Recurrent IgA Nephropathy with Graft Dysfunction in Patients with Crescentic versus Non-Crescentic IgA Nephropathy in Their Native Kidneys

Study Purpose and Rationale

IgA nephropathy is the most common glomerulopathy in the world [1]. IgA nephropathy was once thought to have a benign clinical course, but more recent evidence shows that up to 50% of patients with long-standing IgA nephropathy develop a slow progression to end-stage renal disease often over 20-25 years of observation [2]. Of these patients with long-standing IgA nephropathy who develop ESRD, many are fortunate enough to receive kidney transplants. However among these transplanted patients, it is estimated that ~20-60% of them will develop recurrent IgA nephropathy post-transplant [3]. Just like IgA nephropathy in native kidneys, recurrent IgA nephropathy after transplantation does not always follow a benign clinical course. Studies show that in a mean follow-up period of 63 months in 67 patients studied, there was a 15% incidence of significant graft dysfunction and 7% incidence of graft loss due to recurrent IgA nephropathy [4]. Another retrospective analysis from Australia reports that the 10 year incidence of graft loss due to recurrent IgA nephropathy in 532 allograft recipients with primary IgA nephropathy was 9.5% [5]. Graft dysfunction and loss are particularly disheartening for both patients and doctors especially when so much time & effort are spent in securing/managing transplants for these patients. There currently is little data that explores which patients with IgA nephropathy are more prone to recurrent IgA nephropathy with graft dysfunction after transplantation.

Recent studies suggest that the prognosis of kidney transplants in patients with IgA nephropathy may be linked to the initial histological aggressiveness of their native kidney biopsies. It was shown that patients with a special histologic type of IgA nephropathy called crescentic IgA nephropathy in their native kidneys at diagnosis showed a 5-year graft survival of 71% vs. 100% among patients with non-crescentic IgA nephropathy [6]. Based on this study, it is unclear whether or not the decreased graft survival in the crescentic group could be attributed to recurrent IgA nephropathy.

Crescentic IgA nephropathy is simply a specific type of rapidly progressive glomerulonephritis. Like other RPGNs, crescentic IgA nephropathy is quite aggressive & can lead to end-stage renal disease over a relatively short period of time (i.e. days, weeks or months). Unfortunately, there is no universal histologic definition of crescentic IgA nephropathy, but there needs to be at least 1 cellular crescent found in a kidney biopsy slide for a nephropathy to be considered "crescentic." In terms of prevalence of crescentic IgA nephropathy, estimates suggest that roughly 3-5% of all IgA nephropathies are considered crescentic when crescents are seen in more than 50% of glomeruli, and ~30% of all IgA nephropathies are recorded as crescentic if any number of involved glomeruli is taken into account [7].

Not a lot of data exists concerning how patients with crescentic IgA nephropathy do after they receive renal transplants. Our study aims to shed more light on this subject by seeing how often patients with crescentic IgA nephropathy in their native kidneys develop recurrent IgA nephropathy with graft dysfunction after transplant. Figuring out which types of patients with IgA nephropathy are more prone to recurrent IgA nephropathy with graft dysfunction after transplantation is an important issue that has major implications in organ allocation & post-transplant monitoring.

Study Design and Statistical Analysis

Goal:

The aim of this study will be to compare the incidence of recurrent IgA nephropathy with graft dysfunction between patients with crescentic vs. noncrescentic IgA nephropathy in their native kidneys.

Hypothesis:

We hypothesize that patients with crescentic IgA nephropathy in their native kidneys will have a higher incidence of recurrent IgA nephropathy with graft dysfunction post-transplant when compared to the incidence of recurrent IgA nephropathy with graft dysfunction in the non-crescentic group.

Study Overview:

This is a retrospective cohort study & the patient population will be extracted from the Columbia University Medical Center Registry for Kidney Transplants. Specifically, patients who received renal allografts between 1985-2005 who have IgA nephropathy listed as the reason for transplant will be examined. Based on estimates, there should be a total of ~500 transplant patients that meet those criteria. All these patients should have pre-transplant biopsies on file as a prerequisite to receiving a kidney transplant. Among this cohort, there needs to be a determination of whether or not the patient had crescentic or non-crescentic IgA nephropathy before they were transplanted. As mentioned earlier, there is no universal histologic definition for crescentic IgA nephropathy, but for our purposes, we defined crescentic IgA nephropathy as the presence of any number of cellular crescents in glomeruli with underlying IgA deposits examined under the pre-transplant biopsy slide. We will enlist the help of a renal pathologist to review all biopsy slides.

The primary outcome of our study will be determining the incidence of recurrent IgA nephropathy with graft dysfunction in the crescentic IgA nephropathy group vs. the non-crescentic IgA nephropathy group.

Recurrent IgA nephropathy with graft dysfunction will be defined as follows (all criteria must be met):

1. Mesangial +/- endocapillary IgA dominant or codominant deposits in renal allograft on immunofluorescence microscopy
2. No evidence of rejection
3. Serum creatinine > 150% over baseline creatinine

In standard practice, not every patient receives a kidney biopsy after transplant. Only patients that show renal/graft dysfunction (i.e hematuria, proteinuria or serum creatinine elevation) get a biopsy after transplant to determine etiology of their dysfunction. Patients who regularly follow up with their nephrologist at least every 2 years & do not have a post-transplant biopsy on file are assumed to have normal graft function. Regardless of when the patient received his/her transplant, both groups will be assessed for the primary outcome up until Jan 1, 2012. Previous studies suggest that recurrence of IgA nephropathy becomes a relevant cause of graft failure around 5 years after transplantation [8]. Since the patient population will include transplant recipients from 1985-2005, this should give roughly enough time for patients transplanted in 2005 to show evidence of graft dysfunction if they are to exhibit it at all.

Inclusion Criteria/Exclusion Criteria:

To be included in the study, subjects must:

-be greater than 18 years of age

-have pre-transplant biopsies to categorize the patient

-have IgA nephropathy listed as reason for transplant

-have a checkup by a nephrologist at least every 2 years to make sure they are not lost to follow up

-have no evidence of rejection in their graft

Statistical Analysis:

Based on previous studies, the assumed incidence of recurrent IgA nephropathy with graft dysfunction in patients with non-crescentic IgA nephropathy in their native kidneys is 20% [3]. Unfortunately, there are no large studies estimating the incidence of recurrent IgA nephropathy with graft dysfunction in patients with crescentic IgA nephropathy in their native kidneys; however, the

assumed incidence based on smaller studies is estimated to be ~40% [9]. The estimated effect size between the two groups would thus be 20%. Studies suggest that crescentic IgA nephropathy, as we have defined it in our study, represents about 25% of all IgA nephropathy cases.

Using the chi-square test for 80% power & 5% type 1 error rate, the number needed is 58 in the crescentic group and 174 in the non-crescentic group for a total of 232 participants. Incidence of recurrent IgA nephropathy with graft dysfunction will be determined in both groups & these results will undergo chi-square testing to determine p values & statistical significance. Multiple logistic regression will be performed also to control for covariates.

Study Procedures

This is a retrospective study, so all procedures including renal biopsies will have already been done. No additional procedures are needed for this study.

Study Drugs/Medical Devices

N/A

Study Questionnaires

N/A

Study Subjects

As outlined above.

Recruitment

As outlined above.

Confidentiality of Study Data

All study data will be kept in a password protected computer & file. Each participant will be identified by a randomly generated number & all identifying data will be securely discarded once the study is over.

Potential Conflict of Interest

N/A

Location of the study

New York Presbyterian – Columbia University Medical Center Hospital

Potential Risks

N/A

Potential Benefits

No direct benefits to patients being studied.

Alternative Therapies

N/A

Compensation to Subjects

N/A

Costs to the Subjects

N/A

Minors

N/A

R. Radiation

N/A

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