Renal transplantation in patients with primary immunoglobulin A nephropathy

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Abstract
Background. Opinions on the clinical course and outcome of renal transplantation in patients with primary immunoglobulin A nephropathy (IgAN) have been controversial.
Methods. We conducted a retrospective single-centre study on 542 kidney transplant recipients over the period 1984–2001. Long-term outcome and factors affecting recurrence in recipients with primary IgAN were analysed.
Results. Seventy-five patients (13.8%) had biopsy-proven IgAN as the cause of renal failure, and their mean duration of follow-up after transplantation was 100 ± 5.8 months. Fourteen (18.7%) of the 75 patients had biopsy-proven recurrent IgAN, diagnosed at 67.7 ± 11 months after transplantation. The risk of recurrence was not associated with HLA DR4 or B35. Graft failure occurred in five (35.7%) of the 14 patients: three due to IgAN and two due to chronic rejection. Three (4.9%) of the 61 patients without recurrent IgAN had graft failure, all due to chronic rejection. Graft survival was similar between living-related and cadaveric/living-unrelated patients (12-year graft survival, 88 and 72%, respectively, P = 0.616). Renal allograft survival within the first 12 years was better in patients with primary IgAN compared with those with other primary diseases (80 vs 51%, P = 0.001). Thereafter, IgAN patients showed an inferior graft survival (74 vs 97% in non-IgAN patients, P = 0.001).
Conclusions. Our data suggested that around one-fifth of patients with primary IgAN developed recurrence by 5 years after transplantation. Recurrent IgA nephropathy in allografts runs an indolent course with favourable outcome in the first 12 years. However, the contribution of recurrent disease to graft loss becomes more significant on long-term follow up.

Keywords: graft survival; IgA nephropathy; outcome; recurrence; renal transplantation

Introduction
Primary immunoglobulin A nephropathy (IgAN) is one of the most common types of glomerulonephritis worldwide. The clinical course of this disease was originally considered to be benign. However, hypertension and progressive deterioration of renal function resulting in maintenance dialysis treatment are not as rare as originally thought. Actuarial curves of renal survival are now available from several series. When 20-year follow-up data became available, it was apparent that, each year, a constant percentage of patients with IgAN developed end-stage renal failure (ESRF). These reports show a 5–15% incidence of ESRF at 5 years, 10–20% after 10 years, 15–30% after 15 years and 20–50% after 20 years [1–5]. The overall prognosis of patients with IgAN remains to be determined. Actuarial renal survival at 10 years in adults was between 80 and 85% in most of the European and Asian studies, but it was lower in studies from the USA [4]. Notably, 14% of children with IgAN had poor long-term prognosis with ESRF [5]. 

Recurrent disease is common after transplantation and has been reported in 13–60% of patients depending on the duration of follow-up and the biopsy policy of respective transplant centres [6–16]. Berger et al. [6], who first described recurrence of mesangial IgA deposits in renal allografts, reported a relatively favourable clinical course of recurrent IgAN after renal transplantation. Subsequent studies with longer follow-up by Odum et al. [8], Kessler et al. [10] and Ohmacht et al. [11] have suggested otherwise. Similarly, there is controversy regarding the differential risk of recurrent IgAN pertaining to the type of donor or HLA. We aimed to resolve some of these issues and to determine the recurrence rate as well as
the clinical course of IgAN after renal transplantation by performing a single-centre long-term retrospective analysis over a period of 18 years on 75 renal allograft recipients with IgAN as the cause of renal failure, of which 14 developed recurrent IgAN. We have also compared and reviewed current literature on post-transplant recurrence of IgAN.

Subjects and methods

All transplant recipients who had been followed-up at the Queen Mary Hospital, Hong Kong, from 1 January 1984 to 31 December 2001 were analysed. After exclusion of mechanical causes of renal deterioration and acute cyclosporin nephrotoxicity, indications for renal biopsy included (i) deterioration in renal function, (ii) significant proteinuria with one or more grams of urinary protein per day or (iii) gross haematuria. Immunofluorescence staining for IgA deposition was performed in all patients with primary IgAN who had undergone graft biopsy. The policy for transplant biopsy was followed throughout the study. Recurrence of IgAN was diagnosed in patients who had biopsy-proven IgAN as the cause of renal failure and the graft biopsy showed mesangial proliferation with predominant deposition of IgA. Time of graft failure was defined as either the time of the recommencement of chronic dialysis or the time of the second transplant, whichever was earlier. Graft loss was attributed to recurrent IgAN when the renal histology showed diffuse mesangial proliferative expansion and glomerular sclerosis. Graft loss was attributed to chronic rejection if there were chronic inflammatory cell infiltrates, interstitial fibrosis, tubular atrophy and chronic vascular changes in the biopsy irrespective as to whether concomitant IgA deposition was documented.

Related donors are donors who were genetically related to the recipients, which included parent-child or sibling relationships. Non-related donors were either cadaveric or living-unrelated donors. Statistical analysis was performed using the chi-square test and Fisher's exact test for categorical data and the Mann–Whitney test for continuous variables. The Kaplan–Meier and log-rank tests were used for description and comparison of graft survival. Graft survival was censored at the time of death in patients who died with a functioning graft. Breslow–Day’s procedure was used to test homogeneity of independent odds ratios, and the Mantel–Haenszel method was used to find the common odds ratios. All values were expressed as mean ± SE and \( P < 0.05 \) was considered statistically significant.

Results

Five hundred and forty-two Chinese patients received kidney transplants during this period. Seventy-five patients had biopsy-proven IgA nephropathy as the underlying cause of renal failure before transplant. The majority of these patients received triple immunosuppressive therapy consisting of cyclosporin A, prednisolone and azathioprine, except nine patients, of whom seven had identical tissue typing and were given steroid and azathioprine. Two patients received tacrolimus and one patient received mycophenolate mofetil. Graft biopsy had been performed in 35 patients for clinical symptoms of renal impairment, proteinuria or haematuria. Recurrence of IgAN was documented in 40% of the patients who had undergone biopsy (14 patients). Eleven patients (78.6%) with recurrent IgAN presented with proteinuria alone or in combination with other symptoms. Two patients (14.2%) presented with renal impairment and only one patient (7%) presented with gross haematuria. The mean level of proteinuria for patients with recurrent IgAN was significantly higher than those without recurrence (1.8 ± 0.5 vs 0.6 ± 0.3 g/day, \( P = 0.046 \)). The mean time from transplantation to the biopsy documentation of recurrence was 67.7 ± 11 months, which was significantly longer than the 23.7 ± 8 months from transplantation to the biopsy diagnosis of other causes (including acute tubular necrosis, acute and chronic rejections and glomerulonephritis other than IgAN) of similar clinical symptoms (\( P = 0.005 \)). The 14 patients with recurrent IgAN had concomitant lesions of chronic transplant nephropathy in the renal biopsies, two of which subsequently had graft loss due to chronic rejection. There was no significant difference in the demographic data between the group with recurrence and those without recurrence (Table 1). Nearly all non-related donors were cadaveric donors. The only exception was a spousal transplant from his wife in a patient with primary IgAN. The mean age of the patients at transplantation was 32.0 ± 1.6 years for the recurrence group and 34.6 ± 1.3 years for the non-recurrence group. There was a predominance of male patients among the transplant population but the sex ratios for both groups were similar. The mean duration of follow-up of the recurrence group was 130.8 ± 10.6 months which was significantly longer than the non-recurrence group which had a mean duration of follow up of 93.0 ± 6.4 months.

The renal function for both recurrence and non-recurrence groups were comparable for the first 5 years. The mean serum creatinine was 140.8 ± 7.5 \( \mu \text{mol/l} \) for the recurrence group and 125.6 ± 4.5 \( \mu \text{mol/l} \) for the non-recurrence group at the end of the fifth year (Table 1). Thereafter, the renal function of the recurrence group tended to deteriorate faster. By the eighth year, the mean serum creatinine of the recurrence group was significantly higher than the non-recurrence group (193.28 ± 17.6 vs 133.3 ± 10.7 \( \mu \text{mol/l} \), \( P = 0.002 \)). Five grafts were lost from the recurrence group at a mean duration of 141.8 ± 9.6 months, three due to recurrence of IgAN and two due to chronic rejection. Three grafts were lost from the non-recurrence group, with a mean duration of 105.3 ± 14.3 months, due to chronic rejection.

Full data of HLA typing were available in 58 patients, 12 of whom were identically matched (Table 1). No significant difference in the frequency of HLA DR4 (54.5 vs 23.4%, \( P = 0.064 \)) and HLA A2 (72.7 vs 57.4%, \( P = 0.499 \)) were detected between the
recurrence and non-recurrence group. None of the patients in the recurrence group had HLA B35 ($P = 1.000$) or B46 ($P = 0.075$).

Related donors appeared to have a higher frequency of recurrence ($29\%$ vs $11.4\%, P = 0.081$). However, a transplant with identically matched grafts did not confer a higher recurrence rate than that with one haplotype matched or totally mismatched grafts ($41.7\%$ vs $21\%, P = 0.240$). With respect to the long-term graft survival in relation to the donor type, there was no significant difference in the graft survival between related and non-related donors. The 12-year graft survival for the related donor was $88\%$ while that for the non-related donor was $72\%$ ($P = 0.616$) (Figure 1).

We compared the long-term graft survival between patients with IgAN as the primary disease and patients with other aetiologies of renal failure who had received renal transplants during the same period. The 17-year graft survival for IgAN patients was $61\%$ as compared with $70\%$ of non-IgAN patients (Figure 2). As the two survival curves crossover around year 12, stratified analysis was performed. For patients with a follow-up shorter than 12 years ($n = 433$), five grafts were lost from 61 IgA patients, while 100 grafts were lost from 372 non-IgA patients; the graft survival of IgAN patients was significantly better with a graft survival of $80\%$ as compared with $51\%$ of non-IgAN patients ($P = 0.001$). However, for patients with a follow-up longer than 12 years ($n = 109$), three grafts were lost.
from 14 IgA patients while two grafts were lost from 95 non-IgA patients; the renal survival of patients with primary IgAN was significantly poorer with a graft survival of 74% as compared with 97% of non-IgA patients ($P = 0.001$).

**Discussion**

IgA nephropathy is the most common glomerulonephritis worldwide. The course of the primary disease is highly variable; some patients will enjoy normal renal function for years while others have progressive deterioration in renal function requiring renal replacement therapy. The recurrence rate of IgAN following renal transplantation ranges between 20 and 40% worldwide, with no major difference between Asia-Pacific, Europe and USA (Table 2). Since most of the centres do not perform protocol biopsy in asymptomatic patients, the actual incidence of recurrent IgAN may have actually been higher.

Initially, the course of recurrent IgAN had been reported to be benign [6]. As more long-term data is becoming available, it is apparent that graft loss due to recurrence of IgAN occurs in 2–16% of patients [7–18] (Table 2). Most of the previous studies only report short-term results. Herein, we report, for the first time, data of recurrent IgAN up to 18 years post-transplantation. In our centre, we performed renal biopsy only in patients with clinical symptoms, thus our definition of IgA recurrence was mainly clinical and might underestimate the number of patients with recurrent disease. In our study, patients with documented recurrent disease had significantly longer duration of follow-up, which was in line with the observations of other studies [8,17]. The mean time from transplantation to the occurrence of clinical symptoms and documentation of recurrence by biopsy was 5 years, which was significantly longer than those who had clinical symptoms secondary to other causes. The majority of these patients presented with proteinuria. Their renal functions were well preserved for the first few years with 100% graft survival at the end of the fifth year since transplantation, suggesting that even patients with recurrent disease enjoyed a symptom-free period of years before their renal function started to deteriorate. Hence, difference in the graft survival would not be apparent unless these patients had been followed for a sufficiently long period. This time frame is in keeping with the slowly progressive and relentless nature of primary IgAN.

Several studies reported an association of HLA DR4 or B35 with increased susceptibility to recurrent IgAN [13,19], while other studies [7–8,12,15], including ours, did not document any correlation of these two antigens with disease recurrence. A recent study from our locality reported a possible protective effect of HLA A2 against recurrence of IgAN in Chinese patients [17]. After pooling these data from Wang et al. [17] with ours, which were also derived from an identical ethnic population in the same geographical locality, we failed to substantiate this observation with a larger patient number. This report also suggested a greater risk for graft dysfunction in living-related transplants than non-related transplants. However, we failed to observe any difference in the long-term graft survival with respect to different donor type. When we pooled all available data from the literature that contained information on graft loss in relation to donor type [7,12,14,17], no difference was documented in the risk of graft loss due to recurrent IgAN between patients with related or non-related donors (common odds ratio = 1.78, $P = 0.319$) (Table 3). Whether a related...
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Table 3. Risk of graft loss from recurrent IgA nephropathy according to donor type

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Graft loss</th>
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<tbody>
<tr>
<td></td>
<td>RD</td>
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<tr>
<td>Bachman et al. [7]</td>
<td>5</td>
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<tr>
<td>Frohnert et al. [12]</td>
<td>8</td>
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<tr>
<td>Bumgardner et al. [14]</td>
<td>6</td>
</tr>
<tr>
<td>Wang et al. [17]</td>
<td>6</td>
</tr>
<tr>
<td>Choy et al. (current)</td>
<td>9</td>
</tr>
<tr>
<td>Pooled data</td>
<td>34</td>
</tr>
</tbody>
</table>

RD, related donor; NRD, non-related donor.
Percentage of graft loss from RD, 32.4% and NRD, 25.0%. Breslow–Day test of homogeneity of odds ratio: \( \chi^2 = 6.89, \text{df} = 4, P = 0.142 \). Mantel–Haenszel estimate of common odds ratio: 1.78 (95% CI = 0.57, 5.55; \( P = 0.319 \)).

Table 4. Risk of recurrence of IgA nephropathy in related and non-related transplant

<table>
<thead>
<tr>
<th>No. of allografts</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RD</td>
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<tr>
<td>Berger et al. [6]</td>
<td>13</td>
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<tr>
<td>Bachman et al. [7]</td>
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<tr>
<td>Kessler et al. [10]</td>
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<td>Freese et al. [15]</td>
<td>47</td>
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<tr>
<td>Kim et al. [16]</td>
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<td>Wang et al. [17]</td>
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<tr>
<td>Ponticelli et al. [18]</td>
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<tr>
<td>Choy et al. (current)</td>
<td>32</td>
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<tr>
<td>Pooled data</td>
<td>258</td>
</tr>
</tbody>
</table>

RD, related donor; NRD, non-related donor.
Recurrent rate for RD, 30.2% (78/258) and NRD, 22.7% (80/352). Breslow–Day test of homogeneity of odds ratios: \( \chi^2 = 10.2, \text{df} = 9, P = 0.334 \). Mantel–Haenszel estimate of common odds ratio: 2.17 (95% CI = 1.43, 3.30; \( P < 0.001 \)).

*Included five patients suffering from underlying Henoch–Schönlein purpura.

The most intriguing and novel finding in our present analysis is the long-term graft survival in recurrent IgA. Lim and Terasaki [20] had reported a better 5-year graft survival in patients with primary IgAN when compared with recipients with other diseases. The proposed mechanism included increased occurrence of allo-reactive IgA anti-HLA antibodies, which may serve to block the deleterious effect of IgG and IgM antibodies on the graft, and the immunological dysfunction of patients with IgAN. When comparing the graft survival in relation to the underlying cause of renal failure, we observed a superior graft survival in the initial years in patients with primary IgAN than recipients with other underlying causes of renal failure who had received a renal transplantation during the same period. Our data showed that, despite the better graft survival of IgAN patients for the early post-transplantation period, the graft survival became worse than non-IgAN patients with a longer follow-up period (beyond 12 years). There was no doubt that recurrent disease did contribute to late graft loss with increasing time following renal transplantation [7–18]. Our observation suggests that recurrent IgAN in allograft follows an indolent course similar to primary IgAN that exhibits a sharp rise of incidence of ESRF at 15 years after the onset of the disease [1–4]. The development of progressive renal deterioration in some recipients with recurrent IgAN occurs despite adequate immunosuppressive therapy for rejection. Hence, transplant recipients with recurrent IgAN should be followed regularly despite an initial stable renal function. Our present finding again raises the caution of using living-related donors in patients with primary IgAN.

While there is still on-going controversies on the fate of IgAN after renal transplantation, new multi-centre prospective studies employing uniform biopsy policy and uniform histopathological criteria to differentiate between chronic rejection and recurrent IgAN are needed to provide clinicians a better understanding of the disease course in renal allograft.

Conflict of interest statement. None declared.

References

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