44. Routledge FS, Campbell TS, McFetridge-Durdle JA *et al.* Improvements in heart rate variability with exercise therapy. Can J Cardiol 2010; 26: 303–312
45. Deligiannis A. Cardiac adaptations following exercise training in hemodialysis patients. Clin Nephrol 2004; 61(Suppl 1): S39–S45.
46. Kouidi E, Karagiannis V, Grekas D *et al.* Depression, heart rate variability, and exercise training in dialysis patients. Eur J Cardiovasc Prev Rehabil 2010; 17: 160–167
47. Kramer JM, Beatty JA, Plowey ED *et al.* Exercise and hypertension: a model for central neural plasticity. Clin Exp Pharmacol Physiol 2002; 29: 122–126
48. Laterza MC, de Matos LD, Trombetta IC *et al.* Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. Hypertension 2007; 49: 1298–1306
49. Mimura J, Yuasa F, Yuyama R *et al.* The effect of residential exercise training on baroreflex control of heart rate and sympathetic nerve activity in patients with acute myocardial infarction. Chest 2005; 127: 1108–1115
50. La Rovere MT, Bersano C, Gnemmi M *et al.* Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. Circulation 2002; 106: 945–949
51. Iellamo F. Prognostic role of baroreflex control of heart rate: further insights from dynamic assessment of baroreceptor-cardiac reflex? J Hypertens 2007; 25: 51–53
52. Kouidi E. Central and peripheral adaptations to physical training in patients with end-stage renal disease. Sports Med 2001; 31: 651–665
53. Kouidi E. Exercise training in dialysis patients: why, when, and how? Artif Organs 2002; 26: 1009–1013

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ORIGINAL ARTICLE

The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival*

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Keywords: IgA nephropathy, renal transplantation, recurrent glomerulonephritis

ABSTRACT

Background. Few data are available on allograft survival at 15 years, the impact and the predictors of recurrence of the original disease in renal transplanted patients with IgA nephropathy (IgAN).

Methods. In this retrospective study, we compared the long-term outcome of renal transplant in 190 patients with IgAN

with that of 380 non-diabetic controls and evaluated the impact of recurrence of IgAN on the graft outcome.

Results. At 15 years, the patient survival was 88.3% in IgAN patients and 82.6% in controls (P = 0.12), while the death-censored graft survival was 62.6 and 72.4%, respectively (P = 0.038). IgAN had a higher cumulative incidence of graft failures in comparison with controls even considering death as a competing risk (P = 0.025). At multivariate analysis, IgAN [relative risk (RR) = 1.468, P = 0.026], delayed graft function recovery (RR = 2.394, P = 0.000) and acute rejection (RR = 2.51, P = 0.000) were predictive of graft loss. IgAN recurred in 42 grafts (22.1%), of them, 12 were lost for recurrence and in another 6 recurrence was considered a concomitant cause of graft loss. The 15-year death censored graft survival was 68.3% in non-recurrent and 51.2% in recurrent patients (P = 0.069). Pure graft survival of non-recurrent IgAN patients was similar to that of controls (P = 0.406). At Cox analysis, the recurrence of IgAN significantly reduced from 1981 to 2010 (P = 0.0065, RR = 0.936).

Conclusions. IgAN emerged as an independent predictor of worse graft outcome in the long-term. Recurrence of IgAN seems to progressively reduce in transplants performed from 1981 to 2010.

ORIGINAL ARTICLE

INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide [1], and causes end-stage renal disease in 20–40% of patients at around 20 years after its diagnosis [2]. Kidney transplant is the treatment of choice for patients with end-stage renal disease secondary to glomerulonephritis. The available comparisons between the graft survival of IgAN patients and that of a control group underline that during the first 5 years after transplantation, allograft survival for primary IgAN patients is better than that of patients with other primary diseases [3–5], at 10 years, graft survival of IgAN patients becomes comparable with that of other diseases [3, 6] or is even worse after 12 years [7]. Few data are available on the outcome of IgAN-transplanted patients after 10 years [7, 8]. Ponticelli and Glassock [9] suggest that with the prolongation of the follow-up, the recurrence of IgAN may become a substantial risk factor for graft failure. As a matter of fact, the possibility of recurrence of the original glomerulonephritis in the allograft is a well-established complication [10]. Recurrence is a time-dependent event, whose prevalence increases as the duration of follow-up grows, and it is reported to be the third cause of graft loss 10 years after kidney transplantation [11]. In IgAN patients, routine graft biopsies [12] demonstrated a histological recurrence in 53% of cases although some patients had no clinical manifestations. The recurrence rate of patients receiving graft biopsies for clinical indication only ranged from 13 to 50% [3, 4, 6, 7, 13–24]. This wide range in the rate of recurrence can be attributed to the different policy of graft biopsy of the different centres and to the differing durations of follow-ups of the published studies. Graft loss from recurrence was reported to be between 1.3 and 16% [3, 4, 6, 7, 12–23]. The aims of this single-centre retrospective analysis were (i) to compare the long-term patient and renal allograft survival of IgAN patients with those of a well-matched control group and (ii) to evaluate the rate, outcome and predictors of recurrence in renal transplant recipients with IgAN.

SUBJECTS AND METHODS

Patients

One hundred and ninety patients with end-stage renal disease due to biopsy-proven primary IgAN received a renal transplantation in our unit between 1981 and 2010. Thirteen of these patients lost the graft and received, in the same period, a second renal transplant. In six of these patients, the first graft was lost for recurrence 33–224 months after transplant. Recurrence developed in only one of the second grafts and this graft was lost for recurrence again 152 months after transplant. Some of these patients are included in a previously published paper [6].

Thirty-six first transplantations were from living-related donors (18.9%) and 154 were from deceased donors.

Patients receiving a renal transplant in the same period (+/−3 months before or after), matched for age (+/−5 years), gender and source of the donor were chosen as controls. Of 380 controls, 76 patients were carriers of autosomal dominant polycystic kidney disease, 72 had hypertensive nephrosclerosis, 61 chronic pyelonephritis, 59 urological malformations/pathologies, 24 Alport syndrome, 43 interstitial nephritis, 6 nephronophthisis, 31 systemic diseases and 8 other causes. None of the controls had diabetes as original disease.

Definitions

Biopsy policy. Whenever an acute episode of renal dysfunction of doubtful origin, persistent proteinuria >0.5 g/day or persistent microscopic haematuria of non-urological origin developed, the patient was subjected to graft biopsy. In addition, all patients with progressive renal dysfunction received one more more graft biopsy.

Evaluation of renal biopsies. All biopsies were evaluated by light microscopy and by immunofluorescence. Electron microscopy was performed in about one-third of cases.

Diagnosis of recurrence of IgA. Diagnosis of recurrence of IgA was performed by immunofluorescence positive staining for IgA in the mesangial area. Recurrent biopsies were evaluated according to the Oxford classification [25].

Definition of graft loss causes. Graft loss was attributed to recurrent IgAN when renal histology showed diffuse mesangial proliferation and/or segmental necrosis of the tuft associated with extracapillary proliferation and glomerular sclerosis. These lesions were usually associated with progressive worsening of proteinuria and severe haematuria. When interstitial inflammation and transplant arteriopathy were observed, the failure of the graft was attributed to chronic active T-cell-

mediated rejection. The presence of peritubular capillary deposition of C4d associated with the positivity of anti-HLA antibodies in the serum of patients suggested the diagnosis of chronic active antibody-mediated rejection. In some cases, the failing graft showed only interstitial fibrosis and tubular atrophy.

When the previously described glomerular and vascular lesions were coexisting, the graft loss was attributed to a mixture of IgAN and rejection.

Delayed graft function recovery. Delayed graft function recovery was defined by a slow decrease in serum creatinine, either requiring dialysis or not and persisting for at least 2 weeks.

Acute rejection. Acute rejection was diagnosed on the basis of a double-checked increase of ≥30% of plasma creatinine over the baseline, not explained by other causes.

The severity of rejection and the classification of chronic lesions were scored retrospectively according to the recently revised Banff classification [26].

Immunosuppression

The immunosuppressive therapy of IgAN patients and of controls is reported in Table 1. Acute T-cell-mediated rejections were treated with intravenous methylprednisolone pulse therapy, and antibodies-mediated rejections with anti-thymocyte globulins.

Statistical analysis

The statistical package S-Plus was used to analyse sample data. Since most of the variables showed non-normal distribution, the median and interquartile ranges were used for descriptive analysis. As well, the non-parametric Wilcoxon test was used to evaluate the differences between the two groups of patients. Cross-tabulated data were analysed by the Chi-square test or by the Fisher test when the expected cell count was less than five. Patient survival, graft survival and recurrence-free survival curves were drawn using the Kaplan–Meier estimate and compared using the log-rank test. Univariate Cox proportional hazards models were used to investigate the significance of each prognostic factor for graft loss and for recurrence. All factors reported in Table 1 were tested as predictors of graft loss, and those reported in Table 2 were tested as predictors of recurrence. In addition, the year of transplant was tested as predictor or recurrence. Statistically significant factors were then tested in multivariate analysis. Only acute rejections occurring within the first post-transplant year were considered for analysis as non-time-dependent variables. Relative risk (RR) for each covariate was derived from the Cox model as the antilogarithm of its estimated coefficient, and 95% confidence interval (CI) was computed as the antilogarithm of coefficient ± 1.96 × standard error of the coefficient. Competing risk analyses were performed with NCSS software considering the cumulative incidence of graft failure and death. The significance of differences between cumulative incidence curves was estimated by the Gray test [27].

RESULTS

The median values with interquartile ranges of demographic and clinical characteristics of IgAN patients and of controls are reported in Table 1. The only significant differences between the two groups were a significantly longer duration of dialysis in controls (P = 0.014) and a higher number of hypertensive patients in the IgAN group (P = 0.0017).

Patient and graft survival

The median post-transplant follow-up was 113.1months (60.5–165.1) for IgAN patients and 115 months (59.2–174.2) for controls (P = ns).

The actuarial 15-year patient survival rates were 88.3% in IgAN patients and 82.6% in controls (P = 0.12) (Figure 1A). Fourteen patients in the IgAN group died (7.36%) after a median follow-up of 73.2 months (32.6–111.8). In the control group, 50 patients died (13.2%) after a median follow-up of 109.2 months (48.9–172).

Fifty-eight out of 190 grafts (30.5%) in IgAN patients were lost at 98.4 months (44.6–132.9) after transplantation. In the control group, 87 graft failures (22.8%) occurred at 115.3 months (64.4–171.3) after transplantation.

The actuarial death-censored graft survival rates at 15 years were 62.6% in IgAN patients and 72.4% in the control group (P = 0.038) (Figure 1B). The cumulative incidence of graft failure of IgAN patients confirmed to be higher (86%) than that of controls (39%) even considering death as a competing risk (P = 0.025).

The variables reported in Table 1 were tested as predictors of graft loss for the whole population in the study. At univariate analysis, delayed graft function recovery (P = 0.000, RR = 2.57, CI 1.81–3.67), the occurrence of acute rejection within the first year after transplant (P = 0.000, RR = 2.72, CI 1.95–3.78), less than three immunosuppressive drugs (P = 0.013, RR = 0.665, CI 0.47–0.91) and IgAN in the original kidneys (P = 0.039, RR = 1.42, CI 1.01–1.98) were predictors of graft loss. At multivariate analysis, IgAN (P = 0.026, RR = 1.468, CI 1.0459–2.0607), delayed graft function recovery (P = 0.000, RR = 2.394, CI 1.6725–3.4269) and acute rejection (P = 0.000, RR = 2.51, CI 1.79–3.5) were independent predictors of graft loss.

In IgAN patients transplanted from deceased donors, patient and death-censored graft survivals at 10 years were 93 and 73.8%, respectively, similar to the 89 and 85.2% observed in those transplanted from living-related donors. (P = ns, both for patient and graft survival).

Outcome of transplant patients with IgAN in their native kidneys

During a median follow-up of 113.1 months, 113 patients with IgAN (59.5%) were subjected to graft biopsy (46 patients received two or more renal biopsies). Recurrence of IgAN was documented in 42 patients accounting for 22.1% of the total number of IgAN-transplanted patients and for 37.2% of patients subjected to graft biopsy. Recurrence developed in 11 out of the 36 grafts (30%) from living-related donors and in 31 out of 154 grafts from deceased donors (20.12% P = ns). The

Table 1. Demographic, clinical and laboratory characteristics and outcome of renal transplant recipients with IgAN and controls

	IgAN (*N* = 190)	Controls (*N* = 380)	P*
Age (years) at transplant, *N* (%)	42.5 (33.6–51.4)	42.3 (32.9–51.4)	0.92
Sex (male/female)	149/41	298/82	0.96
Living/deceased donors, *N*	36/154	72/308	0.91
Duration of dialysis, months	30.2 (14.2–52.8)	38.3 (19.5–61.6)	0.014
Type of dialysis HD/CAPD/pre-emptive	162/27/1	322/58	0.85
HLA match *N*	3 (2–3)	3 (2–3)	0.84
Panel-reactive antibodies %			
Mean ± standard deviation	4.65 ± 13.9	5.22 ± 14.6	0.65
Cold ischaemia (hours)	14.4 (11.8–18.4)	15.3 (11.5–19.2)	0.33
Delayed graft function recovery, *N* (%)	27 (14%)	77 (20%)	0.08
P + azathioprine, *N*	5	12	0.93
P + cyclosporine, *N*	44	104	0.32
Cyclopsorine, *N*	7	5	0.32
P + cyclosporine + azathioprine, *N*	36	79	0.68
P + cyclosporine + mycophenolate, *N* (%)	31	54	0.58
P + tacrolimus + azathioprine, *N*	1	2	0.55
P + tacrolimus + mycophenolate, *N*	43	93	0.70
m TOR inhibitors + cyclosporine, *N*	1	1	0.80
P + tacrolimus *N*	3	5	0.90
P + m TOR inhibitors + cyclosporine *N*	15	17	0.12
P + m TOR inhibitors + mycophenolate, *N*	4	8	0.75
Induction with anti-CD25 antibodies			
Basiliximab, *N* (%)	53 (27.8)	96 (25.3)	0.52
Mycophenolate, *N* (%)	78 (41)	155 (40.7)	0.99
Tacrolimus, *N* (%)	47 (24.7)	100 (26.3)	0.66
m TOR inhibitors, *N* (%)	20 (10.5)	26 (6.8)	0.13
Triple immunosuppression, *N* (%)	130 (68.4)	245 (64.4)	0.39
Acute rejections within the first year			
N (%)	77 (40.5)	125 (32.8)	0.08
Arterial hypertension, *N*(%)	177 (93.1)	315 (82.9)	0.0017
Follow-up post-transplant, months	113.1 (60.5–165.1)	115 (59.2–174.2)	0.42
Grafts lost for recurrence, *N* (%)	12 (6.3)		
Grafts lost for chronic active T-cell-mediated rejection, *N* (%)	21 (11)[a]	34 (8.9)	0.51
Grafts lost for chronic active antibody-mediated rejection, *N* (%)	6 (3.15)[b]	13 (3.4)	0.93

Continued

Table 1. Continued

	IgAN (*N* = 190)	Controls (*N* = 380)	P*
Grafts lost for interstitial fibrosis and tubular atrophy, *N* (%)	10 (5.3)	13 (3.4)	0.4
Grafts lost for other causes, *N* (%)	9 (4.7)	27 (7.1)	0.36
Total grafts lost, *N* (%)	58 (30.5)	87 (22.8)	0.038

IgAN, IgA nephropathy; P, prednisone; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis. All the values are reported as median and interquartile ranges if not differently specified.
*P-value refers to the statistical significance of the variables either in the Cox proportional hazard regression (for a continuous variable) or in the log-rank test for survival curve differences (for a discrete or discretized variable).
[a]Recurrence was considered as a concomitant cause of graft loss in two cases of chronic/active T-cell-mediated rejection.
[b]Recurrence was considered as a concomitant cause of graft loss in four cases of chronic active antibody-mediated rejection.

clinical presentation of recurrences developed in median 44.8 (21.6–78.9) months after transplantation with isolated microscopic haematuria in 5, isolated proteinuria in 8, microscopic haematuria and proteinuria in 12, increase in plasma creatinine in 17: isolated in 4, associated with haematuria or haematuria and proteinuria in the other cases. Proteinuria and haematuria developed during the subsequent follow-up in the four patients with isolated increase in serum creatinine at renal biopsy, instead in seven patients all the urinary abnormalities regressed during a median follow-up of 203 months.

A renal biopsy was performed 4.9 months (range 1.64–22.2 months) after the clinical presentation of the recurrence. The Oxford classification [25] of the histological lesions of recurrent grafts is reported in Table 3.

The outcome of IgAGN patients is reported in the Gantt chart (Figure 2).

Twenty-two out of 42 recurrent grafts (52.4%) were lost within 176.8 months (86.1–166.5). Twelve graft losses were attributed to recurrence (54.5%), and in another six grafts, recurrence was considered a concomitant cause of graft loss. Altogether, 52.4% of recurrent grafts were lost at 176.8 months (86.1–166.5) after transplant in comparison to 24.3% of non-recurrent grafts lost at 62 months (19.7–110.3) after transplant.

The death censored graft survival at 15 years was 51.2 in recurrent patients versus 68.3 in non-recurrent patients (P = 0.069) (Figure 3A). Graft survival in non-recurrent patients was not significantly different from that of controls (P = 0.406) (Figure 3B).

Crescents in at least 30% of glomeruli were documented in 9 out of the 43 biopsies of recurrent grafts (including the recurrence in one of the second transplants): of them 8 lost the graft (88.8%) versus 13 graft losses out of 34 recurrences without crescents at renal biopsy (38.2%, P = 0.02).

Predictors of recurrence

At Cox analysis, the recurrence of IgAN significantly reduced from 1981 to 2010 (P = 0.0065, RR = 0.936, CI 0.8921–0.9816). For descriptive purposes, the Kaplan–Meier curves were drawn referring to three decades (1981–1989, 32 patients; 1990–1999, 97 patients; 2000–2010, 74 patients). As shown in Figure 4, the log-rank test shows a significant difference between the three curves (P = 0.018) (Table 2).

At univariate analysis, in addition to the year of transplant, younger age (P = 0.0054), treatment without mycophenolate (P = 0.016) and less than three immunosuppressive drugs (P = 0.006) were predictive of recurrence. We found significant correlations of the above-mentioned variables among them. In detail, the year of transplant showed a direct correlation with the age of patients at transplant (Pearson correlation coefficient = 0.39, P < 0.000), with mycophenolate (Spearman rho = 0.72, P < 0.0001) and with triple immunosuppressive therapy (Spearman rho = 0.56, P < 0.0001). Due to these significant correlations, the only independent variables at multivariate analysis were age at transplant (P = 0.038, RR = 0.971 for each year CI 0.9451–0.9984) and triple immunosuppressive therapy (P = 0.055, RR = 0.529 for each year, CI 0.42346–1.54998).

Treatment of recurrences

Twenty-six out of 42 recurrent patients (69%) were treated with angiotensin-converting inhibitors alone, and 15 of them lost the graft (57.6%). Eight patients with declining graft function were treated with three intravenous methylprednisolone pulses (associated with angiotensin-converting inhibitors in two patients), five of these grafts were lost (62.5%). The other eight patients continued with the basal immunosuppressive therapy, two of them lost the graft.

DISCUSSION

In this paper, we have reported the findings of a single-center concerning renal transplantation in patients with IgAN. One hundred and ninety patients were included in the study and their outcome has been compared with that of an age- and sex-matched control group including 380 patients. The only significant differences between the two groups were a longer duration of dialysis in control patients and a higher number of hypertensive patients in the IgAN group. IgAN patients and controls have been followed for up to 10 years after renal transplantation, one of the longest follow-ups reported until

Table 2. Demographic, clinical and laboratory characteristics and outcome of patients with IgAN who recurred and those who did not

	Recurrent grafts 42	Non-recurrent grafts: 148	P*
Age at tx (years)	37.4 (26.1–43.1)	44.1 (35.3–51.8)	0.0054
Sex of the recipient (male/female)	34/8	115/33	0.93
Duration of dialysis (months)	19.37 (10.6–40.4)	34.8 (16.9–54.6)	0.23
Type of dialysis HD/CAPD/pre-emptive	39/3	123/24/1	0.38
Deceased/living donors	31/11	123/25	0.11
HLA match, *N*	3 (2–3)	3 (2–3)	0.11
Panel-reactive antibodies %			
Mean ± standard deviation	4.07 ± 12.17	4.78 ± 14.4	0.81
Cold ischaemia (hours)	13.4 (10–19.2)	15 (12.2–18.32)	0.37
Delayed graft function recovery			
N (%)	5 (12.2)	22 (15.1)	0.89
Induction with anti-CD25 antibodies [basiliximab, *N* (%)]	4 (9.5)	49 (33.1)	0.06
Mycophenolate therapy, *N* (%)	8 (19)	70 (47.3)	0.016
Triple immunosuppression, *N* (%)	21 (50%)	109 (73.6)	0.006
Tacrolimus, *N* (%)	4 (9.5)	43 (29.5)	0.1
m TOR inhibitors therapy, *N* (%)	5 (11.9)	15 (10.1)	0.66
Arterial hypertension, *N* (%)	41 (97.6)	136 (91.9)	0.49
Acute rejection, *N* (%)	22 (52.3)	55 (37.2)	0.11
Follow-up post-tx (months)	132.7 (77.4–176.8)	100.7 (55.7–157.0)	0.01
Grafts lost for recurrence, *N* (%)	12 (28.5)	0	
Grafts lost for chronic active T-cell-mediated rejection, *N* (%)	3 (7.1)[a]	18 (12.2)	0.52
Grafts lost for chronic active antibody-mediated rejection, *N* (%)	4 (9.5)[b]	2 (1.3)	0.03
Grafts lost for interstitial fibrosis and tubular atrophy, *N* (%)	2 (4.7)	8 (5.4)	0.82
Grafts lost for other causes, *N* (%)	1(2.4)	8 (5.4)	0.68
Total grafts lost, *N* (%)	22 (52.3)	36(24.3)	0.0001
Infections, *N* (%)	20 (47.6)	71 (47.9)	0.89
Deaths, *N* (%)	4 (9.5)	10 (6.7)	0.78

tx, transplant; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis .
All the values are reported as median and interquartile ranges if not differently specified.
*P-value refers to the statistical significance of the variables either in the Cox proportional hazard regression (for a continuous variable) or in the log-rank test for survival curves difference (for a discrete or discretized variable).
[a]Recurrence was considered as a concomitant cause of graft loss in two cases of chronic/active T-cell-mediated rejection.
[b]Recurrence was considered as a concomitant cause of graft loss in all four cases of chronic active antibody-mediated rejection.

now to the best of our knowledge. The length of the observation is important in the evaluation of the graft outcome in IgAN patients. As a matter of fact in published studies, the graft survival of IgAN patients seems to worsen in the long-term in comparison to that of controls. In the first 5 years after transplantation, graft survival in IgAN patients was reported

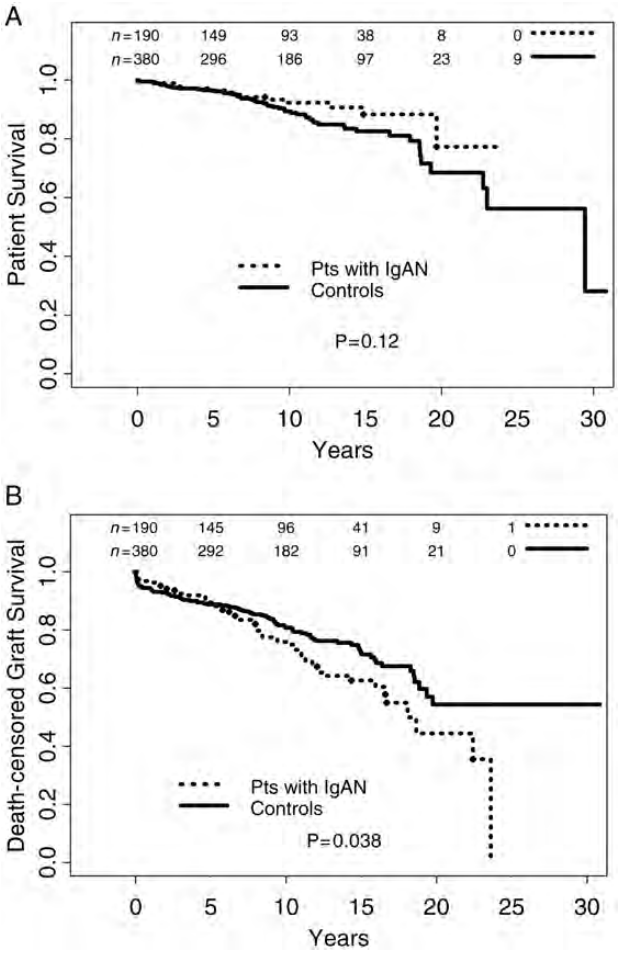

FIGURE 1: (A) Kaplan–Meier estimates of patient survival in patients with IgAN (dashed line) and in controls (solid line). (B) Kaplan–Meier estimates of death-censored graft survival in patients with IgAN (dashed line) and in controls (solid line).

to be better than that of controls [3, 4, 5, 28], at 10 years the graft survival of the two groups became similar [3, 6, 8] or was even worse in IgAN patients [7, 5]. Choy *et al.* [7] reported that the graft survival after 10 years was worse in IgAN patients than in controls; in particular, the two survival curves crossover at around 12 years. In our cohort, the death censored graft survival in IgAN patients was worse than in controls even considering death as a competing risk. Whilst at 5 years, the graft survival of IgAN patients was slightly better than that of controls, after 5 years the graft survival of IgAN patients became progressively worse than that of controls. To strengthen this result, we performed a multivariate Cox regression analysis to predict graft loss pooling together IgAN patients and controls. IgAN emerged as an independent predictor of graft loss at multivariate analysis together with the occurrence of acute rejection and delayed graft function recovery.

Recurrence of IgAN developed in 21.2% of our transplant patients and in 35.5% of patients subjected to graft biopsy after a median follow-up of 4 years after transplantation, ranging from a few months to 15 years. In our centre, patients receive graft biopsy only when they present with clinical manifestations; thus, our rate of recurrence might be underestimated, considering that histological recurrences have been demonstrated in the absence of clinical symptoms [12, 29]. The outcome of grafts with silent recurrent IgA deposits is controversial: in some cases, the disease progressed to overt IgAN, [15] and in others, IgA deposits disappeared in subsequent biopsies [16]. These data underline that the course of the recurrence of IgAN can be extremely variable. As a matter of fact, in seven of our recurrent patients who presented with microscopic haematuria and proteinuria, the urinary abnormalities completely disappeared during the follow-up. In contrast, 12 grafts of our cohort were lost due to recurrence and in 6 other grafts, the recurrence was considered as a concomitant

Table 3. Classification of the histological lesions of recurrent grafts according to Oxford classification (25)

	A functioning grafts at last follow-up: (16[a] patients)	B grafts lost for recurrence: (12 patients)	P (A versus B)	C grafts lost for recurrence + other causes: (6 patients)	D grafts not lost for recurrence: (4 patients)
Mesangial hypercellularity >50% of glomeruli	3	10	0.003	3	1
Segmental glomerulosclerosis present	3	12	0.000	5	1
Endocapillary hypercellularity present	6	11	0.012	5	1
Tubular atrophy/ interstitial fibrosis >25% of specimen	0	6	0.036	2	3

[a]Excluded the four patients who died with a functioning graft.

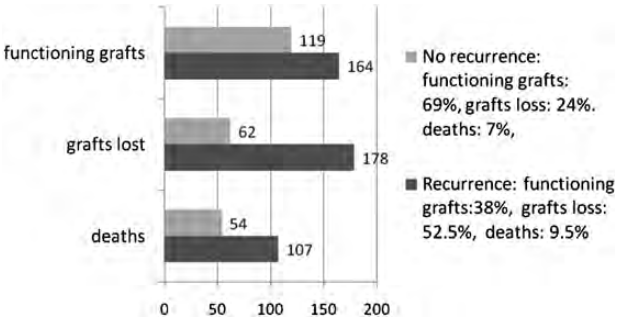

FIGURE 2: Gantt chart reporting the outcome of IgAGN patients with and without IgA recurrence. Numbers at the end of the bars refer to the median follow-ups in months.

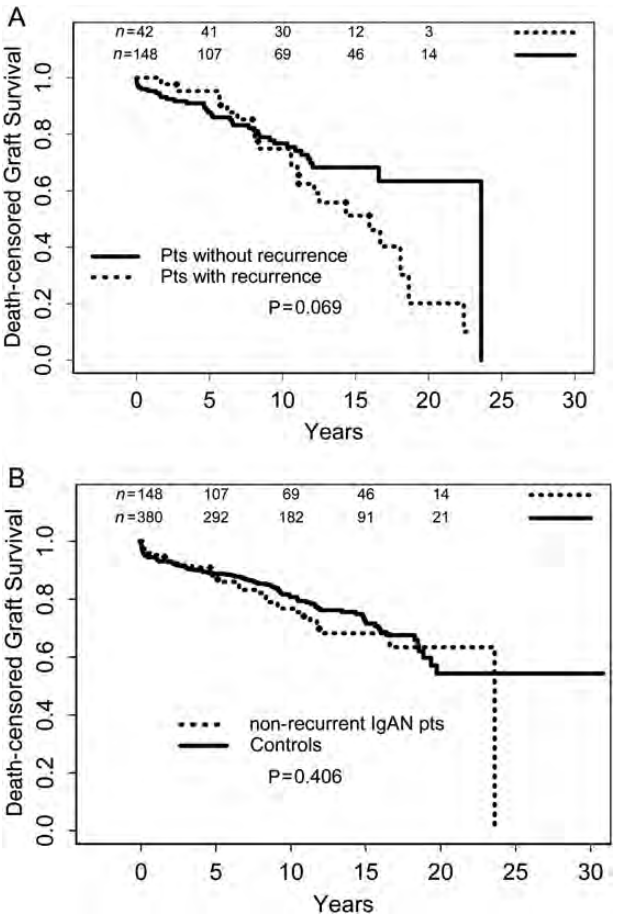

FIGURE 3: (A) Kaplan–Meier estimates of death censored graft survival in patients with recurrence of IgAN (dashed line) and in those without recurrence (solid line). (B) Kaplan–Meier estimates of death-censored graft survival in patients with IgAN who do not develop recurrence (dashed line) and in controls (solid line).

cause of graft failure. Thus, graft loss due to recurrence accounted for 8.4% of our IgAN transplanted patients, comparable with the reported rate in the literature, which ranges from 1.3 to 16% [3, 4, 6, 7, 12–23]. In large cohorts of transplanted recipients, the histological recurrence of any type of glomerulonephritis emerged as a significant cause of graft loss associated with a significant reduction in graft survival [10, 11, 30].

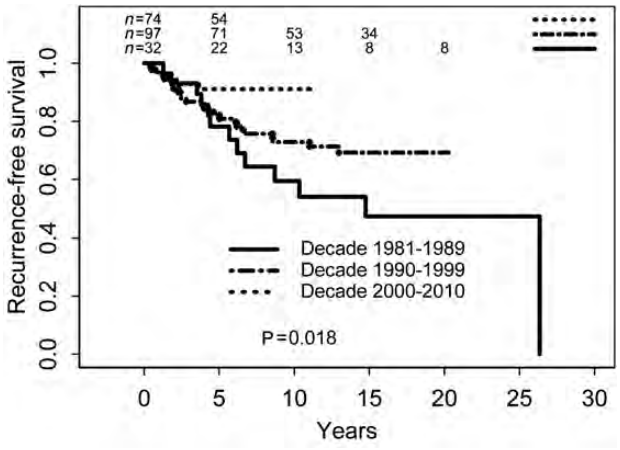

FIGURE 4: Kaplan–Meier estimates of the probability of recurrence of IgAN in the decades 1981–1989 (number of patients 32, number of recurrences 13), 1990–1999 (number of patients 96, number of recurrences 23), 2000–2010 (number of patients 74, number of recurrences 6).

For IgAN, not all authors were able to demonstrate a negative impact of recurrence on graft survival [3, 21–24]. In our cohort, recurrent patients tended to have a worse graft survival than non-recurrent patients, in particular from 10 years after renal transplantation, while graft survival of non-recurrent patients was similar to that of controls. These data seem to suggest that recurrence could be one of the factors responsible for the worse graft survival of IgAN patients in comparison to controls.

As suggested for IgAN in the native kidney [25], the Oxford classification applied to recurrent graft biopsies seems to be able to identify patients with a worse graft outcome.

Another unsolved question is whether living donor kidneys have a higher risk of recurrence and graft deterioration than the kidneys from deceased donors. Some studies have failed to detect a significant difference [3, 6, 16, 21], while others noted a negative impact of living donors on the graft outcome [18–20, 23, 30]. In our cohort, patient and graft survival of recipients from living-related donors were not different from that of recipients from deceased donors and no difference emerged in the rate of recurrence between the two groups.

In the evaluation of the predictors of recurrence, we found, in contrast to that reported in another paper [30], that the transplant year was associated with the risk of recurrence: recurrence of IgAN significantly reduced from 1981 to 2010 and in particular, recurrences occurred less frequently in transplants performed during the decade 2000–2010. There is no clear explanation for our results: one possibility could be the new immunosuppressive approach employed in kidney transplantation in recent years. In actual fact, in contrast to other papers [21, 23, 30], our results at univariate analysis underline a possible role of maintenance immunosuppressive therapy in reducing the risk of recurrence. Patients treated with mycophenolate and those who received any type of triple immunosuppressive therapy had a lower risk of recurrence. Among the other features evaluated

in univariate analysis, only the young age at renal transplantation was associated with a higher risk of recurrence as demonstrated by others [6, 22, 23].

At multivariate analysis, the older age of patients and any triple immunosuppressive therapy were independent protective factors against the recurrence of IgAN. However, multivariate Cox regression analysis could have been impaired by the small number of patients showing recurrence ($n = 42$). These data need to be confirmed in larger prospective studies.

As reported by others [31, 32], we found that the presence of crescents at graft biopsy in recurrent IgAN patients is associated with a worse graft outcome.

No guidelines for the treatment of recurrence of IgAN in renal transplant are currently available. Recently, Mulay *et al.* [33] reported that, after adjusting for important covariates, the use of cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus or prednisone was not associated with graft failure due to recurrent glomerulonephritis, including IgAN, while Clayton *et al.* [34] suggested that steroid withdrawal may increase the graft loss risk because of recurrence of IgAN. Notably, both of these two papers [33, 34] reported an apparent reduction in graft loss from recurrence of IgAN in recent years. The use of angiotensin-converting enzyme inhibitors was not associated with an improvement of graft survival in our recurrent patients, in contrast to what has been reported in other studies [35].

The limitations of our study are obviously its retrospective nature, the relatively low number of patients evaluated, the non-uniformed immunosuppressive regimen due to the long duration of the observation and the lack of control biopsies: this does not allow us to draw firm conclusions about the predictors of recurrence. With these limitations, our results suggest that in the long term death-censored graft survival of IgAN transplant patients seems to be worse in comparison to that of controls; this result is strengthened by the demonstration that IgAN emerged as an independent predictor of graft loss. Recurrence seems to be one of the factors responsible for the worse graft outcome of IgAN patients, as those who did not develop recurrence had a graft survival not different from that of controls.

The progressive reduction of recurrences suggested by our data and the apparent reduction in graft loss from recurrent IgAN reported by other authors [33, 34] in recent years may portend a progressive improvement in the prognosis of renal transplant in IgAN patients in the near future.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Floege and Gröne. Recurrent IgA nephropathy in the renal allograft: not a benign condition. *Nephrol Dial Transplant* 2013; 28: 1070–1073.)

REFERENCES

1. Levy M, Berger J. Worldwide perspective of IgA nephropathy. Am J Kidney Dis 1988; 12: 340–347
2. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med 1987; 64: 709–727
3. Kim YS, Moon JI, Jeong HJ *et al.* Live donor renal allograft in end-stage renal failure patients from immunoglobulin A nephropathy. Transplantation 2001; 71: 233–238
4. Andresdottir MB, Hoitsma AJ, Assmann KJ *et al.* Favorable outcome of renal transplantation in patients with IgA nephropathy. Clin Nephrol 2001; 56: 279–288
5. Chacko B, George JT, Neelakantan N *et al.* Outcomes of renal transplantation in patients with immunoglobulin A nephropathy in India. J Postgrad Med 2007; 53: 92–95
6. Ponticelli C, Traversi L, Feliciani A *et al.* Kidney transplantation in patients with IgA mesangial glomerulonephritis. Kidney Int 2001; 60: 1948–1954
7. Choy BY, Chan TM, Lo SK *et al.* Renal transplantation in patients with primary immunoglobulin A nephropathy. Nephrol Dial Transplant 2003; 18: 2399–2404
8. Andresdottir MB, Haasnoot GW, Doxiadis II *et al.* Exclusive characteristics of graft survival and risk factors in recipients with immunoglobulin A nephropathy: a retrospective analysis of registry data. Transplantation 2005; 80: 1012–1018
9. Ponticelli C, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. Clin J Am Soc Nephrol 2010; 5: 2363–2372
10. Hariharan S, Adams MB, Brennan DC *et al.* Recurrent and de novo glomerular disease after renal transplantation: a report from Renal Allograft Disease Registry (RADR). Transplantation 1999; 68: 635–641
11. Briganti EM, Russ GR, McNeil JJ *et al.* Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 2002; 347: 103–109
12. Berger J, Noël LH, Nabarra B. Recurrence of mesangial IgA nephropathy after renal transplantation. Contrib Nephrol 1984; 40: 195–197
13. Bachman U, Biava C, Amend W *et al.* The clinical course of IgA-nephropathy and Henoch-Schönlein purpura following renal transplantation. Transplantation 1986; 42: 511–515
14. Hartung R, Livingston B, Excell L *et al.* Recurrence of IgA deposits/disease in grafts. An Australian Registry Survey 1980–1990. Contrib Nephrol 1995; 111: 13–27
15. Kessler M, Hiesse C, Hestin D *et al.* Recurrence of immunoglobulin A nephropathy after renal transplantation in the cyclosporine era. Am J Kidney Dis 1996; 28: 99–104
16. Frohnert PP, Donadio JV, Jr, Velosa JA *et al.* The fate of renal transplants in patients with IgA nephropathy. Clin Transplant 1997; 11: 127–133
17. Ohmacht C, Kliem V, Burg M *et al.* Recurrent immunoglobulin A nephropathy after renal transplantation: a significant contributor to graft loss. Transplantation 1997; 64: 1493–1496

18. Bumgardner GL, Amend WC, Ascher NL *et al.* Single-center long-term results of renal transplantation for IgA nephropathy. Transplantation 1998; 65: 1053–1060
19. Freese P, Svalander C, Nordén G *et al.* Clinical risk factors for recurrence of IgA nephropathy. Clin Transplant 1999; 13: 313–317
20. Wang AY, Lai FM, Yu AW *et al.* Recurrent IgA nephropathy in renal transplant allografts. Am J Kidney Dis 2001; 38: 588–596
21. Chandrakantan A, Ratanapanichkich P, Said M *et al.* Recurrent IgA nephropathy after renal transplantation despite immunosuppressive regimens with mycophenolate mofetil. Nephrol Dial Transplant 2005; 20: 1214–1221
22. Berthoux F, El Deeb S, Mariat C *et al.* Antithymocyte globulin (ATG) induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy. Transplantation 2008; 85: 1505–1507
23. Han SS, Huh W, Park SK *et al.* Impact of recurrent disease and chronic allograft nephropathy on the long-term allograft outcome in patients with IgA nephropathy. Transpl Int 2010; 23: 169–175
24. McDonald SP, Russ GR. Recurrence of IgA nephropathy among renal allograft recipients from living donors is greater among those with zero HLA mismatches. Transplantation 2006; 82: 759–762
25. Working Group of the International IgA Nephropathy Network and the Renal Pathology SocietyRoberts IS, Cook HT, Troyanov S *et al.* The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int 2009; 76: 546–556
26. Solez K, Colvin RB, Racusen LC *et al.* Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy (CAN). Am J Transplant 2007; 7: 518–526
27. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988; 16: 1141–1154
28. Lim EC, Terasaki PI. Outcome of renal transplantation in different primary diseases. Clin Transpl 1991; 293–303
29. Odum J, Peh CA, Clarkson AR *et al.* Recurrent mesangial IgA nephritis following renal transplantation. Nephrol Dial Transplant 1994; 9: 309–312
30. Chailimpamontree W, Dmitrienko S, Li G *et al.* Genome Canada Genome Canada biomarkers in transplantation group. Probability, predictors, and prognosis of posttransplantation glomerulonephritis. J Am Soc Nephrol 2009; 20: 843–851
31. Benabdallah L, Rerolle JP, Peraldi MN *et al.* An unusual recurrence of crescentic nephritis after renal transplantation for IgA nephropathy. Am J Kidney Dis 2002; 40: E20
32. Jeong HJ, Kim YS, Kwon KH *et al.* Glomerular crescents are responsible for chronic graft dysfunction in post-transplant IgA nephropathy. Pathol Int 2004; 54: 837–842
33. Mulay AV, van Walraven C, Knoll GA. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. Am J Transplant 2009; 9: 804–811
34. Clayton P, McDonald S, Chadban S. Steroids and recurrent IgA nephropathy after kidney transplantation. Am J Transplant 2011; 11: 1645–1649
35. Oka K, Imai E, Moriyama T *et al.* A clinicopathological study of IgA nephropathy in renal transplant recipients: beneficial effect of angiotensin-converting enzyme inhibitor. Nephrol Dial transplant 2000; 15: 689–695

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