

Incidence of Rejection in Renal Transplant Surgery in the LVHN Population Leading to Graft Failure: 6 Year Review

Jessica Ludolph¹

Lynsey Biondi, MD^{1,2} and Michael Moritz, MD^{1,2}

¹Department of Surgery, Lehigh Valley Health Network

²Research Scholar Program Mentor

Abstract

To obtain optimal outcomes, it is vital to continually investigate variables potentially effecting rejection and graft failures. 407 renal transplant recipients who were transplanted at The Transplant Center of the Lehigh Valley from January 2009 to December 2014 were analyzed using descriptive statistics. Variables potentially influencing graft survival, including delayed graft function, and cell mediated and antibody mediated rejection, were compared. Demographic information, donor characteristics, and cold ischemic time were also investigated.

Rejection of one or more types occurred in 39% of patients. Cellular rejection (35% of total patients) occurred more commonly than antibody mediated rejection (8% of total patients), with borderline cellular rejection the most common (40% of rejections). Antibody mediated rejection negatively impacted graft survival ($p=0.0917$) whereas cellular rejection did not show a statistically significant effect. Delayed graft function was common (29% of patients), but patients with delayed graft function have similar rejection rates as patients without delayed graft function (29% for both). Delayed graft function was associated with significantly lower graft survival.

Background

Typical solid organs transplanted are the kidneys, heart, liver, pancreas, and lungs. Kidneys are the most common solid organ transplant performed. The Transplant Center of the Lehigh Valley performs a large volume of kidney transplant surgeries and maintains a large database with the details of these procedures. This project will quantify recent outcomes data related to incidences of the different types of rejection as compared to other variables. These variables include transplant type, cause of renal failure, and time on dialysis prior to transplantation. Currently, there is debate about the impact of acute rejection episodes on graft survival. More recent studies demonstrate a reduction in incidences of rejection over time, but not a similar reduction in renal graft failure.⁵ Further studies have also seen that graft failures are less dependent on the acute rejection episode itself but rather that an acute rejection can initiate a chronic pathological process that ultimately leads to graft failure.⁸

Rejection can be broken down into two major types; cell-mediated and antibody mediated rejection. Severity is graded on the Banff '97 scale. This scale is broken down into seven different categories, in order of increasing severity: Borderline, Grade 1A, Grade 1B, Grade 2A, Grade 2B, Grade 3, and Grade 4, aimed at providing a standard classification system for the

varying pathologies seen on histological examination. In addition to the Banff scale, clinical vs. subclinical rejection becomes an important metric for evaluating the ultimate outcome of the allograft. An incidence of subclinical rejection is diagnosed from biopsies performed routinely based on protocol rather than for a change in transplant function. LVHN performs protocol biopsies at 1, 6, and 12 months post-transplant. Additional biopsies are performed when clinically indicated, usually a negative change in transplant function. In some studies, rejection episodes that do not cause a decrease in renal function have a lesser impact on graft survival.⁵ It can be postulated then, that subclinical rejection episodes do not have as significant of an impact on graft survival as clinical rejection episodes.

The occurrence of cell mediated versus antibody mediated rejection can have vastly different effects on outcomes. These two types of rejection should not be thought of as completely separate entities, but rather overlapping, where an episode of unresolved cell-mediated rejection can lead to antibody mediated rejection.⁸ This study aims to further investigate the relationships between the different types of rejection and the graft failure as well as look at other compounding factors that might also show correlation with either the incidence of rejection or the ultimate outcome of the graft.

Methods

A retrospective study was conducted at the Transplant Center of the Lehigh Valley in Allentown, Pennsylvania. The 407 patients that underwent renal transplantation from January 2009 to December 2014 were included in the study. During this period, a uniform protocol for immunosuppression, post-transplant care, and biopsy by protocol and clinical indication was in place. Patient data was collected from the Organ Transplant Tracking Record (OTTR) database and included transplant date, graft survival time, patient survival time, donor type, types of rejections, treatments received, and demographic information. Those patients who experienced one or more episodes of rejection were then further analyzed to see if there is a correlation between the other factors including, transplant type (living vs. deceased donor, PHS higher risk), demographics (age, sex), delayed graft function (defined as the patient needing dialysis within 7 days of transplant), time on dialysis prior to transplant, cold ischemic time, and the ultimate outcome of the graft.

Data from the OTTR was coded so it could be statistically analyzed. Primary disease category was done based on the categories used by the Scientific Registry of Transplant Recipients (SRTR): Glomerular diseases, Tubular and Interstitial diseases, Polycystic Kidneys, congenital/familial/metabolic, Diabetes, Renovascular and Vascular diseases, Neoplasms, and Hypertensive Nephrosclerosis. Most of the data was coded using 0=No and 1=Yes for types or rejection, delayed graft function, and whether or not the patient received a particular treatment. Cell mediated rejection and antibody mediated rejection were compared for history of delayed graft function and graft survival.

Descriptive statistics were performed on age, gender, type of donor (living vs. deceased), graft failure, delay of graft function, time on dialysis, cold ischemic time, and incidence of rejection and the proportion of each type of rejection. Patients who died with a functioning graft were excluded in graft survival. Survival analysis was used to analyze cell mediated rejection, antibody mediated rejection, and delayed graft function, versus graft survival time.

Results

Of 407 total patients included in the study, 159 experienced at least one episode of rejection (39%) and 248 experienced no rejection (61%). (See Table 1) Of those who experienced rejection, the mean age was 57 years old, 32% were female, 19% had a living donor, 23% had graft failure ($p=.0254$), 29% had delay of graft function. The mean time on dialysis was 1401 days, and the mean cold ischemic time was 712 minutes. Looking at those who experienced no rejection, the mean age was 58 years old, 30% were female, 23% had a living donor, 16% had graft failure, 29% had a delay in graft function, the mean time on dialysis was 925 days, and the mean cold ischemic time was 719 minutes. Only graft failure was statistically significantly different.

Regarding all types of rejection, cell mediated borderline rejection was the most common encompassing 40% of all rejections, followed by Acute Cellular Rejection Banff Grade 1B (20%), Acute Cellular Rejection Banff Grade 1A (19%), Antibody mediated rejection (17%), and Grade 2A and 2B (2%). Antibody mediated rejection is associated with a statistically higher incidence ($p<0.0001$) of graft failure than cell mediated rejection. Of the 36 patients with antibody mediated rejection, 11 had graft failure, and of the 143 with cell mediated rejection, 15 experienced graft failure ($p<0.0001$). Antibody mediated rejection decreased graft survival time ($p=.0197$) while cell mediated rejection was questionable ($p=.0530$).

Delayed graft function was also shown to have an influence on graft survival time ($p<0.0001$). When looking at delayed graft function, of the 407 patients included in the study, 118 (.29) had delayed graft function. 46 of 118 patients with delayed graft function experienced at least one episode of rejection. 80% of those rejections were cell mediated and 20% were antibody mediated. Of the 289 that did not have delayed graft function, 39% (112) had at least one incidence of rejection with 76% of the 112 being cell mediated and 24% being antibody mediated.

Discussion

In the LVHN population of renal transplant patients, less severe types of cellular rejection are more common (i.e. Borderline, Grade 1B). Overall, there were fewer instances of antibody mediated rejection compared to cell mediated rejection; 31% of the antibody mediated rejections ended in graft failure while only 10% of cell mediated rejections ended in graft failure. While there was a correlation between antibody mediated rejection and graft survival time, the same correlation was not as strong for cell mediated rejection with a p value of (>0.05). Antibody

mediated rejection appears to have a greater negative effect on graft survival than cell mediated rejection.

In addition to examining the impact of rejection on the outcome of the graft, it is important to also consider factors that can impact episodes of rejection. In this study, delayed graft function and the presence and type of rejection were examined. For all patients, cell mediated rejection was more common than antibody mediated rejection. The incidence of all types of rejection was similar for delayed graft function and non-delayed graft function patients. Previous studies show delayed graft function after Donation after Cardiac Death (DCD) donors does not have the same negative influence on survival as delayed graft function after brain death. Further investigation into delayed graft function patients and types of donors is warranted.

When analyzing graft survival as a continuous variable delayed graft function had a large impact, with the lowest mean graft survival time with a standard error of 53, and cell mediated rejection had the second lowest graft survival time with a similar standard error of 51. Interestingly, antibody mediated rejection had the highest mean graft survival time, but it also had the largest standard error of 114, indicating that its mean is not as well-known as the other two. This can be due to the smaller number of individuals experiencing antibody mediated rejection (36) compared to 118 with delayed graft function and 143 with cell mediated rejection. Late rejections may also influence this data. A survival analysis would have to be run on this data to determine the true relationship between these conditions and graft survival time. Comparing low level (Borderline/1A) with high level cellular rejection may also be useful.

This study serves to provide a brief overview of the characteristics of the LVHN Renal transplant population. It is a springboard for future investigation of the rejection process and graft survival.

Conclusions

Acute cellular rejection (particularly borderline) is more common than antibody mediated rejection. Antibody mediated rejection has a statistically significant ($p < 0.0001$) negative impact on graft survival. Delayed graft function is common but is not associated with an increased risk of rejection, cellular or antibody mediated. Delayed graft function is associated with shorter graft survival time than other patients. Overall, the type of rejection is important when considering graft survival time along with other factors. This study is only the first step towards analyzing this population for risks of rejection and graft survival.

References

1. Controversial Issues. (n.d.) *West's Encyclopedia of American Law, edition 2*. (2008). Retrieved February 23 2015 from <http://legal-dictionary.thefreedictionary.com/Controversial+Issues>
2. Lamb, K.E., Lodhi, S., & Meier-Kriesche, H.U. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant* 2011, 11:450-462.

3. Racusen, L.C., Colvin, R.B., Solez, K., et al. Antibody-Mediated Rejection Criteria-an Addition to the Banff '97 Classification of Renal Allograft Rejection. *American Journal of Transplantation* 2003, 3: 708-714.
4. Gaber, L.W., Moore, L.W., Alloway, R.R., et al. Correlation between Banff classification, acute renal rejection scores and reversal of rejection. *Kidney International* 1996, 49: 481-487.
5. Meier-Kriesche, H.U., Schold, J.D., Srinivas, T.R., & Kaplan, B. Lack of Improvement in Renal Allograft Survival Despite a Marked Decrease in Acute Rejection Rates Over the Most Recent Era. *American Journal of Transplantation* 2004, 4:378-383.
6. El-Zoghby, Z.M., Stegall, M.D., Lager, D.J., et al. Identifying Specific Causes of Kidney Allograft Loss. *American Journal of Transplantation* 2009, 9:527-535.
7. Wu, K., Budde K., Lu, H., et al. The Severity of Acute Cellular Rejection Defined by Banff Classification Is Associated With Kidney Allograft Outcomes. *Transplantation* 2014, 97:1146-1154.
8. El Terse, M., Grande, J.P., Keddiss, M.T., Rodrigo, E., et al. Kidney Allograft Survival After Acute Rejection, the Value of Follow-Up Biopsies. *American Journal of Transplantation* 2013, 13:2334-2341.

Appendix

Table 1: Characteristics of patients with at least one incidence of rejection vs. those with none (n=407)

	With at least 1 incidence of rejection (n=159)	With no rejection episodes (n=248)	p-value
Age (mean years +/- SD)	57 +/- 14	58 +/- 13	.6605
Female Gender	52 (.32)	75 (.30)	.5538
Living Donor Transplant	30 (.19)	57 (.23)	.3464
Graft Failure	37 (.23)	41 (.16)	.0254*
Delay of Graft Function	46 (.29)	72 (.29)	.9657
Time on dialysis (mean days +/- SD)	1401 +/- 3597	925 +/- 3601	.1935
Cold Ischemic Time (mean min +/- SD)	712 +/- 372	719 +/- 379	.8510
CMV	33 (.21)	43 (.17)	.3621

*Influence of rejection as the independent variable. All other variables show incidence of rejection as the dependent variable. Graft failure only includes those who had graft failure unrelated to patient death.

Figure 1: Includes types of cell mediated rejections Banff Scale (Grade 1A, 1B, 2A, 2B, 3, 4, Borderline)

Types of Rejection

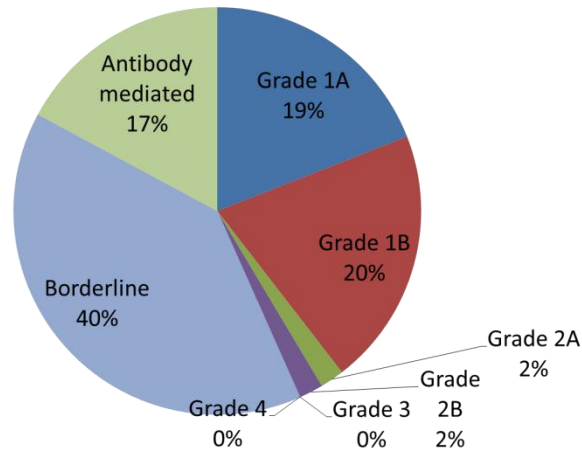


Figure 2: Delayed graft function is defined as anyone receiving dialysis within 7 days post-transplant.

{ Mean graft survival time in days } Delayed Graft Function (DGF)

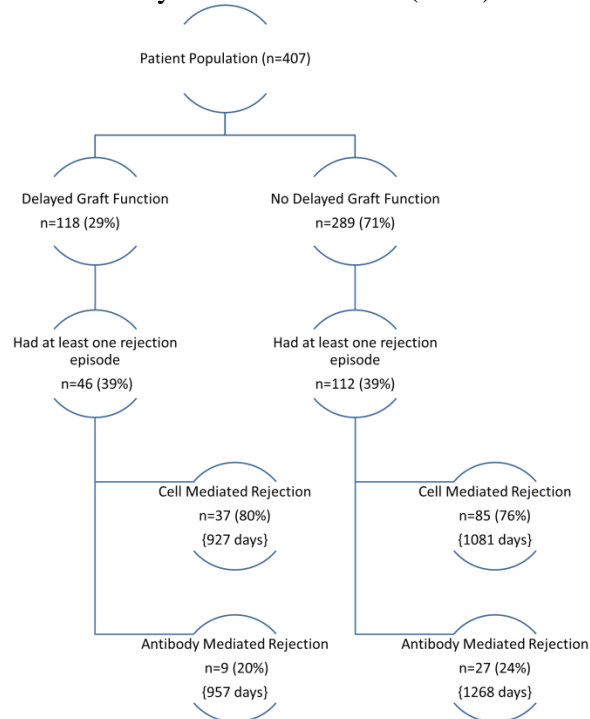


Figure 3: Graft failure only included patients who had graft failure unrelated to patient death.
Effect of antibody mediated rejection on graft failure $p < 0.0001$

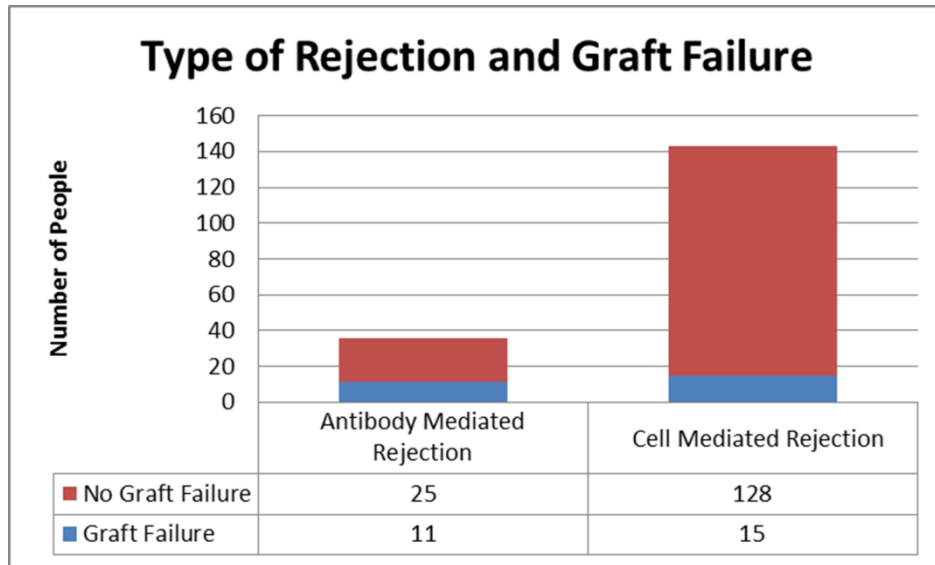


Figure 4: Delayed Graft Function $p < 0.0001$, Antibody Mediated Rejection $p = .0197$, Cell Mediated Rejection $p = .0530$

