Does angiotensin blockade influence graft outcome in renal transplant recipients with IgA nephropathy?

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Abstract

Background. IgA nephropathy (IgAN) is a frequent cause of end-stage renal disease (ESRD) and recurrent disease causes deterioration and graft loss in transplant recipients. No definitive management is known to reduce the risk or severity of recurrent IgAN, and the evidence to support the use of renin–angiotensin system blockade in such patients is limited.

Methods. All 1137 renal transplants performed at the Belfast City Hospital over a 27-year period were reviewed. A total of 75 patients with ESRD due to biopsy-proven IgAN were identified; 39 of them had been prescribed an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II type 1 receptor blocker (ARB).

Results. The two groups were well-matched in terms of demographic details, immunosuppressive regimens and duration of follow-up (median 65 months, range 18–261 months). The 5- and 10-year graft survivals were higher in those prescribed ACEi/ARB therapy compared with those who were not, although these differences did not reach statistical significance (92.9% vs 86.5%; \( P = 0.34 \) and 81.6% vs 72.7%; \( P = 0.32 \), respectively). These results were similar when censored for death with a functioning graft. In the group where an ACEi/ARB was not prescribed, all four with biopsy-proven recurrent IgAN progressed to ESRD, compared with three out of nine in the group treated with an ACEi/ARB.

Conclusions. In transplant recipients with ESRD due to biopsy-proven IgAN, a trend towards improved 5-year and 10-year graft survival was seen in those prescribed ACEi/ARBs. All with recurrent IgAN in their grafts who were not treated with ACEi/ARB therapy progressed again to ESRD.

Keywords: IgA nephropathy; recurrent glomerulonephritis; renal transplantation; renin–angiotensin system
We retrospectively studied patients with biopsy-proven IgAN as a cause of ESRD who received a renal transplant in our institution, to assess the influence of angiotensin blockade on graft survival, and on the course of recurrent IgAN.

Subjects and methods

Patients

All patients who had received a renal transplant at the Belfast City Hospital, UK, between 28 August 1977 and 27 April 2004 because of biopsy-proven IgAN were identified. Those with graft loss due to technical complications, (e.g. renal vein thrombosis), and rejection within the first month of transplantation were excluded from subsequent analyses. Data recorded included gender, age, previous transplant, maintenance immunosuppression, the prescription or not of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II type 1 receptor blocker (ARB), the prescription or not of antihypertensive medication, biopsy-proven recurrence of IgAN, and graft and patient survival. The median duration of follow-up was 65 months (range 18–261 months).

Immunosuppression

Immunosuppressive regimens were individualized but general trends evolved over the 27-year period. Prednisolone and azathioprine was the usual maintenance therapy until 1989; ciclosporin introduction after 1989 allowed triple induction therapy with maintenance ciclosporin monotherapy, or dual therapy with either prednisolone or azathioprine in most patients; mycophenolate mofetil was introduced in 1998 and subsequently 26% of the patients had calcineurin inhibitor-free maintenance regimes; tacrolimus has been used as the calcineurin inhibitor of choice since 2002.

Era of transplantation

There have been significant advances in surgical technique and the immunosuppressive armamentarium over the period of this study. To allow for this variability the cohort was considered in two parts in categorical analysis: the first from 28 August 1977 until 31 December 1990 and the second from the 1 January 1991 until the 27 April 2004, (both of 160-months period).

Angiotensin blockade

If an ACEi/ARB had been prescribed for at least 12 months the patient was categorized as having received angiotensin blockade. No distinction was made between an ACEi and an ARB in the analysis.

Antihypertensive medication

A patient was recorded as receiving antihypertensive therapy if they were prescribed any of the following agents: calcium channel antagonist, β-blocker, α-blocker, diuretic or centrally acting agents.

Graft outcome

No protocol or surveillance biopsies were performed. Clinical indications for biopsy were increasing proteinuria, rising serum creatinine values or both. The tissue was processed for light microscopy and immunofluorescence. IgAN was defined by standard criteria [16] with the recognition that the presence of IgA on immunofluorescence may occur without glomerular change and is not in itself diagnostic of IgAN. Graft loss was attributed to IgAN when there were diffuse mesangial proliferative lesions with glomerular sclerosis, and the absence of significant changes consistent with chronic allograft nephropathy, rejection or calcineurin toxicity.

Statistical analysis

Statistical analysis was performed using the chi-squared test and Fisher’s exact test for categorical variables, and the independent t-test for continuous variables. The Kaplan–Meier curves and log-rank tests were used for description and comparison of graft survival, employing SPSS for Windows® (SPSS® Inc., Chicago, IL, USA) version 13.0.

Results

Of the 1137 transplants performed in our institution between 28 August 1977 and 27 April 2004, 85 (7.5%) grafts were for patients with biopsy-proven IgAN. There were 73 Caucasian patients and one Asian patient. Eleven patients had a second transplant and were included twice. There was one post-operative death (day 1 post transplant) and five graft failures for technical complications or severe acute rejection in the first month. These were excluded from further analyses. One patient was lost to follow-up due to emigration. Data on ACEi/ARB prescription were unavailable for three patients.

Of the 75 cases for which complete data were available, 39 were prescribed angiotensin blocking medication and 36 were not. The characteristics of the two groups are summarized in Table 1. There were no significant differences in demographics, the era of transplantation, the proportion receiving their first transplant, maintenance immunosuppressive therapy or prescription of antihypertensive medication.

The median duration of follow-up was 70 months (range 19–261 months) for those on ACEi/ARB therapy vs 71 months (range 18–208 months) for those who were not.

There were three deaths with a functioning graft in the first 120 months after transplantation. These were due to ischaemic heart disease, malignancy and a road traffic accident. The 5- and 10-year recipient survivals were 95 and 92%, respectively.

The 5-year graft survival was higher in those prescribed ACEi/ARB therapy compared with those who were not (92.9 vs 86.5%), but the difference was not statistically significant (p = 0.34). Similarly there was a trend to improved 10-year graft survival in those prescribed ACEi/ARB treatment (81.6 vs 72.7%; p = 0.32) (Figure 1). These results were similar when
censored for death with a functioning graft. In those with functioning grafts, the mean glomerular filtration rate at the end of the study period was 55.4 ml/min (SD 26.2) and 55.9 ml/min (SD 24.7) in those with and without angiotensin blockade, respectively ($p = 0.95$).

A similar proportion of patients were biopsied in each group, 16 (41%) in those on an ACEi/ARB and 9 (25%) in those who were not ($p = 0.33$). Biopsies in the first 3 months post-transplant were excluded from analysis. In patients with more than one transplant biopsy, the findings were summated so each graft was counted only once. In patients with angiotensin blockade, 10 grafts had IgA-positive immunofluorescence with nine reported as IgAN. Three have returned to dialysis (7.7% of the 39 in this group and 33% of those with IgAN). The difference in rates of recurrent IgAN was not significant ($P = 0.27$). The other histological diagnoses were rejection, calcineurin toxicity and chronic allograft nephropathy. These did not differ significantly between the two groups (Table 2).

**Discussion**

Extending graft survival remains a major challenge for the transplant community. It is established that proteinuria and hypertension are adverse prognostic indicators in the transplanted kidney as well as in native kidneys [14,17], and evidence is now emerging to support the intuitive prescription of angiotensin blockade for grafts with chronic allograft nephropathy [18].

In patients with end-stage renal disease on the basis of IgAN who receive a transplant, recurrence of the native disease is now accepted to be a significant contributor to graft failure [4,5,7,8,19]. There is limited evidence on the best therapy to minimize this risk, but it is generally accepted that calcineurin inhibitors do not alter the natural course of recurrent IgAN.

A recent review of 152 patients also concluded that mycophenolate mofetil does not influence the clinical incidence or severity of recurrent IgAN [19].

Proteinuria and hypertension are common features of clinically relevant recurrent IgAN, and the use of ACEi/ARB therapy seems a logical extension of the application of these drugs in other areas of nephrology. These agents may influence graft survival and favourably modify cardiovascular disease morbidity and mortality following transplantation [20]. The data to support the use of ACEi/ARB therapy in this group of patients is limited.

In a recent review, Chandrakantan and colleagues [19] stated that ‘neither... using an angiotensin-converting enzyme inhibitor [nor] angiotensin-II type 1 receptor blocker ameliorated the clinical course after a biopsy documented recurrent IgAN’. This conclusion was based on 13 patients treated with ACEi/ARB therapy, with a reduction of at least a third in serial urinary protein excretion in only one patient.

In contrast, Ponticelli’s group [8] commented that in those with histologically proven recurrent disease, progression to ESRD occurred in seven of the 16 that were not treated with ACEi compared with three

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**Table 1.** Characteristics of recipients who were receiving angiotensin blockade and those who were not

<table>
<thead>
<tr>
<th></th>
<th>ACEi/ARB</th>
<th>No ACEi/ARB</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>39 (52%)</td>
<td>36 (48%)</td>
<td></td>
</tr>
<tr>
<td>Age (years) mean (SD)</td>
<td>39.5 (13.4)</td>
<td>39.8 (15.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Male</td>
<td>35 (89.7%)</td>
<td>29 (80.6%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Era of transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1 January 1991</td>
<td>3 (7.7%)</td>
<td>6 (16.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>After 1 January 1991</td>
<td>36 (92.3%)</td>
<td>30 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>First transplant</td>
<td>32 (82.1%)</td>
<td>32 (88.9%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Maintenance immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>22 (56.4%)</td>
<td>19 (55.6%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td>27 (69.2%)</td>
<td>29 (80.6%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>24 (61.5%)</td>
<td>29 (80.6%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>36 (92.3%)</td>
<td>34 (94.4%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Table 2.** Histological diagnoses of renal transplant biopsies in recipients who were receiving angiotensin system blockade and those who were not

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>ACEi/ARB</th>
<th>No ACEi/ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Rejection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chronic allograft nephropathy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Calcineurin inhibitor toxicity</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Fig. 1.** The Kaplan–Meier graft survival curves in renal transplant recipients with ESRD due to IgAN, with and without angiotensin blockade.
Angiotensin system blockade and graft outcome in IgA nephropathy

of the 21 that were. The limited patient numbers precludes meaningful statistical analysis.

Oka and colleagues [15] reported on 21 Chinese patients with recurrent IgAN, 10 of whom were prescribed ACEi therapy. There was a significant reduction in hypertension and proteinuria in this group during a mean follow-up of 12.8 months. Longer follow-up would be necessary to assess any impact on graft survival. However, the histological finding in this study of prominent glomerular hyper-trophy in recurrent IgAN conceptually supports the use of angiotensin blockade in the management of hypertension and hyperfiltration in recurrent IgAN.

Our study is considerably larger than those previously reported with a total of 39 transplant recipients with a primary disease of biopsy-proven IgAN receiving ACEi/ARB therapy. The 36 transplant recipients who were not prescribed with an ACEi/ARB provide a useful comparison group. The two groups were well-matched demographically, with regard to the maintenance immunosuppression and duration of follow-up. Over 90% of the patients in both the groups were prescribed antihypertensive therapy, 49% of all those on blood pressure-lowering therapy were not on an ACEi/ARB. The grafts with primary non-function or loss in the first month were excluded from the study to prevent confounding in the data.

The 5-year graft survival was 92.9% in those prescribed angiotensin blockade vs 86.5% in those who were not, and the 10-year graft survival was 81.6 vs 72.7%, respectively. While perhaps clinically re this improvement was not statistically significant (p = 0.34 and p = 0.32). This study has a power of almost 75% to detect a 5% difference in graft survival at the statistically significant level of 5%. Therefore, although considerably larger than previous reports, the possibility of a type II error still exists. Thus, the failure to provide conclusive statistical evidence of improved graft survival with angiotensin blockade does not preclude such an effect.

The impact of angiotensin blockade was also of interest when the outcome of biopsy-proven recurrent IgAN in transplanted kidneys was examined. Overall, 17% of our patients had histologically confirmed recurrent IgAN, which is likely to be an underestimate of the actual recurrence rate given the biopsy policy of our institution. The biopsy-proven IgAN recurrence rate was comparable in both the groups. All four in the group who were not prescribed an ACEi/ARB progressed to ESRD compared with three of the nine in the group treated with an ACEi/ARB. This is similar to Ponticelli’s findings [8], where a greater proportion of the patients receiving angiotensin blockade maintained self-supporting renal function despite recurrent IgAN.

The advantages of our study are the much larger patient numbers than previously reported, the presence of a valid comparison group, and the completeness and long duration of follow-up. Of interest, Choy and colleagues [5] suggested that recurrent IgAN did not become clinically relevant until at least 12 years after transplantation and with a longer follow-up period the trend for improved survival when prescribed an ACEi/ARB may become statistically significant. Registry data, where the original cause of ESRD is accurate and the cause of graft failure is diagnosed on biopsy, could help to establish the true impact of recurrent IgAN on graft outcome. The risk of graft loss from recurrent glomerulonephritis has been described from an Australian transplant registry [9], but in this report follow-up was <10 years and no data were available on the prevalence of recurrent IgAN that did not lead to graft loss.

In conclusion, this large retrospective single-centre study, with prolonged follow-up, identified all patients with ESRD due to biopsy-proven IgAN. A non-significant trend towards improved 5- and 10-year graft survival was seen in transplant recipients who were prescribed an ACEi/ARB. All of the transplant patients with recurrent IgAN in their graft who were not treated with ACEi/ARB therapy progressed again to ESRD. A larger multi-centre study should help to clarify the suggested beneficial effects of ACEi/ARB treatment on graft outcome in patients with ESRD due to IgAN.

Conflict of interest statement. None declared.

References


\textit{Received for publication: 23.6.06 Accepted in revised form: 31.7.06}