar in both groups. The rate of global obsolescence and the average score of interstitial fibrosis in post-transplant IgAN were significantly greater than in primary IgAN (*P* < 0.05). The lesions analysed here have been used to compare the activity or chronicity of lesions in primary IgAN [20,23]. In the previous works, mesangial proliferation and cellular crescents were considered as active lesions. Segmental sclerosis, global obsolescence, and interstitial fibrosis were considered as chronic changes.

**The relationship between the degree of glomerular lesion and the prevalence of glomerular obsolescence**

Figure 2 depicts the relationship between the rate of glomerular obsolescence and the severity of glomerular lesions in primary IgAN and in post-transplant IgAN. In primary IgAN the rate of glomerular obsolescence correlated with the severity of the glomerular lesion. In contrast, in post-transplant IgAN a high percentage of glomerular obsolescence was observed irrespective of the severity of the glomerular lesion.

**The relationship between interstitial fibrosis and glomerular lesion**

Figure 3 shows the relationship between the severity of interstitial fibrosis and the severity of glomerular lesions in primary IgAN and in post-transplant IgAN. In primary IgAN, severe interstitial fibrosis was found in patients with severe glomerular lesions. In contrast, in post-transplant IgAN no correlation was noted.

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**Table 1. Clinical data of patients with primary IgAN and post-transplant IgAN**

<table>
<thead>
<tr>
<th></th>
<th>Primary IgA GN</th>
<th>Post-transplant IgA GN</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>63</td>
<td>21</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>40/23</td>
<td>16/5</td>
</tr>
<tr>
<td>Age</td>
<td>29.4 ± 10.4</td>
<td>29.2 ± 11.7</td>
</tr>
<tr>
<td>Kidney age</td>
<td>48.6 ± 14.3</td>
<td>48.6 ± 14.3</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>0.75 ± 0.8</td>
<td>1.2 ± 1.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.8 ± 0.2</td>
<td>1.5 ± 0.6*</td>
</tr>
<tr>
<td>Days after transplantation</td>
<td>7 years</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Duration of disease prior to renal biopsy (years)</td>
<td>7 years</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>119 ± 14.7/70.4 ± 14.5</td>
<td>142 ± 15.8*/91.1 ± 11.1*</td>
</tr>
</tbody>
</table>

*P* < 0.01 vs primary IgAN.
The relationship between glomerular diameter and the prevalence of glomerular obsolescence

Figure 4 depicts the relationship between the glomerular diameter of the remnant glomeruli with the rate of glomerular obsolescence in primary IgAN and in post-transplant IgAN. In primary IgAN, glomerular diameter significantly correlated with the rate of glomerular obsolescence. In post-transplant IgAN, glomerular diameter was already about 200 μm even in the absence of glomerular obsolescence, and did not correlate with the proportion of glomerular obsolescence.

The relationship between segmental sclerosis and urinary protein excretion

We compared the prevalence of segmental sclerosis between the patient subgroups with 1.0 g/day or more urinary protein and those with less than 1.0 g/day in post-transplant IgAN (Table 2). There was a significant correlation between the prevalence of segmental sclerosis and proteinuria in post-transplant IgAN ($P < 0.05$), suggesting that segmental sclerosis is related to the higher urinary protein excretion in post-transplant IgAN.

Effects of trandolapril on hypertension and proteinuria

In light of the histological characteristics of post-transplant IgAN discussed above, we believe that treatment with ACE inhibitors may be efficacious in decreasing urinary protein excretion and further preventing progression of graft function loss. Ten patients of post-transplant IgAN with mild to moderate proteinuria were chosen for ACE-inhibitor treatment. All the 10 patients completed the study protocol. Figures 5 and 6 show the changes in blood pressure and urinary protein excretion before and after ACE-inhibitor treatment in individual patients. The blood pressure was $150 \pm 19/100 \pm 11$ mmHg (mean arterial pressure 116.8 ± 13.9) before ACE-inhibitor treatment and was significantly decreased to $124 \pm 11/82 \pm 11$ mmHg (mean arterial pressure 96.0 ± 11.1) after the treatment. No acute renal graft function deterioration was observed after the initiation of the treatment with trandolapril.

Table 2. Relationship between segmental sclerosis and urinary protein excretion

<table>
<thead>
<tr>
<th>Urinary protein</th>
<th>Segmental sclerosis</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>$&lt; 1$ g/day</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>$\geq 1$ g/day</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Primary IgAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 1$ g/day</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>$\geq 1$ g/day</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>
Histopathology of post-transplant IgAN and the effect of ACE inhibition

Histopathological characteristics may result from the pathophysiological conditions of the allograft kidneys. Consideration of the underlying factors will provide a useful insight into the therapeutic approach towards protecting the allograft kidneys from deteriorating graft function.

We speculate that one of the underlying mechanisms of low prevalence of acute lesions in post-transplant IgAN is the effects of immunosuppressive medications such as corticosteroids, azathioprine, and CsA. In primary IgAN, prednisolone alone or prednisolone and azathioprine therapy were shown to improve histologically active lesions [24–26]. Schwarz et al. [27] reported that CsA did not prevent the recurrence of post-transplant glomerulonephritis including IgAN, but possibly suppressed the disease progression in patients after kidney transplantation. CsA and tacrolimus interfere with the early stage of lymphocyte proliferation by blocking interleukin-2 (IL-2) synthesis. It has been reported that a spontaneous hyperproduction of IL-2 occurred in patients with primary IgAN and that during the acute phase of the disease, such as the macrohaematuria episode, further elevation of IL-2 was observed [28]. In addition, there has been a case report of a patient who developed crescentic IgAN following treatment with recombinant IL-2 [29]. These reports suggest the involvement of IL-2 in acute glomerular lesions such as crescents, and therefore support the potential effect of CsA on the acute glomerular lesions.

In primary IgAN it has been shown that the degree of glomerular lesions is closely correlated with that of tubulointerstitial lesions [25,30]; this was also confirmed in the present study. In addition we found a similar relationship between the degree of glomerular lesions and the prevalence of glomerular obsolescence in primary IgAN. In contrast, in post-transplant IgAN, no correlation was noted between the degree of glomerular lesions and the prevalence of glomerular obsolescence, or the severity of interstitial fibrosis. The potential explanations for this lack of correlation between glomerular obsolescence or interstitial fibrosis with the glomerular lesions are listed below. Glomerular obsolescence may result from ischaemic injury/collapse of glomeruli due to arteriolsclerosis. Interstitial fibrosis may be due to the toxic effect of CsA, or result from ureteral obstruction, or may represent the scarring process of acute rejection [31].

No renal biopsy specimen of the post-transplant IgAN revealed chronic rejection defined as oblitative intimal thickening with reduction of vascular lumina. Increases in glomerular size were more prominent in post-transplant IgAN than in primary IgAN, especially in the absence of glomerular obsolescence. In primary IgAN, glomerular hypertrophy occurred in accordance with the progression of glomerular obsolescence, supporting the idea that glomerular hypertrophy results from a reduction in the number of functioning nephrons by any aetiology [32]. On the contrary, in

**Fig. 5.** The changes of blood pressure before and after ACE-inhibitor treatment in individual patients. ACEI, ACE inhibitor.

**Fig. 6.** The changes of urinary protein excretion before and after ACE inhibitor treatment in individual patients. ACEI, ACE inhibitor.

Before treatment, nine out of 10 patients had moderate urinary protein excretion (>1.0 g/day). The mean value of urinary protein excretion in the patients before treatment was 2.7 ± 1.5 g/day (range 0.3–4.8), and was significantly decreased to 0.89 ± 0.65 g/day (range 0.27–1.9) at the end of this study (P < 0.001). There was no apparent correlation between the percentage decrease of blood and the percentage decrease of proteinuria (data not shown). The ACE-inhibitor treatment effectively improved hypertension as well as proteinuria.

**Discussion**

In the present study we have studied the histological characteristics of post-transplant IgAN and primary IgAN. As far as we are aware, this is the first systematic analysis of histopathology of post-transplant IgAN. The main findings are as follows: (i) acute lesions such as mesangial proliferation, crescent formation were rarely found in post-transplant IgAN; (ii) chronic lesions such as glomerular obsolescence and interstitial fibrosis were observed irrespective of the severity of the glomerular changes; (iii) in post-transplant IgAN, glomerular hypertrophy was observed at any grade of glomerular obsolescence.
renal allografts, glomerular hypertrophy was observed irrespective of the degree of glomerular obsolescence, suggesting the impact of the single kidney on the remnant glomeruli. In addition, initial nephron loss may occur during preservation and transplantation of the allograft. Kasisek et al. [33] reported that the size of intact glomeruli increased with time after transplantation over a period of 0–5 years. In the present study, the time after transplantation at renal biopsy was at least 3 years, and about 6 years as a mean. We found that there was no effect of time on the glomerular diameter (data not shown). We speculate that there was already enough of a growth response in the glomeruli 3 years after transplantation. Glomerular hypertrophy has been found as a frequent concomitant finding with increased glomerular pressure [34]. It has been widely accepted that glomerular hypertrophy may reflect glomerular hypertension/hyperfiltration. In renal allografts, glomerular hypertrophy was reported to be a risk factor of focal glomerulosclerosis [35] and a predictor of risk of late allograft dysfunction [36]. Focal and segmental sclerosis is also thought to result from glomerular hypertension/hyperfiltration [37], and is also considered to be related to proteinuria. In addition we found that segmental sclerosis was more frequently found in the patients with heavier proteinuria (more than 1.0 g/day).

It has become evident that several non-immunological factors such as systemic hypertension, glomerular hypertension, and heavy proteinuria may affect long-term graft outcome [38,39]. In patients with a renal allograft, a state of hyperfiltration, one of the main non-immunological factors, can occur secondarily to a reduction in the functioning renal mass by various circumstances (e.g. repeated acute rejection episodes, CsA nephrotoxicity, small renal graft size, or post-transplant glomerulonephritis). Thus, hyperfiltration is considered to play an important role in the progression of renal insufficiency in the late post-transplant period [40].

ACE inhibitors have been proven to possess beneficial effects in the treatment of progressive renal diseases of various aetiologies [17,41]. In the renal graft, Bochicchio et al. [42] demonstrated that ACE inhibitor increased renal functional reserve by reducing glomerular capillary pressure and hyperfiltration. In light of the histological characteristics of post-transplant IgAN discussed above, we consider that treatment with ACE inhibitors may be efficacious in preventing progression toward renal failure in the late post-transplant period by a reduction in glomerular hyperfiltration and also by an antiproteinuric effect. Recently, Luft et al. [19] reported that the antiproteinuric efficacy of fosinopril in transplant patients was inversely correlated with the extent of chronic tubulointerstitial damage. In the data presented here, the mean reduction in urinary protein excretion was approximately −67%, which is more prominent than that of −38% reported by Luft et al. This difference may be attributed to the difference in the histopathological features of the patients; that is, our IgAN patients revealed presumably less tubulointerstitial lesions than their patients, which included patients with chronic rejection.

In conclusion, in post-transplant IgAN, histopathological lesions indicative of acute inflammatory insults were suppressed; but glomerular hypertrophy, which relates to haemodynamic burden such as hyperfiltration, was prominent. These histological features support the use of ACE inhibitors in the treatment of hyperfiltration/hyperfiltration in post-transplant IgAN.

Preliminary study of ACE inhibitor treatment in 10 patients showed favourable effects. Future long-term follow-up studies are required to establish the effectiveness of ACE inhibitors in the treatment of post-transplant IgAN.

References

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