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When Post-Transplant IgA Deposition is not Recurrent Disease

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Abstract

Background: Post-transplant immunoglobulin A (IgA) deposition can represent donor-related or *de novo* disease. We aimed to examine post-transplant outcomes in the setting of donor-related or *de novo* IgA deposition.

Methods: All renal biopsy records from 1/1/1995 to 31/12/2012 (n=7296) were reviewed. Cases with post-transplant IgA deposition were categorised as donor-related (<6 months post-transplant), *de novo* (>6 months post-transplant) or recurrent. Donor-related and *de novo* cases had a clearly documented alternative cause of end-stage renal disease. The National Kidney Transplant Service (NKTS) database was accessed to facilitate a comparison of patient and graft outcomes in these cohorts and all other renal transplant recipients.

Results: Fifteen cases of post-transplant IgA deposition were deemed to be donor-related and had a mean MEST score of 1.4 (range 0-3). Serial biopsies in seven of these cases showed resolution of the deposits over time. Eight cases were deemed to represent *de novo* IgA deposition. The mean MEST score was 2.4 (range 0-4). There were no differences in patient and graft survival rates in these groups compared to all other transplants performed during a similar time period. Cox regression multivariate analysis did not identify either donor-related or *de novo* IgA deposition as a contributing factor to patient or graft survival.

Conclusions: Cases of donor-related or *de novo* IgA deposition were infrequently encountered in our review of 'for-cause' biopsies. Neither condition, when histologically mild-moderate, was found to impact on patient or graft survival rates. This information is important for prognostication and counselling purposes in selected future cases.

Keywords: Immunoglobulin A; Kidney transplant; Kidney donor; Glomerulonephritis

Abbrevations: IgA: Immunological A; NKTS: National Kidney Transplant Service; MPGN: Membrano-Proliferative Glomerulonephritis; ADPKD: Autosomal Dominant Polycystic Kidney Disease; FSGS: Focal

Segmental Glomerulosclerosis; HLA: Human Leucocyte Antigen

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and an important cause of end-stage renal disease (ESRD) [1,2]. The diagnostic hallmark is the presence of IgA deposits in the glomerular mesangium [3]. Beyond that, several key histological features may be present and help prognosticate. The Oxford Classification system of these features has standardised reporting and facilitated research in this area (*Appendix 1*) [4].

		0	1	2
M	Mesangial Hypercellularity	Mesangial score ≤0.5	Mesangial score >0.5	
E	Endocapillary Hypercellularity	Absent	Present	
S	Segmental glomerulosclerosis	Absent	Present	
T	Tubular atrophy/interstitial fibrosis	0-25%	26-50%	>50%

Appendix 1: Summary of the Oxford Classification of IgAN, which assigns a MEST score that, facilitates prognostication and research.

Note the mesangial hypercellularity score was calculated for each glomerulus by assessing the most cellular mesangial area. The sum of the mesangial scores was divided by the number of scorable glomeruli to give an overall mesangial score. If the overall mesangial score was ≤0.5, M0 was assigned. If the overall mesangial score was >0.5, M1 was assigned. The clinical presentation ranges from haematuria and/or proteinuria on urinalysis in an asymptomatic person with normal renal function, to a crescentic, rapidly progressive glomerulonephritis with accelerated progression to ESRD. Mesangial IgA deposition in an asymptomatic person with normal renal function is termed latent IgA nephropathy/deposition.

Most centres do not routinely biopsy and perform pre-transplant immunofluorescence (IF) on deceased donor kidneys. Therefore, deceased donor latent IgAN may not be recognised until the post-transplant period, when a transplant biopsy is performed for clinical reasons. The reported prevalence of latent IgAN is variable, as demonstrated by several autopsy and donor nephrectomy case series. IgA deposition was present in twelve of 250 (4.8%) autopsy cases in one series; notably six of these cases had cirrhosis [5]. Another group identified latent mesangial IgA deposition in eight of 74 consecutive autopsy cases (11%) [6]. A Japanese series (where IgAN is particularly common) in which time-zero biopsies were performed in 510 healthy donor kidneys (446 living donor; 64 deceased donor) demonstrated IgA deposition in 16.1% [7]. There was no statistical difference between the prevalence in living donors (16.8%) and deceased donors (15.6%), or between related (16.8%) and unrelated (14.5%) living donors. A Chinese group identified IgA deposition in 83 of 342 (34%) consecutive deceased donor kidney biopsy samples [8]. It is important to note that the epidemiology of IgA nephropathy has a marked geographical variation with a particularly high prevalence in Asian countries [9,10].

In the context of living donation, latent IgA deposition/nephropathy would ideally be identified during routine donor medical evaluation. Potential living donors (LD) with IgA deposition identified on biopsy are declined as donors from most international transplant centres for fear of future progression in a solitary kidney. Therefore, post-donation follow-up reports of LDs with IgA deposition are extremely limited. Certainly some have a poor long-term outcome [11]. Long-term clinical follow-up of the 72 Japanese LDs with IgA deposition mentioned above [7] has not been published to date.

In terms of recipient outcomes where the donor had latent IgAN, the limited available data is mixed. An early case series reported resolution of the mesangial IgA deposits over months but severe rejection in three of four patients [12]. The Japanese group (cited above) reported their recipient outcomes [13]. They identified donor IgA deposition as a risk factor for recurrent IgAN in those patients with IgAN as cause of ESRD. In this cohort, 38.5% of those with recurrent IgAN also had donor IgA deposition, whereas 9.1% of those without recurrence had donor IgA deposition. The Chinese group cited above also reported resolution of the IgA deposits on serial histological specimens over months. However, short-term complications, most notably acute rejection, were more common in the group with donor-related IgA deposits. Long-term graft survival was similar to the group without donor-related IgA deposition [8].

Less again is understood about those patients in whom IgAN was not the original cause of ESRD yet go on to develop IgA deposition in their transplanted kidney over time; this is termed *de novo* IgAN. This may represent co-

incidental occurrence (or perhaps recurrence) of a relatively common condition in a patient that also happens to have another cause of ESRD. Little has been written about this group of patients, and the impact of *de novo* IgAN on graft outcomes is unknown as outcomes are usually reported in conjunction with recurrent cases [14]. The aims of this study were to investigate transplant outcomes in Irish kidney transplant recipients with donor-related IgA deposition or *de novo* IgA deposition post-transplant, and to compare outcomes to those in all other transplants performed in Ireland during the same time period.

Methods

Setting & Participants

Beaumont Hospital, Dublin is the National Kidney Transplant Service (NKTS) centre for the Republic of Ireland. All adult renal transplant surgery and all living donor (LD) evaluations are carried out in this hospital. Between 150-190 kidney transplants are performed annually (deceased and living donor transplants). It is Irish transplant practice that potential living donors with histological evidence of mesangial IgA deposition are declined [15]. Beaumont Hospital is also home to the NKTS recipient database, which has detailed longitudinal data on all renal transplants performed in Ireland since 1964.

Deceased donors are approved based on clinical characteristics (including current and historic laboratory results and urinalysis where possible). Pre-implant biopsies are performed in expanded criteria donors and those in whom there is some clinical concern regarding kidney disease/function. An on-call renal pathologist reports light microscopic findings (without immunofluorescence) in such cases. The histology report is considered in light of the clinical context and a decision made regarding transplantation. Post-transplant renal biopsies are performed when clinically indicated (no protocol biopsies), with immunofluorescence and electron microscopy performed on all samples if indicated and sufficient tissue is available.

Study design

All renal biopsy records from 1/1/1995 to 31/12/2012 (n=7296) were analysed to identify those with evidence of post-transplant IgA deposition. A retrospective review of these case records was performed and IgA deposition was categorised as donor-related, recurrent or *de novo* IgA deposition based on the donor and recipient records. Donor cases had a clear alternative cause for ESRD (exceptions detailed in results section) and were identified within six months of transplant. *De novo* cases also had a clear alternative cause for ESRD and were identified after six months post-transplant. Cases were deemed recurrent if they had a biopsy-proven diagnosis of IgA nephropathy in the native kidneys or if they presented with advanced renal disease, diagnostic work up did not yield an alternative cause and the cause was deemed likely end-stage IgA nephropathy.

Those cases deemed to be donor-related or *de novo* were the group of interest for this paper. A senior pathologist formally reported all biopsies. A second pathologist performed formal mesangial hypercellularity scoring at a later date and retrospectively assigned an Oxford Classification score (MEST score, Appendix 1) [4].

The NKTS recipient database was accessed in December 2016 to examine outcomes in the two cohorts of interest and all other transplants performed during the same time period. Of note, the comparison group was different for both analyses: all cases of *de novo* IgA nephropathy were identified pre-2000 and so the comparison group used for this analysis was first transplants performed 1984 – 2000. The donor-related group was compared to all other first transplants 1999 – 2012. Kaplan-Meier (KM) methods were used to graph patient and transplant outcomes and Cox proportional hazards models were used to asses risk of outcome in the presence of potential confounding variables. All data were recorded in a coded format on an Excel database. Data analysis was performed using Stata SE (version 13, College Station, Texas) software.

Results

Review of histology archives yielded 73 transplant recipients with IgA deposition over the seventeen-year period. All clinical cases records were reviewed in detail to facilitate classification into one of the three categories. Fifteen were classified as donor-related IgA deposition, eight patients had *de novo* deposition and fifty patients had recurrent IgA nephropathy. Basic demographic details (data accessed from NKTS) are summarised in Table 1.

Variable	Donor IgA (n=15)	De Novo IgA (n=8)	NKTS Database (n= 3,057)
Age at transplantation in years: mean (range)	45.1 (22-55)	32.8 (15-47)	44.3 (3 - 77)
Male Sex: n (%)	12 (80)	6 (75)	1,950(63)

Prevalence of Hypertension: n (%)	12 (80)	4 (50)	NA
Primary Renal Disease: (n) - MPGN - Membranous glomerulonephritis - ADPKD - Reflux Nephropathy - Hypertension - IgA Nephropathy** - FSGS - Familial Amyloidosis - Diabetes - Nephrolithiasis - Other / Unknown	 3 2 3 1 1 2 1 1 1	 1 1 1 1 1 3	
Time from diagnosis to ESRD; years: mean (range)	13.5 (5-29)	2.9 (0-7)	NA
Duration of dialysis pre-transplant; years: mean (range)	3.3 (0-12)	1.8 (0.25-5)	2.3 (0 – 18.8)
Immunosuppressive Regimen: % Tacrolimus-based / Cyclosporin-based / Other	73.3/ 20.0/ 6.7	12.5/ 75.0 /12.5	48.0/ 47.1/ 4.9
Donor age at transplantation in years: mean (range)	39.3 (19-57)	35.8 (16-55)	40.9 (1 – 73)
Donor Male sex: n (%)	9 (60)	4 (50)	1,687 (60)
Donor Terminal Creatinine (umol/ml): mean (range)	74.6 (45-116)	NA	NA
Nature of transplant: deceased donor n (%) Living donor n (%)	14 (93.3) 1 (6.7)	8 0	2,945 (96.3) 112 (3.7)
Number of HLA mismatches (of 6): mean (range)	3.5 (0-6)	2.1 (1-3)	2.9 (0 – 6)
Delayed graft function post-transplant: n (%)	6 (40)	1 (12.5)	395 (13.5)
Time between transplant and biopsy: mean (range)	27.1 days (9-98)	8.42 years (1-16 years)	NA

Table 1: Baseline demographics of the patients included for study.

Donor-related IgA deposition

Two patients with a background history of biopsy-proven native IgA nephropathy were deemed to have donor-related IgA deposition on an early post-transplant biopsy. This was group consensus following extensive case review. In both cases, the mate kidney also had an early post-transplant biopsy with evidence of IgA deposition in the setting of an alternative cause of recipient ESRD (polycystic kidney disease and biopsy proven membrano-proliferative glomerulonephritis with negative immunofluroescence for IgA).

Of the fifteen cases, one case was in the context of LD. A forty-year-old woman had intermittent trace dipstick haematuria during LD evaluation. 24-hour urinary protein was 0.06g/day; serum creatinine was 52µmol/l; cystoscopy was normal. On balance, she was approved for donation without pre-donation biopsy, but with extensive information and education regarding potential risks and the need for follow-up. Most recent review (two years later) showed normal blood pressure with serum creatinine of 65µmol/l and trace haematuria on urinalysis. Lifelong annual follow-up is routine in all Irish living donors and will be important here given the additional risk factor for chronic kidney disease. The remaining fourteen cases were in the context of deceased donation. None of the donors had known kidney disease and the mean terminal creatinine was excellent at 74.6µmol/l (range 45-116µmol/l).

The MEST score was retrospectively applied to the fifteen biopsies that demonstrated donor-related IgA deposition. The mean MEST score was 1.4 (median 1, range 0-3). Twelve cases (80%) had mesangial hypercellularity; two cases demonstrated endocapillary hypercellularity, three demonstrated segmental glomerulosclerosis and four cases had 26-50% tubular atrophy/interstitial fibrosis. The histological severity was, therefore, generally mild. The transplant biopsies in this group were performed at a mean of 31 days post-transplantation (median 19 days; range 6-105 days). The biopsy indications were acute

graft dysfunction (n=11), persistent delayed graft function (DGF) (n=3) and proteinuria/haematuria (n=1). Excluding the three patients with ongoing DGF and dialysis dependence, the mean creatinine at biopsy was 207µmol/l.

Three patients, whose biopsies showed acute T-cell mediated rejection (as well as donor-related IgA deposition), received pulse corticosteroid (500mg methylprednisolone IV for three days) and maintenance immunosuppression was optimised. Two patients underwent tacrolimus dose reduction (on the basis of a supra-therapeutic tacrolimus trough level on the day of biopsy and histological features of tacrolimus toxicity). Eight patients had no immunosuppression changes following the transplant biopsy. Serial biopsies were performed and available for analysis in nine of the fifteen donor-related cases. There was insufficient tissue for immunofluorescence in one case. One demonstrated on going IgA positivity although this was performed shortly after the first biopsy (four weeks later). The remaining seven were negative for IgA deposition on follow-up biopsies. In all nine cases, the mesangial hypercellularity (M) scores remained persistently elevated and the tubular atrophy/interstitial fibrosis (T) scores increased on serial biopsies.

Patient survival was identical at both five and ten years at 89.9% (43.3% - 98.4%) in the group with donor-related IgA deposits and was not different from all other transplants performed during a similar time period (Figure 1a; p=0.4096). One patient with donor IgA deposition died from metastatic non-small cell lung carcinoma with a functioning transplant five years post-transplant. Two patients died some years after graft failure from sepsis and unknown causes respectively. Cox regression multivariate analysis identified recipient age, DGF and diabetes as significant contributors to patient survival; donor IgA deposition did not contribute significantly (Table 2).

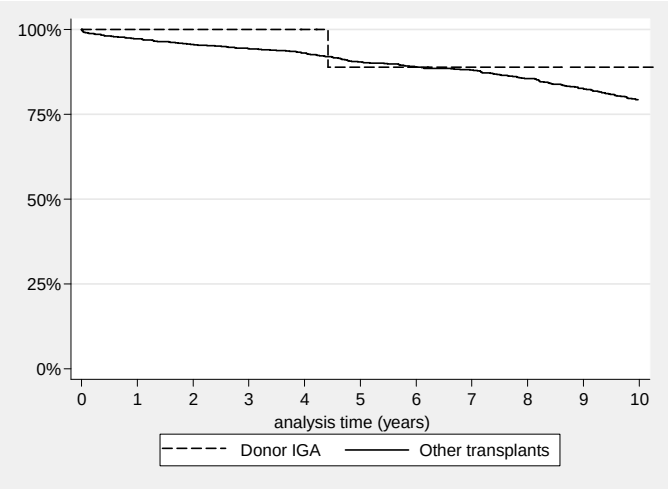

Figure 1a: Patient survival in those with donor-related IgA deposition compared to all other first transplants 1999 - 2012 (p=0.4096).

	Graft Survival		Patient Survival	
Variable	**Hazard Ratio [95% C.I.]**	**P value**	**Hazard Ratio [95% C.I.]**	**P value**
Donor IgA	1.737 [0.765-3.945]	0.187	0.879 [0.121-6.351]	0.898
Recipient Age at Transplant	1.024 [1.016-1.033]	<0.001	1.078 [1.064-1.092]	<0.001
Recipient Sex	0.906 [0.742-1.107]	0.335	0.878 [0.665-1.158]	0.358
Donor Age	1.004 [0.996-1.011]	0.354	1.002 [0.992-1.013]	0.605
Donor Sex	0.912 [0.752-1.105]	0.346	0.979 [0.753-1.274]	0.878
Delayed Graft Function	1.691 [1.340-2.134]	<0.001	1.804 [1.327-2.452]	<0.001
Biopsy-proven Rejection	1.659 [1.302-2.114]	<0.001	1.302 [0.905-1.874]	0.155
Cold Ischaemia Time	1.000 [0.981-1.019]	0.979	1.004 [0.976-1.033]	0.756

PRA group †	1.053 [0.932-1.190]	0.404	1.077 [0.895-1.297]	0.434
HLA mismatch	1.009 [0.941-1.083]	0.789	1.026 [0.930-1.132]	0.610
Diabetes	1.582 [1.146-2.184]	0.005	2.205 [1.509-3.221]	<0.001
Immunosuppression (TAC v CYA)	0.653 [0.515-0.828]	<0.001	0.707 [0.511-0.978]	0.037
Duration of Dialysis	1.007 [0.977-1.038]	0.642	0.997 [0.959-1.036]	0.871

Table 2: Cox regression multivariate model to assess the impact of a number of clinical variables on graft and patient survival in the group with donor-related IgAN and comparable transplant recipients (NKTS data).
PRA = Panel Reactive Antibody; HLA = Human Leucocyte Antigen; TAC = tacrolimus; CYA = cyclosporine A
† PRA group: 0-10%, 11- 49%, 50 – 84%, 85 – 100%

Graft survival at five and ten years post transplant was 77.6% (44.9% – 92.1%) and 46.4% (15.9% - 72.6%) respectively in the group with donor-related IgA deposits, and was not different from all other transplants performed during a similar time period (Figure 1b; p = 0.3056). Seven patients experienced graft failure at a mean of 7.2 years post-transplant, with return to haemodialysis (n=5) or pre-emptive transplantation (n= 2). One individual is approaching graft failure at twelve years post-transplant; six patients are alive with functioning grafts (at 3-12 years post-transplant); one was lost to follow-up. A Cox regression multivariate model was utilised to assess the impact of several clinical variables on graft survival (Table 2). In this model recipient age, the presence of DGF, an episode of rejection and maintenance immunosuppression (which largely correlates to pre-2005 (cyclosporine) and post-2005 (tacrolimus)) reached statistical significance in terms of contribution to graft survival; the presence of donor IgA deposits did not.

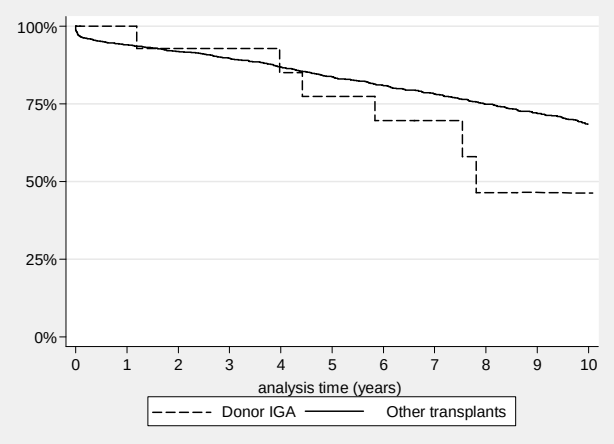

Figure 1b: Graft survival in those with donor-related IgA deposition compared to all other adult transplants 1999 - 2012 (0.3056).

De novo IgA deposition

All cases of *de novo* IgA deposition were identified the context of first deceased donor transplantation. In the *de novo* group, the mean time to development of clinically significant IgAN (ie date of transplant to date of biopsy) was 8.4 years (range 1-16 years). Biopsy indication was rising creatinine in all cases, mean creatinine at the time of biopsy was 259µmol/l . None of these patients had comorbidity specifically associated with IgA nephropathy (such as cirrhosis or inflammatory bowel disease).

At the time of *de novo* IgAN identification, the mean MEST score was 2.4 (median 2.5, range 0-4) with >50% tubular atrophy / interstitial fibrosis (T) seen in five of eight cases. One case had a single crescent evident among thirteen non-sclerosed glomeruli. Several other disease processes were identified on these biopsies, rendering the MEST score less specific for grading the severity of IgA nephropathy. All were treated conservatively from an IgAN viewpoint (either no specific therapy or addition of an ACE-inhibitor).

Patient survival at five and ten years was 100% and 87.5% (38.7% - 98.1%) respectively in the group with *de novo* IgA deposits and was not different from all other transplants performed during a similar time period (Figure 1c; p=0.6024). There were four patient deaths; one of these were in the setting of a functioning transplant. The causes of death were encapsulating peritoneal sclerosis, pneumonia, heart failure and unknown. There were no reported malignancies in this patient group. A Cox regression multivariate analysis identified recipient age, donor age, acute rejection and HLA mismatch as significant contributors to patient survival; *de novo* IgA deposition did not contribute significantly (Table 3)

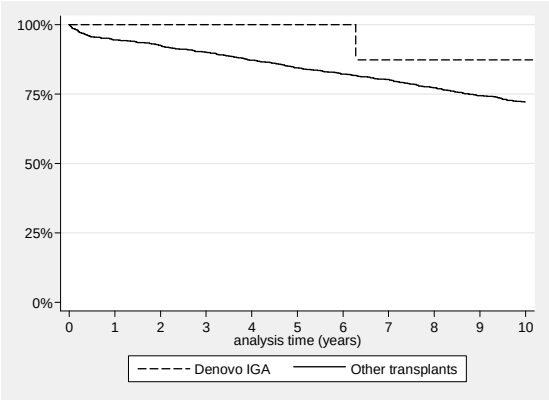

Figure 1c: Patient survival in those patients with *de novo* IgA deposition compared to all other first deceased donor grafts performed 1984 – 2000 (p=0.6024).

	Graft Survival		Patient Survival	
Variable	**Hazard Ratio [95% C.I.]**	**P value**	**Hazard Ratio [95% C.I.]**	**P value**
De novo IgA	0.978 [0.391-2.443]	0.962	0.832 [0.202-3.426]	0.799
Recipient Age at Transplant	1.013 [1.007-1.019]	<0.001	1.065 [1.057-1.073]	<0.001
Recipient Sex	1.099 [0.934-1.294]	0.256	1.474 [1.196-1.815]	<0.001
Donor Age	1.007 [1.002-1.013]	0.005	1.008 [1.002-1.015]	0.008
Donor Sex	0.909 [0.778-1.062]	0.232	0.983 [0.809-1.193]	0.860
Delayed Graft Function	1.067 [0.836-1.367]	0.605	1.125 [0.847-1.494]	0.416
Biopsy-proven Rejection	1.646 [1.394-1.944]	<0.001	1.528 [1.241-1.881]	<0.001
Cold Ischaemia Time	1.002 [0.989-1.014]	0.809	1.009 [0.993-1.027]	0.238
PRA group †	1.185 [1.055-1.332]	0.004	1.091 [0.947-1.257]	0.228
HLA mismatch	0.961 [0.901-1.025]	0.229	0.918 [0.848-0.993]	0.033
Immunosuppression (TAC v CYA)	1.150 [0.776-1.706]	0.486	1.114 [0.589-2.105]	0.740
Duration of Dialysis	0.996 [0.953-1.041]	0.877	1.042 [0.989-1.099]	0.121

Table 3: Cox regression multivariate model to assess the impact of a number of clinical variables on graft and patient survival in those with *de novo* IgAN and comparable transplant recipients (NKTS data).
PRA = Panel Reactive Antibody; HLA = Human Leucocyte Antigen; TAC = tacrolimus; CYA = cyclosporine A
† PRA group: 0-10%, 11- 49%, 50 – 84%, 85 – 100%

Graft survival at five and ten tears post transplant was 87.5% (38.7% – 98.1%) and 37.5% (8.7% - 67.4%) respectively in the in the group with *de novo* disease, and was not different from all other transplants performed during a similar time period (Figure 1d; p=0.6839). *De novo* disease was not considered the main cause of graft failure in any of the cases. Graft failure was due to polyoma virus in one case, the remaining cases failed in the setting of advanced chronic changes on biopsy, likely due to chronic rejection and/or calcineurin toxicity. The median time between diagnosis of *de novo* disease and graft loss in the six cases with subsequent graft loss was cases was 2.65 years (range three months to ten years). Graft half-life was 9.8 years for the transplant group in

general and 8.4 years in the *de novo* IgA group. A Cox regression multivariate model identified recipient age, an episode of acute rejection and immunologic risk (as measured by strata of panel reactive antibody - PRA) as contributors to graft survival; *de novo* IgA deposition was not (Table 3). Graft and patient survival were worse in the *de novo* analysis than in the donor-related analysis, which likely represents an era effect.

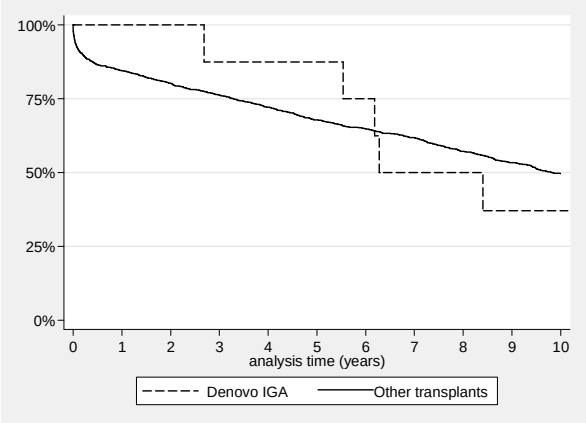

Figure 1d: Graft survival in those patients with *de novo* IgA deposition compared to all other first transplants performed 1984 – 2000 (p=0.6839).

Discussion

It is unsurprising that latent, donor-related IgA deposition was less common in this review (where a 'for-cause' biopsy practice was observed in a predominantly Caucasian population), than reported in other studies where protocol or consecutive biopsies were performed in predominantly Asian patients [3]. The cases of donor-related IgA deposition were histologically mild based on retrospectively applied MEST scores, and clinically latent with excellent donor kidney function even in the terminal phase of life. Those with serial biopsies demonstrated resolution of the IgA positivity over time although the mesangial hypercellularity persisted and tubular atrophy/interstitial fibrosis (which are not specific to IgAN) developed.

In light of previous literature, we looked specifically at those two patients with IgA nephropathy as cause of ESRD who received a kidney with donor-related IgA nephropathy [13]. Neither experienced rejection during their transplant course (seven and four years). Interestingly, both experienced moderate-severe recurrent IgA nephropathy three and seven years later, which ultimately led to graft loss in both cases. Patient and graft survival rates were similar to those seen in a comparable group. We therefore suggest that if donor IgA deposition is identified in the context of deceased donation, this should not deter from proceeding as a donor, if no other contraindication exists. We also suggest that these results are not transferable to the living donor setting as our study included just one living donor with medium-term follow-up to date.

With regard to *de novo* IgA depostition, there were numerous acute and chronic pathologies evident on the biopsies rendering MEST scoring less specific for IgAN. The tubular atrophy/interstitial fibrosis (T) scores were more severe; this is a final common lesion in a variety of kidney injuries and not specific for IgAN. There were no floridly active, crescentic cases. We suggest that the focus of management in cases of *de novo* IgA deposition with mild/moderate activity should be control of blood pressure and proteinuria rather than additional immunosuppression. Again, patient and graft survival rates (without additional immunotherapy) were similar to those seen in a comparable group of transplant recipients. We were interested to note all cases of *de novo* IgA nephropathy were identified prior to 2000, with 75% on cyclosporin-based immunosuppression.

In conclusion, cases of donor and *de novo* IgA deposition are infrequently encountered post-transplant but, if histologically mild-moderate, are not associated with reduced patient and graft survival.

Consent: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its

later amendments or comparable ethical standards. For this type of study (retrospective), formal consent is not required.

Ethical Approval: Granted from Hospital Research Ethics Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Informed Consent: All patients consented to participation in the NKTS database for research purposes.

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