Recurrence and Outcome of Anti−Glomerular Basement Membrane Glomerulonephritis After Kidney Transplantation

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Introduction: Recurrence of anti-glomerular basement membrane (anti-GBM) glomerulonephritis in the kidney graft is a rare event, described in limited reports. The aim of this study was to evaluate, in a large cohort of patients with long follow-up, the risk of recurrence of anti-GBM disease, the risk factors associated with clinical recurrence, and the long-term patient and graft survival.

Methods: This was a multicenter retrospective study. Inclusion criteria were patients with anti-GBM glomerulonephritis who underwent transplantation of a kidney between 1977 and 2015. Exclusion criteria were systemic vasculitis, lupus erythematosus, and cryoglobulinemia. Recurrence was defined as reappearance of clinical signs of glomerulonephritis along with histological signs of proliferative glomerulonephritis and linear IgG staining on kidney biopsy, with or without anti-GBM antibodies.

Results: A total of 53 patients were included. Recurrence of anti-GBM glomerulonephritis in a first kidney transplant occurred in only 1 patient 5 years after transplantation (a prevalence rate of 1.9%) in the context of cessation of immunosuppressive drugs, and resulted in graft loss due to recurrence. Linear IgG staining on kidney biopsy in the absence of histological signs of proliferative glomerulonephritis was observed in 4 patients, in the context of cellular rejection. Patient survival was 100%, 94%, and 89% at 5, 10, and 15 years, respectively. Death-censored first-graft survival rates were 88%, 83%, and 79% at 5, 10, and 15 years, respectively.

Conclusion: The recurrence rate of anti-GBM glomerulonephritis after transplantation is very low but is associated with graft loss. The long-term patient and graft survival rates are excellent.

A nti-glomerular basement membrane (anti-GBM) disease is a rare small-vessel vasculitis mediated by circulating autoantibodies directed predominantly against the noncollagenous domain of the α3 chain of type IV collagen, found in both glomerular and alveolar basement membranes.[1] In most patients (>90%), anti-GBM disease leads to rapidly progressive glomerulonephritis. Kidney biopsy samples usually show crescentic glomerulonephritis on light microscopy, and immunofluorescence reveals the pathognomonic linear deposition of IgG along the glomerular capillaries (although rarely, the antibody may be of the IgA or IgM type).[2] Concomitant alveolar hemorrhage affects 20% to 60% of patients.[3] Serologic testing for anti-GBM antibodies allows a rapid diagnosis of the disease, but false-negative results may occur in patients with low

antibody titers or for technical reasons related to antigen testing.[4]

Early diagnosis, plasma exchange therapy, and immunosuppressive agents have improved the once extremely poor outcome of the disease. However, it remains a rare cause of kidney failure (KF), accounting for less than 1% of all patients with KF[5] and requiring dialysis at presentation in approximately half of the patients.[6] For those with KF, transplantation is the best option. Recurrence of symptomatic anti-GBM disease in the kidney graft is a rare event. Few cases have been reported in the literature,[5,7–16] and although 1 registry study reported 14% of graft failure resulting from disease recurrence 2 decades ago, another more recent registry study found that only 3% of patients developed biopsy-proven recurrent anti-GBM disease after transplantation.[5,13] A recent single-center cohort study from the United States reported a recurrence rate of 3.8%, without providing, however, any information regarding the context and clinical presentation of recurrence.[17]

The aim of this study was to evaluate, in a multicenter, national, large cohort of patients with an extended follow-up and detailed data collection, the risk of recurrence of anti-GBM disease and graft loss caused by recurrence. We also analyzed the complications and the long-term patient and graft survival.

MATERIALS AND METHODS

Study Population
Patients who underwent transplantion with a kidney for anti-GBM disease were considered for inclusion in 6 academic Belgian transplant centers (Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels; Ghent University Hospital, Ghent; University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven; University Hospital Antwerp, Antwerp; Université de Liège, Liège; Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel, Brussels). Inclusion criteria were as follows: (i) a history of anti-GBM disease, defined as a (sub)acute glomerulonephritis (hematuria, proteinuria, increased creatinine) in the presence of a characteristic kidney biopsy result (proliferative extracapillary glomerulonephritis with linear deposits of IgG along the glomerular capillaries on kidney biopsy sample) and/or circulating anti-GBM antibodies; and (ii) a kidney transplantation between 1 January 1977 and 31 December 2015. Patients with systemic vasculitis (except antineutrophil cytoplasmic antibodies [ANCA]), lupus erythematosus, and cryoglobulinemia were excluded.

Table 1. Demographic characteristics of patients with anti-GBM–mediated glomerulonephritis at initial diagnosis (n = 53)

Sex ratio male/female, n (%)	27 (51) /26(49)
Caucasian, n (%)	53 (100)
Age at diagnosis, yr, median (P25–P75)	40 (25–56)
Trigger, n (%)	
Smoking	14 (26)
Organic	5 (9)
Herbicide	1 (2)
Infection	14 (27)
None identified	22 (41)
HLA typing (n = 51), n (%)	
DR15(2)	37 (70)
DR1	3 (6)
DR4	21 (40)
DR7	10 (19)
Pulmonary involvement (n = 47), n (%)	12 (23)
in smokers (n = 14), n (%)	6 (43)
Serology	
Anti-GBM antibodies, n (%)	48 (91)
ANCA positivity	4/36
Low C3	3/33
Treatment, n (%)	
Plasmapheresis	34 (64)
Corticosteroids	47 (89)
Cyclophosphamide	37 (70)
Azathioprine	5 (9)
Dialysis, n (%)	53 (100)
Age at ESRD, yr, median (P25–P75)	41 (10-72)
Modality (n = 52), n (HD/PD/HD+PD)	44/1/7
Time on dialysis, mo, median (P25–P75)	23 (18-38)
Time from diagnosis to ESRD, mo, mean (SD)	21 (13)

ANCA, antineutrophil cytoplasmic antibodies; ESRD, end-stage renal disease; HD, hemodialysis; HLA, human leucocyte antigen; PD, peritoneal dialysis; P25– P75, 25th to 75th percentile.

Adherence to the Declaration of Helsinki and informed consent were respected. The study was approved by the Biomedical Ethics Committee of the Université Catholique de Louvain (Brussels, Belgium) and by the ethics committee of each center.

Definitions
Clinical recurrence was defined as reappearance of signs of glomerulonephritis (hematuria, proteinuria, and increased creatinine), along with histological signs of proliferative glomerulonephritis and linear IgG staining on kidney biopsy, with or without anti-GBM antibodies in a patient with previously documented disappearance of anti-GBM antibodies. Immunohistological recurrence in the graft was defined as linear IgG staining on kidney biopsy in the absence of histologic signs of proliferative glomerulonephritis.

Rejection was defined as treated biopsy-proven acute rejection. Pulmonary involvement was defined as proven alveolar hemorrhage on chest computed tomography or bronchoscopy with bronchoalveolar lavage.

Statistical Analysis

Analyses were conducted using SPSS 25 software (IBM SPSS Statistics for Windows, Version 21.0; IBM Corporation, Armonk, NY) and graphed with GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Continuous variables were expressed as mean ± SD or as median with 25th and 75th percentiles. Categorical variables were reported as counts and percentages. Analysis of progression to graft loss or mortality was estimated using the Kaplan–Meier method. Survival curves were computed with the same method.

RESULTS

Patient Characteristics at Diagnosis of Anti-GBM Disease

The clinical records of 60 patients with a diagnosis of anti-GBM disease were analyzed. Seven patients were excluded because they did not meet the inclusion criteria. In all, 53 patients who underwent transplantation between 1977 and 2015 were included (Table 1). Of these 53 patients, 39 had biopsy-proven IgG linear staining and 48 had anti-GBM antibodies at diagnosis, associated with antineutrophil cytoplasmic antibodies positivity in 4 patients. The human leucocyte antigen (HLA) HLA-DR15(2) risk allele, which is associated with genetic susceptibility, was present in 70% of all included patients. Pulmonary involvement was present in less than 25% of patients. Therapy combining plasmapheresis, cyclophosphamide, and corticosteroids was predominant. All patients had to start dialysis within a mean time of 2 months (SD, 13 months).

Patient Characteristics at Transplantation

A total of 53 patients underwent a first kidney transplantation for anti-GBM disease (Table 2). The median age at transplantation was 43 years (range, 27–59 years). Anti-GBM serology at the time of first kidney transplantation was available in 43 of these patients, and none was positive. Median time between anti-GBM disappearance and first kidney transplantation was 15 months (range, 8–31 months). The most frequent maintenance therapy (n = 35) was a combination of calcineurin inhibitor, mycophenolate mofetil, and corticosteroids.

Recurrence of Anti-GBM

A total of 33 allograft biopsies were performed during follow-up. Of these 33 biopsies, the search for IgG staining was available in 19 biopsy samples: 1 patient had clinical recurrence, whereas 4 had only immunohistological recurrence.

Clinical Recurrence

Clinical recurrence occurred in only 1 recipient after a first kidney transplantation (n = 53), representing a

Table 2. Demographic characteristics of patients with anti-GBM–mediated glomerulonephritis at first kidney transplantation

Age, yr, median (P25–P75)	43 (27–59)
Anti-GBM antibodies (n = 43)	0
Time between anti-GBM disappearance and kidney transplantation, mo, median (P25–P75)	15 (8-31)
Donor deceased/living, n (%)	44 (83)/9 (17)
Immunosuppressive regimen	
Induction (n = 46), n (%)	28 (61)
Maintenance, n (%)	
Calcineurin inhibitors	50 (96)
mTOR inhibitors	4 (8)
MMF	37 (71)
AZA	13 (25)
Corticosteroids	52 (100)

AZA, azathioprine; GBM, glomerular basement membrane; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin; P25–P75, 25th–75th percentile.

prevalence rate of 1.9%. Our group reported this case in 1998.[12] This patient was a 33-year-old woman who was diagnosed with anti-GBM glomerulonephritis at age 24 years when she presented with subacute kidney failure requiring dialysis. There was no lung involvement. Intravenous methylprednisolone followed by oral prednisolone and oral azathioprine failed to improve renal function. She received a kidney transplant from a deceased donor 26 months later. Circulating anti-GBM antibodies had been consistently negative for 14 months. The postoperative immunosuppressive regimen included an induction therapy with anti-thymocyte globulins and a maintenance immunosuppressive regimen with cyclosporine, azathioprine, and prednisolone. Graft tolerance was excellent during the next 5 years. Circulating anti-GBM antibodies were repeatedly negative, and microscopic hematuria was observed intermittently in the absence of proteinuria. Sixty-eight months after transplantation, she stopped her immunosuppressive treatment in the context of social and financial problems, and was admitted 1 month later with severe acute kidney injury, proteinuria, and microhematuria. Recurrence of anti-GBM nephritis was diagnosed based on the reappearance of circulating anti-GBM antibodies and crescentic glomerulonephritis with strong linear staining for IgG along the GBM. The kidney biopsy sample also showed signs of both acute and chronic graft rejection, with acute interstitial inflammation with tubulitis and tubulointerstitial fibrosis. The patient had no pulmonary involvement. Maintenance hemodialysis was required despite treatment with intravenous cyclophosphamide and methylprednisolone. Except for stopping immunosuppressive treatment, no environmental trigger (such as cigarette smoking, hydrocarbon solvents, organic solvents, and herbicides) or infection episode was identified. She

carried the HLA DR15(2) allele, which is associated with an increased susceptibility to the development of anti-GBM antibodies.

Immunohistological Recurrence

Immunohistological recurrence with IgG linear deposits was documented in 4 of the 19 first grafts in which a kidney biopsy sample with IgG staining (IF/IHC) was available. The indications for biopsy in these patients were an increased creatinine in 3 patients and per protocol in 1 patient.

Patient 1 underwent biopsy per protocol 3 months after transplantation and had a borderline acute rejection along with strong linear IgG deposits. Anti-GBM antibodies were negative. He was treated with transient increased oral methylprednisolone. Seven years later, he presented with increased creatinine. A kidney biopsy sample showed transplant glomerulopathy, with no linear IgG deposits and negative C4d. He lost his graft function within 1 month.

Patient 2 underwent biopsy 4 years after transplantation for increased creatinine. Acute vascular rejection and weak linear IgG deposits were observed. Anti-GBM antibodies were not tested. Kidney graft was lost within days.

Patient 3 underwent biopsy for increased creatinine 3 months after transplantation. The biopsy showed a moderate to severe acute cellular rejection and weak linear IgG deposits. She was treated with corticosteroids and anti-thymocyte globulin. Anti-GBM antibody titer was not available at the time of the biopsy, but was negative 2 weeks later and repeatedly thereafter. A second biopsy sample 3 weeks later showed persistent severe acute cellular rejection, but no linear IgG deposits. The kidney graft was lost within weeks.

Patient 4 presented with an acute rise in creatinine (2.1 mg/dl, rising from 1.08 mg/dl) and slight proteinuria (0.48 g/d) without hematuria, 7 weeks after transplantation. Circulating anti-GBM antibodies were weakly positive (despite being negative for 14 months before transplantation). The graft biopsy showed borderline acute cellular rejection, no glomerular lesion, but weak linear glomerular deposits of IgG. The patient was treated with intravenous methylprednisolone, with stabilization of her serum creatinine. Circulating anti-GBM antibodies were thereafter repeatedly negative. Twenty-two years after kidney transplantation, she is alive with stable graft function and absence of hematuria. She also displayed the HLA DR15(2) risk allele.

Posttransplantation Outcomes of Patients Receiving Transplants for Anti-GBM Disease

The median posttransplantation patient follow-up period was 122 months (range, 60−213 months)

Table 3. Post-transplantation outcomes of patients who underwent transplantation for anti-GBM disease (except for recurrence)

Acute rejection, n (%)	22 (43)
Complications, n (%)	
Cardiac	13 (25)
Hypertension	39 (74)
Neoplasia	14 (27)
NODAT	9 (17)
Infection	37 (70)
Loss of first graft, n (%)	
Rejection	12 (23)
Recurrence	1 (1,9)
Renal vein thrombosis	1 (1,9)
Infection	1 (1,9)
NA	1 (1,9)
Death, n (%)	3 (5,7)
Kidney re-transplanted for second/third time, n	7/1
Follow-up, mo, median (P25−P75)	122 (60−213)

NA, not available; NODAT, new-onset diabetes after transplantation; P25−P75, 25th−75th percentile.

(Table 3). Patient survival was excellent: 100% at 5 years, 94% at 10 years, and 89% at 15 years (Figure 1). Three patients died: 1 of a hemorrhagic stroke, 1 of a small cell lung carcinoma, and 1 of infection, 80, 124, and 153 months after transplantation, respectively. The overall death-censored first graft survival rates were 88%, 83%, and 79% at 5, 10, and 15 years respectively (Figure 1). Sixteen first grafts were lost for the following reasons: rejection (n = 12), recurrence (n = 1), infection (n = 1), renal vein thrombosis (n = 1), and cause unknown (n = 1). Twenty-two patients (43%) had a treated biopsy-proven acute rejection. The reason for the graft biopsy is known in 12 of these patients. Eleven biopsies were performed for an increased serum creatinine, and 1 was performed per protocol.

Posttransplantation complications included high blood pressure (n = 39), infections (n = 37), neoplasia (n = 14), cardiovascular disease (n = 13), and new-onset diabetes after transplantation (n = 9). Seven patients underwent transplantation 2 times and 1 patient 3 times.

Evolution of Second and Third Transplantations

Seven patients underwent transplantation for a second time (their first grafts were lost from rejection [n = 5], venous thrombosis [n = 1], and unknown reason [n = 1]). Two patients lost their second graft (1 from rejection and the second from venous thrombosis). One patient underwent a third transplantation, with a still-functional graft at last follow-up. There was no recurrence of their primary kidney disease.

DISCUSSION

In this multicenter analysis, we reviewed the outcome of 53 patients who underwent kidney transplantation
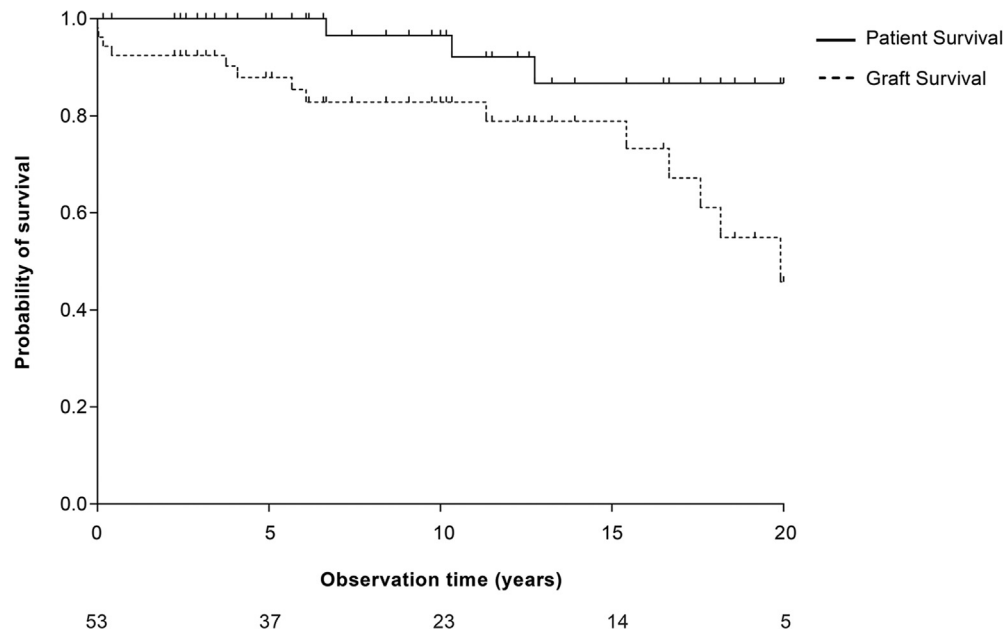
Figure 1. Kaplan—Meier curve. Patient survival and death-censored first graft survival after kidney transplantation for anti—glomerular basement membrane (GBM) glomerulonephritis.

for anti-GBM disease and were followed up for a median of 10 years. We found that clinical recurrence occurred in only 1 patient, a prevalence rate of 1.9%. Recurrence led to graft loss. Patient survival and overall death-censored first graft survival rates were excellent: 100%, 94%, 89%, and 88%, 83% and 79% at 5, 10, and 15 years, respectively.

Clinical recurrence of anti-GBM disease after transplantation was considered non-negligible in early reports. A study in 1973 reported recurrent glomerulonephritis in more than half of the patients who had undergone transplantation for anti-GBM disease. Graft loss from recurrence was noted in 40% of the patients.[8] In 1999, an analysis of the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) registry reported 14% graft failure was recorded as resulting from anti-GBM disease recurrence.[13] A few case reports have described recurrence of anti-GBM disease after kidney transplantation. Seven case reports, including the one describing our patient, pointed to the risk of recurrence of glomerulonephritis.[7,10—12,14—16] In 2013, the Australian and New Zealand Dialysis and Transplantation (ANZ-DATA) registry reported biopsy-proven recurrence of the disease in 6 of 224 patients transplanted for anti-GBM disease between 1963 and 2010 (2.7%) leading to graft failure in 2 cases.[5] Very recently, a single-center cohort study reported a recurrence rate of 3.8%.[17] In line with these recent publications, we found a clinical recurrence of 1.9% for anti-GBM disease after transplantation.

Risk factors for recurrence of anti-GBM glomerulonephritis that emerge from the literature, including our patient, are the presence of anti-GBM antibodies before transplantation and low-dose or no immunosuppressive therapy. Indeed, recurrence occurred in 2 patients who had circulating anti-GBM antibodies before transplantation,[2,15] leading the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group to recommend a period of at least 6 months' sustained seronegativity before undertaking kidney transplantation.[18] Of 4 other patients, 2 were not taking any immunosuppressive agent: 1 patient because he received a kidney from an identical twin[10] and 1 patient because of immunosuppression therapy cessation,[12] and 2 patients because they were on low-dose bi-therapy immunosuppression including cyclosporine and prednisone only.[11,14] This underlines that potent maintenance immunosuppressive therapy is important in suppressing disease activity and maintaining a negative titer of negative anti-GBM antibodies. With cessation or reduction of immunosuppression, not only can the disease reactivate with production of anti-GBM antibodies, but rejection can also occur, causing graft injuries that could reveal an epitope normally hidden from the immune system, and precipitating anti-GBM antibody formation/reactivation.[19] Genetic susceptibility, including HLA allele, could also be associated with disease recurrence.[20]

The incidence of recurrent linear IgG staining in the kidney allograft reached 50% in historical series when transplantation was performed in the presence of anti-GBM antibodies. Only a quarter of these patients

developed clinical anti-GBM disease.[3] In our cohort, biopsies were performed for increased creatinine and per protocol in some patients. Linear IgG deposits were observed concomitant to acute or borderline rejection. Unlike the classical clinical recurrence associated with anti-GBM antibodies reappearance, these linear IgG deposits are observed without other glomerular lesions or crescents in the absence or presence of weak titer of antibodies. A possible explanation could be that rejection unveils normally hidden antigens or that low immunosuppression favors disease reactivation with anti-GBM antibody production. Nevertheless, restoring adequate immunosuppression in case histological lesions are not yet severe could prevent further progression of glomerular lesions.

Patient and graft survival were excellent in our cohort. Patient survival was 100%, 94%, and 89% at 5, 10, and 15 years, respectively. The 10-year patient survival is better than the one reported by Tang et al. in the ANZDATA registry (86%),[5] and is comparable to that in a cohort of patients who underwent kidney transplantation for Henoch—Schönlein purpura nephritis over approximately the same time period (95%).[21] Three patients died of cardiovascular disease, malignancy, and infection, the classical causes of mortality in transplant recipients. Our 10-year graft survival was 83%, much better than the 63% reported by the ANZDATA registry and the 65% reported in the cohort with Henoch—Schönlein purpura nephritis. Unlike a registry study, our study allows an in-depth analysis of patient outcomes during an extended follow-up period.

We acknowledge the limitations of this study. It is a retrospective study with a relatively limited number of patients and no systematic biopsies of the kidney graft. Nevertheless, it is the largest reported cohort study to include patients with this rare disease. Moreover, it gathers patients from a small country with a homogeneous population and detailed data collection, including individual therapy management, laboratory values, and renal histopathology. This allowed us a thorough analysis of recurrence, whereas recent reports mentioned recurrence without further detail. Also, follow-up was very long, allowing a good appreciation of disease evolution.

In conclusion, we found that patient and first graft survival rates after kidney transplantation for anti-GBM disease were excellent. The clinical recurrence rate of anti-GBM disease after transplantation is very low (1.9%) and is associated with graft loss. Delaying transplantation until circulating anti-GBM antibodies have disappeared and maintaining adequate immunosuppression decreases the likelihood of recurrence, which nevertheless should be considered in case of clinical signs.

DISCLOSURE

ACKNOWLEDGMENTS

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