Recurrent IgA Nephropathy After Renal Transplantation

By Jürgen Floege

Recurrence of the original disease is now the third most frequent cause of allograft loss at 10 years after transplantation in patients with underlying glomerulonephritis. IgA nephropathy (IgAN), the most common type of glomerulonephritis, histologically recurs in up to 60% of the patients. Initially considered to be a relatively benign phenomenon, several studies, which included a total of almost 1200 patients with underlying IgAN, have now established that after a mean follow up of 5 years, approximately 13% of the patients will exhibit some recurrence-related renal graft dysfunction and approximately 5% will have lost their graft as a result of recurrent IgAN. The only established predictor of graft loss is the time elapsed since renal transplantation. The risk of recurrence-associated graft loss increases to approximately 25% if a prior graft has already been lost as a result of recurrent IgAN. Whether living, related donor kidneys are at higher risk for recurrence is controversial. Despite all these issues, graft survival in patients with underlying IgAN compared with patients with other renal diseases is excellent. In patients with recurrent IgAN, no specific therapy other than optimal supportive care has been established.

RECURRENCE IS AN important cause of renal graft loss in patients whose original disease was glomerulonephritis. For example, in such patients, an Australian study based on the ANZDATA registry showed that recurrence was the third most frequent cause of allograft loss at 10 years.[1] Given the increase in overall allograft survival rates,[2] it is therefore predictable that the relevance of recurrent glomerulonephritis will increase in the future.

Primary IgA nephropathy (IgAN) represents the most common type of glomerulonephritis in the Western world.[3,4] Affected patients usually represent ideal candidates for a renal graft and therefore account for a significant share of transplant patients, for example, 13% of all transplant patients in the ANZDATA system.[1] Although it has been known for some time that up to 60% of such patients will experience a histologic recurrence of the disease, if protocol biopsies are obtained,[5] it was initially assumed this is a relatively benign condition and hardly ever affects the graft function.[6,7] This view has been changed by a considerable number of studies published during the last 8 years,[1,5,8-16] which are summarized here.

DEFINITION AND CLINICAL MANIFESTATIONS

The major problem in studying the origin of graft failure in patients with underlying IgAN is that it could be very difficult to separate the clinical relevance of recurrent IgAN from other mechanisms of chronic graft failure. By definition, the diagnosis of recurrent IgAN requires an accurate identification and characterization of glomerulonephritis in the native kidneys and subsequent identification of the same disease affecting the transplant kidney. Of note, these basic requirements are often not fulfilled in reports in the literature. In the case of recurrent IgAN, detailed clinical data and biopsy findings (in particular when examined by immunohistology and electron microscopy as well) can usually allow, with some likelihood, to differentiate between the relative contribution of dysfunction resulting from recurrent disease and other reasons, in particular, so-called "chronic rejection." Clinically, manifest recurrent IgAN is often associated with persistent microhematuria and proteinuria exceeding 0.5 g per day but usually remaining below the nephrotic range. Less frequent, albeit possible, is gross hematuria associated with upper respiratory tract infections.[9,17] Histologically recurrence should be associated with the demonstration of mesangioproliferative glomerulonephritis, i.e., not just recurrent mesangial IgA deposits, in the graft. Very rarely, recurrent IgAN could present as crescentic glomerulonephritis with rapidly progressive renal failure.[18]

It is clear, therefore, that data on the relevance of recurrent IgAN are highly dependent on local biopsy policies and techniques of histologic evaluation. Importantly, even if clinical and histologic recurrence of IgAN has been established by graft biopsy, a later graft biopsy sometimes could become negative for IgA deposits.[9] These facts could in part explain the large variability of the data shown in Table 1. This discussion also renders it

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Table 1. Summary of Available Studies on Recurrent IgA Neuropathy After Transplantation

Authors	No. of Patients	Follow-Up in the Whole Study Population (mean and range; mo)	Graft Dysfunction/ Loss Resulting From Recurrence	Follow Up in Patients With Graft Dysfunction/Loss Resulting From Recurrence of IgAN (mean and range; mo)
Odum et al., 1994[5]	46	NA (3-183)	11%/2%	62 (32-75)
Kessler et al., 1996[8]	28*	73 (4-120)*	21%/14%	84 (43-119)
Frohnert et al., 1997[9]	51	NA (<3->156)	19%/6%	NA (12->144)
Ohmacht et al., 1997[10]	61†	54 (7-127)	23%/16%	67 (32-102)
Bumgardner et al., 1998[11]	54	61 (NA)	16%/10%	75 (NA)
Freese et al., 1999[12]	104‡	67§ (11-159)	13%/6%	NA
Kim et al., 2001[13]	89	60 (2-164)	NA/2%	NA
Andresdottir et al., 2001[14]	79	66 (NA)	9%/2%	NA (13-145)
Wang et al., 2001[15]	48	52 (18-155)	10%/8%‖	95 (NA)
Ponticelli et al., 2001[16]	106	70 (12-120)	NA/4%	74 (12-120)
Briganti et al., 2002[1]	532	~56 (<12->120)	NA/3%	NA
Pooled patient population	1198	55 (2-183)	12.5/4.7%	75 (12-145)

Abbreviation: NA, not available.

* Only patients who received a transplant biopsy because of graft dysfunction or urinary abnormalities are included in the data shown. Five patients suffered from underlying Henoch-Schönlein purpura.

† Four patients suffered from underlying Henoch-Schönlein purpura.

‡ 50% of the patients had living donors.

§ Median and range.

‖ Cause of graft loss not specified

likely that the relevance of recurrent disease as a cause of long-term graft loss is underestimated. Despite these limitations, the pattern and significance of recurrent glomerulonephritides, in particular IgAN, has become clearer over time.

EPIDEMIOLOGIC STUDIES

Over the last decade, 11 retrospective single or multicenter studies have assessed the clinical relevance of recurrent IgAN, with renal biopsies mostly performed as indicated for investigation of graft dysfunction, hematuria, and/or proteinuria[1,5,8-16] (Table 1). Importantly, mean follow up in most of these studies was longer than 5 years. This could explain why earlier, more short-term studies failed to detect a clinical impact of recurrent disease,[6,7] because recurrence-related graft deterioration is rare before 3 years after transplantation. In the recent studies, the clear message evolved that recurrent IgAN becomes clinically relevant and significantly contributes to graft failure once a 5-year follow up has passed. At this time, approximately 13% of all patients exhibited some recurrence-related graft dysfunction and approximately 5% had lost their graft due to recurrence (Table 1). In our own study,[10] it also became apparent that the impact of recurrent IgAN could be diluted by the more rapid manifestation of chronic allograft rejection and/or other reasons for graft failure.

PREDICTORS OF CLINICALLY RELEVANT IgA NEUROPATHY RECURRENCE

With respect to predictors of clinically relevant recurrent IgAN after a first renal transplant, most current studies suggest that it represents largely a function of time posttransplantation and cannot be predicted by other variables. In this respect, the recurrent disease exhibits considerable clinical similarities with the original course of progressive IgAN. The only other predictors, which were identified in single but not all studies, could be young age and male sex of the recipient.[1,16] All other recent studies[5,8-13] consistently demonstrated that clinical and laboratory findings before transplantation, the HLA typing or matching, the ACE I/D gene polymorphism, the type of immunosuppression, and various posttransplant parameters were not able to predict graft failure resulting from recurrent IgAN. Also, various biochemical characteristics of circulating IgA did not allow a clear identification of patients with recurrence.[19] Not unexpectedly and similar to the primary disease, in the patients with clinically established recurrence

Table 2. Fate of a Second Renal Transplant in Patients Who Had Previously Lost a Graft as a Result of Recurrent IgA Neuropathy

Authors	No. of IgAN Patients With Repeated Transplantations	Graft Loss as a Result of Repeated Recurrence (%)	Follow-Up (mo) range or mean ± standard deviation
Ohmacht et al., 1997[10]	5	3	21-51
Bumgardner et al., 1998[11]	5	—	54 ± 28
Freese et al., 1999[12]	5	1	3-48
Ponticelli et al., 2001[16]	1	—	92
Pooled patient population	16	25%	

heavy proteinuria, glomerulosclerosis and hypertension were predictive of progression to allograft failure.[20]

The situation appears to be markedly different in patients with a second or third renal transplant. In a study of the European Renal Association registry in patients with any type of glomerulonephritis, it was documented that recurrence of the original disease was dramatically more frequent if a prior graft had been lost as a result of recurrent glomerulonephritis.[21] Our own study[10] (Table 2) in IgAN showed that not only recurrence rates, but also its clinical relevance could increase considerably; of five patients who were retransplanted after graft failure as a result of recurrent IgAN, three again developed end-stage renal disease as a result of repeated recurrence of the primary disease. In the study of Freese et al.,[12] five such patients were retransplanted and one again lost his graft as a result of recurrence at 3 months, whereas the other four exhibited no recurrence. In two other studies,[11,16] a total of six patients were retransplanted of which five patients with repeated, histologically confirmed recurrence of IgAN exhibited good renal function but moderate proteinuria at up to 92 months of follow up (Table 2).

Should transplantation potentially be discouraged in patients with underlying IgAN? Long-term stable courses of up to 183 months even in the face of histologically proven IgAN recurrence have been documented after transplantation.[5,8-13] Compared with many other patients suffering from systemic disorders who enter dialysis, those with IgAN generally have little comorbidity and, as such, represent ideal candidates for transplantation. Graft and patient survival in the first years after transplantation is reported to be superior to that of other transplant patients, possibly related to the increased occurrence of alloreactive IgA anti-HLA antibodies in such patients and their overreactivity of the IgA system. These IgA anti-HLA antibodies could be be less pathogenic than IgG anti-HLA antibodies, resulting in fewer and/or less severe acute rejection episodes.[16,22] More importantly, in comparison to patients with other underlying glomerulonephritides or nonglomerulonephritis disorders, patient and graft survival up to 10 years after grafting in cases of underlying IgAN is not different.[1,13,14,16] Given all these observations, primary IgAN definitely should not prevent transplantation. However, it appears important that both physicians as well as patients with underlying IgAN (particularly those who have already lost a graft as a result of recurrence) are aware of the fact that recurrent disease could cause graft loss after approximately 5 years onward.

A clinically important question relates to living, related donors. At present, it is controversial whether living, related donor kidneys are at a higher risk for recurrence and graft deterioration than kidneys from nonrelated donors. In this respect, many studies have failed to detect a significant difference,[9,11,13,16] one study was indeterminate,[14] and others noted a negative impact of a living, related donor on graft outcome.[12,15] However, even in the studies, in which the risk was increased with living, related donors, graft survival of living, related and nonrelated grafts was identical at 5 years and failed to reach a significant difference at 10 years.[12,15] If a living donor is considered, it is important to remember the frequent familial manifestation of either IgAN or at least of urinary abnormalities.[23] Because familial IgAN carries a markedly increased risk of end-stage renal disease,[24] even apparently minor urinary findings in related donors should be clarified by renal biopsy before donation is accepted.

THERAPY OF RECURRENT IgA NEUROPATHY

At present, the only therapy of recurrent IgAN is the institution of good supportive measures along the recommendations that apply to the original disease,[25] in particular, the usage of angiotensin-converting enzyme inhibitors in such patients.[26] Whether fish oil is also an option, as reported in a study from the Mayo Clinic,[27] has not been finally definitively established and similar concerns as in the case of fish oil treatment in primary IgAN apply, namely, lack of definitive evidence for efficacy[28] as well as a relatively high cholesterol content of many fish oil preparations.

No immunosuppressive drug, including newer drugs such as mycophenolate mofetil (MMF) or rapamycin, can prevent histologic recurrence of IgAN.[16] However, some preliminary data suggest that MMF could affect the clinical course of recurrent IgAN.[29] MMF, unlike currently available immunosuppressive agents, has considerable activity on B lymphocytes in addition to T lymphocytes, and could thereby reduce the exaggerated IgA production in patients with IgAN. Also, recent data suggest that MMF has a direct antiproliferative effect on mesangial cells *in vivo.*[30] Unfortunately, all other data available to date on MMF in patients with underlying IgAN suffer from short-term follow up, and it will therefore take several years to establish the role of this potential new approach for the prevention of recurrent IgAN. Enthusiasm for MMF in recurrent IgAN, however, has recently been dampened by the reported lack of efficacy of MMF (1 g administered twice daily) in patients with IgAN in their native kidneys.[31] Improvement or stabilization of failing graft function has been noted in 11 of 19 patients with recurrent IgAN after conversion from cyclosporine A to tacrolimus.[32] However, in that study, tacrolimus rescue failed in the remaining eight patients and three lost their graft during the observation period. Of note, in the failing patients, serum creatinines were significantly higher than in the successful cases, suggesting that early intervention should be aimed for.[32]

RECURRENT HENOCH-SCHÖNLEIN PURPURA

In contrast to recurrent IgAN, much less is known on the course of Henoch-Schönlein purpura (HSP), considered by many to represent the systemic variant of IgAN, after renal transplantation. A close pathogenetic link between HSP and IgAN is derived from the observation that recurrence of HSP often manifests as isolated renal allograft involvement,[33,34] which is histologically indistinguishable from IgAN. Less frequently, extrarenal manifestations of HSP such as rash, abdominal pain, or arthralgia without affection of the transplant have been noted.

The data available to date suggest that recurrence rates of clinically relevant IgAN in patients with underlying HSP are similar to those observed in patients with underlying IgAN.[10,33] In other studies[14,35] comprising nine and 12 patients with HSP, respectively, no clinically evident recurrence of IgAN or graft loss was noted even with follow up to a mean of 13 years. In contrast, in the ANZDATA system, four of 24 patients, i.e., 17%, lost their graft as a result of recurrence.[1] The only large study published also suggests that delaying transplantation until 1 year after the disappearance of purpura has no effect on the recurrence rate.[33]

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