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Clinical Features, Treatment and Prognostic Factors of Post-Transplant Immunoglobulin A Nephropathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Initially described as a relatively benign condition, recent studies report graft loss in up to 50% of the patients with post-transplant IgA nephropathy. There is no evidence for the best therapeutic approach, and prognostic factors remain to be elucidated.

Material/Methods: Single center retrospective analysis of patients >12 years old, with clinically relevant post-transplant IgA nephropathy (proteinuria ≥1.0 g/g and/or graft dysfunction) and ≥6 months follow-up after diagnosis (n=47).

Results: Living donor transplants represented 85% of cases. Dysmorphic hematuria (100%), blood pressure elevation (95.7%), renal dysfunction (70.2%) and subnephrotic proteinuria (60.6%) predominated at presentation. Using the Oxford Classification, mesangial proliferation was the main histological lesion (91%). Treatment consisted mostly of blockade of the renin angiotensin system (89.4%) and modification of immunosuppression (85.1%), mainly by increasing oral steroids dose (83%), with venous pulse therapy in 63.8% of cases. Partial and complete remission occurred in 48.9% and 17% of cases, respectively. One patient died (sepsis) and 15 patients (31.9%) lost their grafts due to nephropathy. The percentage of decrease in glomerular filtration rate at diagnosis was independently associated with partial remission (HR 0.97, 95% CI 0.94–0.99, p=0.01) and graft loss (HR 1.13, 95% CI 1.06–1.20, p<0.001). Deceased donor (HR 28.04, 95% CI 4.41–178.39, p<0.001) and donor age (HR 1.1, 95% CI 1.04–1.16, p=0.001) were also risk factors for graft loss.

Conclusions: Despite treatment, most patients with post-transplant IgA nephropathy in this cohort study presented unfavorable outcomes, and graft dysfunction at diagnosis appeared to be the main prognostic marker.

MeSH Keywords: Glomerulonephritis, IgA • Immunosuppressive Agents • Kidney Transplantation • Prognosis

Abbreviations: **ACEi** – angiotensin converting enzyme inhibitors; **ARB** – angiotensin II type 1 receptor blocker; **AZA** – azathioprine; **DSA** – donor-specific alloantibody; **IgAN** – immunoglobulin A nephropathy; **MMF** – mycophenolate mofetil; **MPS** – mycophenolate sodium; **RAAS** – renin-angiotensin system

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Background

Recurrence of glomerulonephritis after transplantation is the third most common cause of graft loss and represents a major obstacle to prolong graft survival [1,2]. Immunoglobulin A nephropathy (IgAN) recurs in approximately 30% of patients, reaching 61% when protocol biopsies are considered [3,4]. Initially described as a relatively benign condition, recent studies with longer follow-up have reported graft loss in up to 50% of the patients after recurrence [5–9].

There is no ideal strategy for IgAN prevention or therapy, although there is some evidence about the role of immunosuppression [10]. Data from the United States Renal Data Systems suggest that there are no benefits in choosing the initial immunosuppressive regimen based on the risk of recurrence [6]. After IgAN recurrence, some strategies have been reported, such as high-dose steroids [8,11,12], switching from azathioprine (AZA) to mycophenolate mofetil (MMF) [11,13], cyclophosphamide and plasma exchange [14], and rituximab [15], but the results do not support effective treatment outcomes. Blockade of the renin-angiotensin system (RAAS) appears to be effective in reducing proteinuria and blood pressure [16].

Importantly, prognostic factors remain to be fully elucidated. Previous studies have suggested that transplant from living related donors [17,18], proteinuria, hypertension, and graft dysfunction at diagnosis are associated with inferior graft survival [13,17,19,20] and evidence indicates that the Oxford Classification can be useful in identifying patients with worse outcomes [8,21].

This study aimed to describe the clinical and histological features, treatment, and outcomes of a cohort of patients with clinically relevant post-transplant IgAN and evaluate the risk factors for remission or graft loss due to IgAN.

Material and Methods

Study design and population

This single center retrospective cohort study was approved by the local ethics committee of the Federal University of São Paulo, approval number: 304.541/13. The study comprised adolescent and adult (>12 years of age) recipients of living or deceased donor kidneys transplanted between January 1, 1998 and July 31, 2012, with clinically relevant post-transplant IgAN and with at least six months of follow-up after diagnosis. Patients were identified through a biopsy database and/or were selected from those followed in the Glomerulopathies Section. Patients with post-transplant IgAN associated with systemic diseases were excluded. We also excluded patients whose graft dysfunction and/or proteinuria were considered only secondary to conditions other than IgAN by the assisting medical team. This clinical judgment followed the routine of service and the clinical staff decision. C4d and HLA donor-specific alloantibodies (DSA) were requested when acute or chronic antibody-mediated rejection was suspected. Data were obtained retrospectively through systematic review of medical charts and electronic databases. Renal biopsies were reviewed according to the Oxford Classification [22] by an expert renal pathologist.

Definitions

Post-transplant IgAN was defined by the presence of dominant or codominant IgA at least in the mesangium by immunofluorescence staining with intensity greater than traits. IgG and IgM could be present but not at a higher intensity than IgA, except IgM in areas of marked glomerular sclerosis [23]. Only samples with at least eight glomeruli were considered adequate to review using Oxford Classification [24]. According to the criteria used for IgAN treatment in native kidneys, and based on the clinical characteristics that may negatively affect the outcomes, we considered clinically relevant IgAN on those cases with protein-creatinine ratio in urine ≥1.0 g/g and/or graft dysfunction due to IgAN.

Glomerular filtration rate (GFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) study formula. The baseline serum creatinine was defined as the average of the lowest three serum creatinine values before the diagnosis. Graft dysfunction at diagnosis was defined as ≥0.3 mg/dL or ≥1.5 times increase in baseline serum creatinine, confirmed in two different measurements.

Partial remission was defined as serum creatinine stabilization in a value up to 25% above the baseline associated with reduction of proteinuria by 50% or greater and <3.0 g/g when nephrotic values were initially found. Complete remission was defined as creatinine stabilization associated with proteinuria <0.3 g/g. IgAN reactivation was defined as an increase in proteinuria above the values for partial remission and/or graft dysfunction attributed to disease, confirmed by new biopsy.

The use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin II type 1 receptor blocker (ARB) or statin was considered when used in labeled doses, for at least three months or until graft loss. The dual RAAS blockade was considered when ACEi and ARB was used at any dose and in duration described previously. The prednisone doses used to treat IgAN were grouped and divided into two regimens: low dose (greater than 5 mg/day and lower than 0.4 mg/kg/day, for at least two months) and high dose (greater or equal to 0.4 mg/kg/day, for at least two months). Switching to cyclophosphamide,

MMF, or mycophenolate sodium (MPS) was considered when used for at least two months or until graft loss. Patients were considered non-adherent when this risk was registered on medical records.

Graft loss was attributed to IgAN when progressive deterioration of graft function was associated with proteinuria and biopsy showed glomerular mesangial sclerosis and proliferation, with or without endocapillary hypercellularity and crescents as the main lesions.

Statistical analysis

Categorical variables were expressed as proportions and compared using the chi-square test or the Fisher's exact test. Numerical variables were presented as mean and standard deviation. Comparison between groups was performed using the t-test. Cox regression was used to analyze variables associated with partial remission and graft loss. Variables with $p<0.10$ in univariate analysis were included in the multivariate model. Statistical significance corresponded to $p<0.05$. All analyses were performed using the SPSS program v.18.0 (SPSS Inc., Chicago, IL, USA)

Results

Population

Forty-seven patients with clinically relevant post-transplant IgAN and more than six months follow-up were identified among 9,613 kidney transplants (52.4% from living donors) during the study period. Patients were predominantly men (68.1%), young (34.0±9.6 years old), Caucasian (68.9%), low immunological risk (panel reactive antibodies: 9.9±25.1%, HLA mismatches 1.5±1.6), recipients of living (85.1%), young (41.5±12.9 years old) donors. Only three patients (6.4%) had IgAN confirmed as the cause of end stage renal disease. No patient was diabetic and the single patient with hepatitis C virus had no evidence of liver disease. Most patients (70.2%) received as their initial immunosuppressive regimen a combination of calcineurin inhibitor (cyclosporine or tacrolimus), steroids, and AZA (Table 1).

Clinical characteristics at diagnosis

All patients presented dysmorphic hematuria. At diagnosis, the mean proteinuria was 3.4±2.2 g/g and 39.4% presented nephrotic levels. Mean serum albumin was 34 g/L, mean total serum cholesterol was 5.56 mmol/L and 11 patients (23.4%) were using statins. Forty-five patients (95.7%) presented elevation in blood pressure and 57.4% of patients were using ACEi or ARB. Allograft kidney dysfunction was observed in

Table 1. Demographic and clinical characteristics of patients with posttransplant IgA nephropathy.

	Total (N=47)
Recipient age, years (mean ±SD)	34.0±9.6
Recipient gender: male, N (%)	32 (68.1)
Recipient ethnicity: Caucasian, N (%)	31 (68.9)
BMI, kg/m² (mean ±SD)	21.3±3.4
Cause of chronic kidney disease, N (%)	
Glomerulonephritis	14 (29.8)
IgAN	3 (6.4)
Unknown	30 (63.8)
Time on dialysis before Tx, months (mean ±SD)	22.4±19.3
Type of treatment: hemodialysis, N (%)	44 (93.6)
Retransplantation, N (%)	2 (4.3)
HCV positive, N (%)	1 (2.2)
HBV positive, N (%)	0 (0.0)
HIV positive, N (%)	0 (0.0)
Panel reactive antibodies,% (mean ±SD)	9.9±25.1
HLA mismatches (mean ±SD)	1.5±1.6
HLA B8 DR3, N (%)	1 (2.4)
Donor age, years (mean ±SD)	41.5±12.9
Donor source, N (%)	
Living	40 (85.1)
Deceased	7 (14.9)
ATG induction therapy, N (%)	4 (8.5)
Initial immunosuppressive regimen, N (%)	
CNI+ST+AZA	33 (70.2)
CNI+ST+MMF/MPS	9 (19.1)
CNI+ST+mTORi	4 (8.5)
CNI+ST+FTY720	1 (2.1)
Non-adherence, N (%)	11 (23.4)
Biopsy-proven acute rejection, N (%)	11 (23.4)

BMI – body mass index; IgAN – immunoglobulin A nephropaty; Tx – kidney transplantation; HCV – hepatitis C virus; HBV – hepatitis B virus; HIV – human immunodeficiency virus; ATG – antithymocyte globulin; CNI – calcineurin inhibitors; AZA – azathioprine; MMF – mycophenolate mofetil; MPS – mycophenolate sodium; mTORi – mammalian target of rapamycin inhibitors; ST – steroids.

70.2% of patients and a decrease of 25.2±16.9% in GFR was observed from baseline to the time of biopsy. Of note, two patients presented rapidly progressive glomerulonephritis. Kidney biopsy was performed 49.1±32.7 months after transplant and 25.9±27.5 months after the onset of proteinuria. More detailed information about clinical characteristics at diagnosis is available in Table 2.

Throughout the follow-up period, 14 patients (29.8%) had acute rejections, distributed as follows. Before IgAN diagnosis, five patients (10.6%) presented acute rejection episodes: two patients (4.3%) with IA, one patient (2.1%) with IB, one patient (2.1%) with IIB, one patient (2.1%) with acute antibody-mediated rejection. Eight patients (17%) presented with acute cellular rejection concomitant to IgAN diagnosis: two patients (4.3%) with borderline changes, four patients (8.5%) with IA, two patients (4.3%) with IB. After IgAN diagnosis, 15 patients (31.9%) underwent a new biopsy and three patients (6.4%) showed acute rejection: one patient (2.1%) with borderline changes, one patient (2.1%) with IA, one patient (2.1%) with IB. Forty-one biopsies were available for analyses, with crescents in 9.8%. Among those 41 biopsies, 22 were histologically representative for the analysis of the present study using the criteria proposed by the Oxford Classification for IgAN. The most common histological finding was mesangial proliferation (90.9%), followed by segmental glomerulosclerosis (77.3%), tubular atrophy and interstitial fibrosis (18.2%), and endocapillary hypercellularity (9.1%).

Treatment

Except for one patient, all patients received some treatment (ACEi, ARB, statin, or changes in immunosuppression). After IgAN diagnosis, the use of the blockade of the RAAS increased to 89.4% and the dual RAAS blockade was utilized in 44.7% of cases. Changes in immunosuppression with the objective of treating glomerulonephritis occurred in 85.1% of cases. The steroids in higher doses, orally (83.0%) and in venous pulse therapy (63.8%), were the medications most commonly added to immunosuppressive treatment. The mean prednisone equivalent cumulative dose from the diagnosis to the last follow-up was 0.4±0.7 mg/kg/day. Conversion from an antiproliferative immunosuppressive drug to oral or intravenous cyclophosphamide occurred in 17% of cases and mycophenolic acid formulations were used in 19.1% of cases (Table 3).

Outcomes

Infections occurred in 40% of patients during or after immunosuppressive treatment of IgAN. Pulmonary infections were the most common (20%), followed by urinary tract infection (10%), herpes zoster (5%), cytomegalovirus (5%), skin infection (5%), fungal infection (5%), and sepsis without defined

Table 2. Clinical and laboratory features of posttransplant IgA nephropathy at diagnosis.

	Total (N=47)
Dysmorphic hematuria, N (%)	47 (100)
Proteinuria, g/g (mean ±SD)	3.4±2.2
Proteinuria 0.3–3.5 g/g*, N (%)	20 (60.6)
Nephrotic proteinuria*, N (%)	13 (39.4)
Onset of proteinuria >0.3g/g, months after Tx (mean ±SD)	23.8±15.2
Serum albumin, g/L (mean ±SD)	34±6
Total serum cholesterol, mmol/L (mean ±SD)	5.6±1.7
Statin, N (%)	11 (23.4)
SBP, mmHg (mean ±SD)	133.3±19.2
DBP, mmHg (mean±SD)	82.2±13.2
Blood pressure elevation, N (%)	45 (95.7)
Number of antihypertensive drugs, (mean ±SD)	1.7±0.9
ACEi or ARB, N (%)	27 (57.4)
Biopsy indication	
Allograft dysfunction and proteinuria, N (%)	33 (70.2)
Proteinuria, N (%)	14 (29.8)
Baseline GFR, mL/min/1.73m^2 (mean ±SD)	58.0±13.0
GFR at biopsy, mL/min/1.73m^2 (mean ±SD)	43.6±14.7
Decrease in GFR, % (mean ±SD)	25.2±16.9
Time to biopsy, months after Tx (mean ±SD)	49.1±32.7
Time between proteinuria >0.3 g/g and biopsy, months (mean ±SD)	25.9±27.5
Concurrent acute rejection at diagnosis, N (%)	8 (17.0)

Tx – kidney transplantation; SBP – systolic blood pressure; DBP – diastolic blood pressure; ACEi – angiotensin converting enzyme inhibitors; ARB – angiotensin-II type 1 receptor blockers. * Fourteen patients had no proteinuria measured at the time of biopsy.

etiology (2.5%). With 42.5±33.3 months follow-up after the IgAN diagnosis, partial and complete remission was observed in 48.9% and 17% of the patients, respectively. Relapse of IgAN occurred in 34.8% of patients. Fifteen patients (31.9%) lost the graft, all secondary to IgAN. One patient died due to septic

Table 3. Treatments for posttransplant IgA nephropathy.

	Total (N=47)
ACEi or ARB, N (%)	42 (89.4)
ACEi and ARB, N (%)	21 (44.7)
Statin, N (%)	19 (40.4)
ISS treatment*, N (%)	40 (85.1)
Time between biopsy and ISS treatment, days (mean ±SD)	102.5±264.1
Increased prednisone dose, N (%)	39 (83.0)
Low dose**, N (%)	32 (68.1)
Duration of low dose, months (mean ±SD)	18.8±25.8
High dose#, N (%)	31 (66.0)
Duration of high dose, months (mean ±SD)	5.5±5.0
Methylprednisolone pulse therapy##, N (%)	30 (63.8)
Cumulative pulse dose, g (mean ±SD)	4.1±2.5
Cumulative prednisone equivalent dose, mg/kg/day (mean ±SD)	0.4±0.7
Cyclophosphamide, N (%)	8 (17.0)
Conversion to MMF or MPS, N (%)	9 (19.1)

ACEi – angiotensin converting enzyme inhibitors; ARB – angiotensin II type 1 receptor blockers; ISS – Immunosuppressive; MMF – mycophenolate mofetil; MPS – mycophenolate sodium. * ISS treatment includes any changes in maintenance immunosuppressive regimen with the intention of treat IgA nephropathy; ** Prednisone dose between 5 mg and 0.4 mg/kg/day, for at least two months; # Prednisone dose above 0.4 mg/kg/day, for at least two months; ## Methylprednisolone intravenously dose between 500 and 1000 mg/day, for at least three days.

shock (Table 4). Patients who lost the graft presented lower incidences of partial (20% versus 62.5%, *p*=0.01) and complete remission (6.7% versus 21.9%, *p*=0.4) compared with those who maintained functioning grafts. In addition, during the follow-up after diagnosis, patients who lost the graft presented higher systolic blood pressure (145.1±45.1 versus 133.6±14.2 mm Hg, *p*=0.02), proteinuria (6.2±4.1 versus 4.2±2.8 g/g, *p*=0.05), and incidence of relapse of IgAN (100% versus 25%, *p*=0.03). Interestingly, two patients whose immunosuppression had not been modified presented complete remission. Both were treated with blockers of the RAAS and remission occurred at 0.8 and 65.5 months after the diagnosis. Death-censored allograft survivals were 97.9%, 95.6%, 90.7%, 87.9%, and 63.5% at 1, 3, 5, 7, and 10 years, respectively. The survival after IgAN diagnosis were 93.5%, 79.3%, and 66.2% in 1, 3, and 5 years, respectively.

Table 4. Outcomes of posttransplant IgA nephropathy.

	Total (N=47)
Highest proteinuria, g/g (mean ±SD)	4.8±3.4
Mean SBP*, mmHg (mean ±SD)	137.2±15.4
Mean DBP*, mmHg (mean ±SD)	84.6±9.1
Partial remission, N (%)	23 (48.9)
Time to partial remission, months (mean ±SD)	10.3±12.9
Complete remission, N (%)	8 (17.0)
Time to complete remission, months (mean ±SD)	46.4±22.9
Relapse**, N (%)	8 (34.8)
Death, N (%)	1 (2.1)
Graft loss due to IgAN	15 (31.9)
Follow-up after Tx, months (mean ±SD)	91.4±40.5
Follow-up after biopsy, months (mean ±SD)	42.5±33.3

SBP – systolic blood pressure; DBP – diastolic blood pressure; Tx – kidney transplantation. * Mean of the blood pressure measurements in the appointments after IgA nephropathy diagnosis; ** Among those who have reached at least partial remission.

Prognostic factors

By multivariate analysis, the percentage reduction in GFR at diagnosis was the only variable associated with a lower risk of partial remission (HR 0.97, 95% CI 0.94–0.99, *p*=0.01) (Table 5). Because of the low percentage of complete remission, risk factors for this outcome were not analyzed. The risk factors associated with graft loss secondary to IgAN were: donor age (HR 1.1, 95% CI 1.04–1.16, *p*=0.001), deceased donor (HR 28.04, 95% CI 4.41–178.39, *p*<0.001), the interval between the onset of proteinuria and graft biopsy (HR 0.94, 95% CI 0.90–0.99, *p*=0.01), and the percentage of reduction in GFR at diagnosis (HR 1.13, 95% CI 1.06–1.20, *p*<0.001) (Table 6). Because of the significant number of missing data, histological findings were not included in the multivariate analysis. Despite no statistically significant, crescents (25% versus 3.4%, *p*=0.07) and endocapillary hypercellularity (25% versus 0%, *p*=0.1) were more common in patients who lost their grafts compared to those with functioning grafts at the end of the follow-up. There were no differences in mesangial proliferation (100% versus 85.7%, *p*=0.5), segmental glomerulosclerosis (75% versus 78.6%, *p*=0.9), and tubular atrophy and interstitial fibrosis (25% versus 14.3%, *p*=0.6).

Table 5. Risk factors for partial remission after posttransplant IgA nephropathy.

	Partial remission (N=23)	No remission (N=24)	Univariate analysis p value	Multivariate analysis HR (CI 95%) p value
Recipient age, years (mean ±SD)	35.4±10.6	40.7±8.7	p=0.04	**0.95 (0.91–1.0) p=0.05**
Recipient gender, male, N (%)	18 (78.3)	14 (58.3)	p=0.1	–
Recipient ethnicity, Caucasian, N (%)	14 (63.6)	17 (73.9)	p=0.4	–
BMI, kg/m^2 (mean ±SD)	21.4±3.6	21.3±3.3	p=0.9	–
Donor age, years (mean ±SD)	37.0±10.5	45.6±13.7	p=0.2	–
Deceased donor, N (%)	3 (13.6)	4 (16.7)	p=0.8	–
ATG induction therapy, N (%)	1 (4.5)	3 (12.5)	p=0.9	–
Inicial ISS regimen: AZA, N (%)	17 (73.9)	16 (66.7)	p=0.7	–
Inicial ISS regimen: MMF/MPS, N (%)	4 (17.4)	5 (20.8)	p=0.5	–
Inicial ISS regimen: mTORi, N (%)	2 (8.7)	2 (8.3)	p=0.9	–
Onset of proteinuria >0.3 g/g, mo. after Tx (mean ±SD)	22.4±14.1	25.1±16.3	p=0.4	–
Time to biopsy since proteinuria onset, mo. (mean ±SD)	20.9±18.3	28.4±31.0	p=0.8	–
Proteinuria at diagnosis, g/g (mean ±SD)	3.7±2.7	3.1±1.9	p=0.1	–
Serum albumin at diagnosis, g/L (mean ±SD)	35±6	33±7	p=0.4	–
Total serum cholesterol at diagnosis, mmol/L (mean ±SD)	5.6±1.3	5.3±2.2	p=0.6	–
SBP at diagnosis, mmHg (mean ±SD)	130.0±14.1	136.5±23.2	p=0.1	–
DBP at diagnosis, mmHg (mean ±SD)	81.5±11.4	82.9±15.1	p=0.2	–
Basal GFR, mL/min/1.73m^2 (mean ±SD)	62.7±10.5	53.5±13.8	p=0.05	p=0.8
Allograft disfunction, N (%)	11 (47.8)	22 (91.7)	p=0.01	p=0.7
Decrease in GFR,% (mean ±SD)	16.4±14.1	33.8±15.0	p=0.006	**0.97 (0.94–0.99) p=0.01**
Treatment with ACEi or ARB, N (%)	23 (100.0)	19 (79.2)	p=0.3	–
Treatment with ACEi plus ARB, N (%)	14 (60.9)	7 (29.2)	p=0.2	–
Treatment with statin, N (%)	11 (47.8)	11 (34.4)	p=0.9	–
Time to ISS since diagnosis, days (mean ± SD)	49.5±67.4	128.0±316.9	p=0.2	–
Treatment with increased prednisone dose, N (%)	20 (87.0)	19 (79.2)	p=0.4	–
Treatment with low prednisone dose*, N (%)	18 (78.3)	14 (58.3)	p=0.5	–
Duration of low dose, mo. (mean ±SD)	25.9±31.1	10.9±14.6	p=0.2	–
Treatment with high prednisone dose**, N (%)	17 (73.9)	14 (58.3)	p=0.3	–
Duration of high dose, mo. (mean ±SD)	7.4±6.1	4.2±2.6	p=0.6	–
Methylprednisolone pulse#, N (%)	14 (60.9)	16 (66.7)	p=0.8	–
Cumulative pulse dose, g (mean ±SD)	4.2±2.9	4.0±2.2	p=0.6	–
Cumulative prednisone dose, mg/kg/day (mean ±SD)	0.31±0.25	0.56±0.95	p=0.6	–
Conversion to cyclophosphamide, N (%)	4 (17.4)	4 (16.7)	p=0.8	–
Conversion to MMF or MPS, N (%)	6 (26.1)	3 (12.5)	p=0.6	–
Non-adherence, N (%)	5 (2.7)	6 (19.4)	p=0.9	–

CI – confidence interval; ATG – antithymocyte globulin; AZA – azathioprine; ISS – immunosuppressive treatment; MMF – mycophenolate mofetil; MPS – mycophenolate sodium; mTORi – mammalian target of rapamycin inhibitors; mo. – months; Tx – kidney transplantation; SBP – systolic blood pressure; DBP – diastolic blood pressure; ACEi – angiotensin converting enzyme inhibitors; ARB – angiotensin II type 1 receptor blockers; n.s. – not significant. * Prednisone dose between 5 mg and 0.4 mg/kg/day, for at least two months; ** Prednisone dose above 0.4 mg/kg/day, for at least two months; # Intravenous administration of methylprednisolone: 500 to 1000 mg/day, for at least three days.

Table 6. Risk factors for graft loss due to posttransplant IgA nephropathy.

	Graft loss (N=15)	Functioning allograft (N=32)	Univariate analysis p value	Multivariate analysis HR (CI 95%) p value
Recipient age, years (mean ±SD)	39.5±11.0	37.5±9.5	p=0.8	–
Recipient gender, male, N (%)	10 (66.7)	22 (68.8)	p=0.4	–.
Recipient ethnicity, black, N (%)	0 (0.0)	2 (6.5)	p=0.9	–
BMI, kg/m² (mean ±SD)	20.9±4.5	21.5±3.0	p=0.7	–
Time on dialysis, mo. (mean ±SD)	20.9±18.2	23.1±20.0	p=0.8	–
Panel reactive antibodies,% (mean ±SD)	5.9±22.2	12.1±26.8	p=0.8	–
HLA mismatches (mean ±SD)	1.9±1.4	1.3±1.7	p=0.03	p=0.9
HLA B8 DR3, N (%)	1 (7.7)	0 (0.0)	p=0.6	–
Donor age, years (mean ±SD)	47.1±13.8	38.7±11.7	p=0.008	**1.10 (1.04–1.16) p=0.001**
Deceased donor, N (%)	4 (26.7)	3 (9.4)	p=0.01	**28.04 (4.41–178.39) p<0.001**
ATG induction therapy, N (%)	1 (6.7)	3 (9.3)	p=0.6	–
Acute rejection, N (%)	5 (33.3)	6 (19.4)	p=0.3	–
CMV event, N (%)	1 (6.7)	4 (12.9)	p=0.9	–
Onset of proteinuria >0.3 g/g, mo. after Tx (mean ±SD)	23.5±16.7	23.9±14.7	p=0.4	–
Time to biopsy since the onset of proteinuria, mo. (mean ±SD)	20.9±18.3	28.4±31.0	p=0.06	**0.94 (0.90–0.99) p=0.01**
Proteinuria, g/g (mean ±SD)	3.4±2.1	3.3±2.3	p=0.7	–
Serum albumin at diagnosis, g/L (mean ±SD)	33±8	34±5	p=0.9	–
Total serum cholesterol at diagnosis, mmol/L (mean ±SD)	5.5±2.2	5.6±1.4	p=0.5	–
SBP at diagnosis, mmHg (mean ±SD)	138.3±22.7	130.8±17.2	p=0.7	–
DBP at diagnosis, mmHg (mean ±SD)	82.8±17.3	81.9±11.1	p=0.7	–
Allograft disfunction, N (%)	15 (100.0)	18 (56.2)	p=0.1	–
Decrease in GFR,% (mean ±SD)	36.8±13.1	19.8±15.8	p=0.002	**1.13 (1.06–1.2) p<0.001**
Treatment with ACEi or ARB, N (%)	13 (86.7)	29 (90.6)	p=0.2	–
Treatment with ACEi plus ARB, N (%)	4 (26.7)	17 (53.1)	p=0.07	p=0.4
Treatment with statin, N (%)	8 (53.3)	11 (34.4)	p=0.7	–
Time to ISS since the diagnosis, days (mean±SD)	49.5±67.4	128.0±316.9	p=0.3	–
Treatment with increased prednisone dose, N (%)	12 (80.0)	27 (84.4)	p=0.7	–
Treatment with high prednisone dose*, N (%)	9 (60.0)	22 (68.8)	p=0.9	–
Methylprednisolone pulse**, N (%)	9 (60.0)	21 (65.6)	p=0.5	–
Cumulative prednisone dose, mg/kg/day (mean±SD)	0.6±1.2	0.3±0.3	p=0.004	p=0.4
Conversion to cyclophosphamide, N (%)	5 (33.3)	3 (9.4)	p=0.1	–
Conversion to MMF/MPS, N (%)	3 (20.0)	6 (18.8)	p=0.4	–
Non-adherence, N (%)	4 (26.7)	6 (19.4)	p=0.6	–

CI – confidence interval; mo. – months; ATG – antithymocyte globulin; CMV – cytomegalovirus; Tx – kidney transplantation; SBP – systolic blood pressure; DBP – diastolic blood pressure; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II type I receptor blockers; ISS, immunosuppressive treatment; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; n.s. – not significant. * Prednisone dose above 0.4 mg/kg/day, for at least two months; ** Intravenous methylprednisolone administration: 500–1000 mg/day, for at least three days.

Discussion

This cohort of patients with clinically relevant post-transplant IgAN demonstrated that hematuria, subnephrotic proteinuria, blood pressure elevation, and graft dysfunction were the main clinical presentation of this disease, usually initiated late after transplantation. Histological lesions indicative of disease activity, such as crescents and mesangial or endocapillary proliferation, were more common in severe cases. There was not a standard treatment, but virtually all patients received renoprotective therapy and the majority of patients were treated with immunosuppressive drugs, mainly steroids in high doses. The cohort presented a low rate of remission and a high rate of graft loss. It is of note that the degree of graft dysfunction at diagnosis appeared to be the best marker for poor outcomes.

Except for a higher incidence of living donor transplants, the demography of our cohort was similar to those described in previous studies [4,9,11,17,19,25]. This finding can be partly explained by the young age of recipients, but we could speculate whether there is a higher recurrence rate in living donor transplants, as suggested previously by others [18,26]. However, this was not an objective of the present study and we did not have data to assess the risk of recurrence.

Of note was the high percentage of patients without a native kidney biopsy that could establish or not the diagnosis of IgAN before transplantation, which is consistent with our local reality. According to the last census in 2014 of the Brazilian Society of Nephrology, 9% of patients on dialysis in Brazil did not have a diagnosis of CKD etiology, besides cases that may be mislabeled as hypertensive nephrosclerosis, which corresponds to 35% [27]. Due to the absence of such confirmatory biopsy, this study population was defined as a post-transplant IgAN with unknown native kidney disease. However, as we excluded from this analysis patients with suspected secondary IgA, we considered that this sample was mostly composed of patients with primary IgAN that recurred after transplantation.

As reported previously, the diagnosis occurred predominantly some years after transplantation [4,9,12,17,25]. The higher incidence of graft dysfunction at diagnosis was also found in other studies [7,9,17,20] and in the present study might reflect our center's practice, in which mainly patients with nephrotic proteinuria and/or with graft dysfunction were referred for graft biopsy.

Interestingly, we observed a high incidence of late concurrent acute rejection. This finding leads us to question which one of the injuries was responsible for graft dysfunction in these cases. Importantly, late acute rejection is usually a result of excessive immunosuppression minimization or poor adherence to a regimen. Although not shown in the multivariate analysis, it

is possible that the high rate of concomitant late acute rejection contributed to the high incidence of graft loss. Of note, late acute rejections also usually involve both humoral and cell-mediated immunity, which gives them a worse prognosis. In addition, recent study indicated that recurrent/*de novo* glomerulonephritis is associated with a higher risk of rejection episodes [28].

Although we have made every effort to include in the study only those patients whose graft dysfunction and/or proteinuria was attributed exclusively to IgAN, this differential diagnosis is often difficult. In addition, this is a cohort of transplants performed from 1998 to 2012, and several diagnostic tools for antibody-mediated changes have been recently developed (as solid phase assays). In this study, all losses were attributed to IgAN. However, as we know, the longevity of the renal allograft is determined by several immunological (acute and chronic cellular and/or mediated by antibodies rejections) and non-immunological (infections, nephrotoxicity) events and the causality definition of graft loss is sometimes a difficult task.

Despite not reaching statistically significance, histological lesions suggestive of glomerulonephritis activity, mesangial or endocapillary hypercellularity, and crescents, were more common in patients who have lost the graft, as described in previous studies [8,19,21,29]. Although there was a high frequency of segmental sclerosis, it is of note that the tubulointerstitial compartment was relatively preserved at diagnosis.

To date, the ideal treatment for post-transplant IgAN has not been defined. Previous studies showed that the RAAS blockade was associated with blood pressure reduction, decrease in proteinuria, and possibly better survival [4,16,30,31]. In our study, almost all patients received ACEi and/or ARB and in most of them the maintenance immunosuppressive regimen was modified. However, no treatment was associated with remission or reduced risk of graft loss. The impact of the immunosuppressive agents in IgAN outcomes remains controversial. Previously, it was shown that immunosuppressive regimens containing steroids were strongly associated with a lower risk of graft loss by IgAN and this finding was not replicated in other glomerulonephritis [32]. In contrast, other studies found no association of immunosuppressive regimen with a poor outcome [6,13]. Other authors have shown that after diagnosis there was no benefit in changing the maintenance immunosuppression, mainly by increasing the dose of steroids and adding MPS to the regimen [8,11]. A recent small retrospective study showed that pulse therapy and oral steroids for six months were associated with a reduction in worsening of renal function and proteinuria, although with no difference was found in graft survival [12]. The severity of the disease at diagnosis may also have contributed to the lack of benefit of the treatment in our cohort. Importantly, there was a high

incidence of infections after the changes in immunosuppression that probably led to premature treatment interruptions. This significant percentage (40%) of infections is similar to that reported during the first year of transplantation – a period with higher exposition to immunosuppression – as demonstrated in a study of the same center [33]. In fact, since the treatment of glomerulopathies is based on high-intensity immunosuppression for prolonged periods, a high incidence of infections has been described. In addition, attention should be given to adverse events related to the prolonged use of high doses of steroids, such as Cushing's syndrome, diabetes, hypertension, hyperlipidemia, cataract, osteoporosis and avascular necrosis of the femur head [23,34].

We observed low rates of partial or complete remission, high rate of glomerulonephritis relapse, and a significant incidence of graft loss. Previous studies demonstrated incidences of graft loss of up to 50% after IgAN recurrence with worse outcomes observed in patients with clinically relevant disease, or high-risk disease, similar to those included in our cohort [4,5,9,25,26]. Graft dysfunction at diagnosis was the only variable specific for nephritis associated with a lower risk of remission and increased risk of graft loss; which was similar to results of other researchers [11,17,19]. Although previous studies have suggested worse outcomes of post-transplant IgAN in patients receiving kidneys from living donors [17,18], our results demonstrated that transplantation with deceased donor and the donor age were risk factors for graft loss, consistent with the well-established knowledge that kidneys with lower functional reserve present inferior survival. Interestingly, the earlier the biopsy after the onset of proteinuria, the greater the risk of graft loss. We believe this probably occurred because the most severe cases were biopsied sooner.

Other factors associated with graft loss previously described are: high levels of proteinuria, hypoalbuminemia, systolic hypertension at diagnosis [11,17,19], and not using ACEi during treatment [25]. In our analysis, these variables were not significantly associated with outcomes. The HLA-B8, DR3, recently associated with increased immune activity, and lower renal graft survival in Europeans with IgAN, was uncommon in our sample, and we could not establish an association with outcomes [37].

An observational study reported an association of overweight or obesity with increased proteinuria, severe histological damage, and progression in patients with IgAN in native kidneys [38]. In our cohort, the incidence of overweight was low and there was no association between body mass index (BMI) and outcomes.

This study had important limitations that should be mentioned. The main one was the retrospective single center nature, which impacts the sample size and limits the data collection through medical records. We could not guarantee that all patients had IgAN recurrence, since most patients did not have native kidney biopsies. Although used worldwide, the measurement of proteinuria using protein-creatinine ratio in spot urine samples may not be the ideal tool for transplanted patients with graft dysfunction. Proteinuria is an important marker of clinical response and a well-established prognostic factor in native kidney and allograft IgAN; however, we could not demonstrate the impact of proteinuria at diagnosis on outcomes as only time-average proteinuria was associated with worse prognosis; a similar finding as shown in other studies of native kidneys and allografts [28,35,39]. Importantly, the methodological limitations of our study preclude robust conclusions about the course of proteinuria and its impact on outcomes. This study included 1998 to 2012 cohorts, and the tools for more accurate diagnosis of acute and chronic antibody-mediated rejections were only recently developed. In addition, not all biopsies were available and suitable for review according to the Oxford criteria. Finally, it was not possible to evaluate all possible factors implicated in worse outcomes; in addition, the influence of other pathological conditions for graft losses could not be accurately discarded.

Conclusions

Despite our study limitations, this study reinforces that post-transplant IgAN might have an aggressive course, with early graft loss, especially in kidneys with inferior functional reserve and in those patients with graft dysfunction at diagnosis. There is no ideal treatment, and immunosuppression might be associated with adverse events. This information should be considered when deciding on treatment strategies. Early diagnosis before the onset of renal dysfunction might be a strategy for better outcomes.

Acknowledgments

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