Study Title: Difference Between Living Donor and Cadaveric Liver Transplant with Regards to Renal Function Post Transplant

Brock AW Macdonald

A. Study Purpose and Rational

Over the past 2 decades one of the most important events in the treatment of end-stage liver disease is the development of the orthotopic liver transplant. Rates of liver transplantation are currently increasing, but continue to be surpassed by the need for transplantation. There are currently over 17, 000 patients awaiting liver transplant in the United States (1). The median wait time for Blood type A and B livers was 595 and 498 days for 2001-2002 respectively (1). Time spent awaiting a transplant is associated with an increase in mortality (9). In an attempt to alleviate the burden on the cadaveric organ donation system, in 1989 physicians developed the living related donor transplant (2). Living donor transplants currently comprise 3% of all liver transplants, based on transplantation procedures done from January to June 2005 in the United States (1). Despite the possible benefits of decreased wait-time mortality accomplished by receiving a partial graft earlier, it remains preferable for adult patients to receive a whole liver rather than a partial graft. But given the delicate balance of organ availability, it likewise remains a challenging decision to determine who should receive a living versus cadaveric donor transplant (8).

One of the complications of end-stage liver disease that can develop and progress during wait time on a transplant list is concurrent renal dysfunction (3). There are multiple possible etiologies that are associated with the link between liver and kidney disease. Pathogenic processes that can affect each organ individually, such as viral hepatitis and autoimmune hepatitis, have been implicated in the development of both renal and liver dysfunction. Other patients develop renal dysfunction secondary to mechanisms of splanchnic vasodilitation and concurrent arterial vasoconstriction that result in decreased renal perfusion and ischemia through a proposed "hepatorenal reflex," a disease process that intimately ties these two organs together (6). Referred to as the hepatorenal syndrome, there are two clinical subtypes of this disease: type 1 is characterized by acute development of renal failure, and type 2 is associated with moderate or stable renal failure. Definitive treatment for this disease process is liver transplantation (7). Patients with hepatorenal syndrome evidence poor short-term prognosis and increased mortality while awaiting a transplant (10).

Pre-transplant renal function has been shown to be an important determinant of post-transplant outcome (5). In certain patients liver transplantation is demonstrated to have a beneficial effect on renal function, indicated by a decrease in the serum creatinine post transplant. Patients with likely long-standing kidney disease such as glomerulonephritis, polycystic kidney disease, and diabetic nephropathy are less likely to show benefit in their renal function and are therefore are more likely to obtain a combined liver kidney transplant (3). However, it is often difficult to determine the difference between mild renal impairment secondary to intrinsic renal disease and mild renal impairment secondary to poor renal perfusion (Type II HRS). The current scoring system for acuity for transplant is the model of end-stage liver disease (MELD) score, which includes serum creatinine given its value as a measure of predicted post-transplant mortality, but does not take into account the etiology of renal impairment.

What remains unclear is the impact of cadaveric transplant versus living related donor transplant on renal function. Cold ischemia time (CIT) has been shown to increase the rate of graft dysfunction post-transplant (11). Cadaveric livers post transplant have been shown to have a higher rate of platelet deposition and neutrophil infiltration (12). These events may play a contributing role in early graft dysfunction. Moreover, it is likely that chronic inflammation also has a marked impact on the recovery of renal function post transplant. This question is complicated, however, by the multiple conditions that

predispose the patient to the development of further renal failure. Furthermore, clinical factors that may lead one patient to receive a cadaveric liver transplant versus a living related donor transplant may independently predict for renal recovery. For example, patients who receive cadaveric liver transplants have often spent a longer time waiting for their liver transplant and are therefore likely to be more ill than those who receive a living related donor transplant.

Patients with impaired renal function have a higher short-term mortality while awaiting liver transplantation and would thus be likely to receive an overall benefit by being transplanted sooner via a living donor transplant. However, some patients with renal dysfunction may achieve even further benefit from a combined liver kidney transplant. The purpose of this study is to determine what factors predict renal function recovery post transplant in patients who have received either a cadaveric or a living donor transplant, and if there is a difference in the predictors between the two groups.

B. Study Design and Statistical Analysis:

This study is a retrospective analysis of the total 589 patients who have undergone the liver transplant at the Columbia University Medical Center of the New York Presbyterian Hospital since 1998. Patient information will be derived from the Liver Transplant Database, WEBCIS and paper charts. Patients will be divided into two groups: (a) those who received cadaveric liver transplant, and (b) those who received a living donor transplant. Multiple factors will be identified as possibly impacting renal function in transplant candidates, including but not limited to age, gender, ethnicity, cause of liver failure identified on explant, concurrent medical conditions (HTN, diabetes, CAD, vasculitis), presence of hepatocellular carcinoma, MELD score prior to transplant, INR, serum albumin, serum sodium, urinary sodium, diuretic use prior to transplant, urinary protein (defined by none, +, ++, +++ on urinalysis), presence or absence of blood on urinalysis, and SBP 2 weeks prior to transplant. Cold Ischemic Time will also be assessed as obtained from the Operative Report. The two groups will then be compared using a unpaired two-tailed student's test if they are continuous variables and a chi-square analysis if they are proportions.

Patient pre-transplant creatinine will be determined as the creatinine on the day prior to transplant, or the earliest creatinine on the day of transplant. Post-transplant creatinine will be determined 4 days post transplant as well as 4-8 months post transplant (nearest data to six months post transplant available). Primary outcome is the creatinine post transplant, with secondary outcomes including creatinine six months post-transplant, and mortality. The difference will then be calculated between the pre and post transplant creatinine values. Student's unpaired two-tailed t-test will be used to compare the improvement of creatinine between the two groups. The n for each of these groups is 300 and 100 respectively, allowing us to detect a difference of 0.72 based on a standard deviation of 1.8 within the population.

Upon completion of comparison of the two groups, a multivariate linear regression will be performed to ascertain the impact of each of the variables on the change of creatinine in each of the two groups. These two sets of coefficients will be compared in order to determine if the impact of each factor is different between the two groups.

C. Study Procedure:

No procedures will be performed on patients during this study. All information will be derived from the medical record and WEBCIS.

D. Study Drugs:

This study will not utilize any drugs.

E. Medical Devices:

This study will not utilize any investigational devices.

F. Study Questionnaires

None

G. Study Subjects

Inclusion criteria:

- age greater than 16
- pre-transplant creatinine greater than 1.4
- first time liver transplant patients

Exclusion Criteria:

- prior liver transplant
- joint liver-kidney transplant
- split graft transplant
- pre-transplant sepsis

H. Recruitment of Subjects

All patients within the database who meet inclusion criteria and have no exclusion criteria will be included in the study.

I. Confidentiality of Study Data

All study data will be coded in a way that does not include identifying information that could be traced back to an individual patient. Data will be safeguarded as encrypted files by the study coordinator.

J. Potential Conflict of Interest

None

K. Location of Study

The study will be performed at New York Hospital using data from Columbia Presbyterian Medical Center.

L. Potential Risks

None

M. Potential Benefits:

There is no benefit to the patients currently involved in the study. However, they will be helping to add to the scientific data-base which may benefit future patients.

N. Alternative Therapies

N/A

O. Compensation to Subjects

No compensation is to be offered.

P. Costs to Subjects

Study subjects will incur no costs.

Q. Minors as Research Subjects

No minors will be included in the study.

R. Radiation or Radioactive Substances

No radiation or radioactive substances will be used in the study.

S. References

1. UNOS website: http://www.unos.org/data/default.asp?displayType=usData
2. Kawarsaki H et al. Partial liver transplantation from living related donors. Transplant Proc. 1992 Aug;24(4):1470-2.
3. Campbell et al. Renal Function after Orthotopic Liver transplantation is Predicted by Duration of Pre-transplant Creatinine Elevation. Liver Trans 2005 (9): 1048-1055
4. Validedeoglu E et al. Predictors of Late Kidney Dysfunction Post transplantation. Transpalnt Proc 2002 34: 3315-3316
5. Nair S, Verma S., Thuluvath P, Pretransplant Renal Function Predicts Survival in Patients Undergoing Orthotopic Liver Transplantation. Hepatatology 2002 35(5): 1179-1185
6. Davis C, Gonwa Tm Wilkinson A. Pathophysiology of Renal Disease Associated with Liver Disorders: Implications for Liver Transplantation. Part 1. Liver Transplantation 2002: 8(2): 91-109
7. Moller S Bendtsen F Henriksen J Pathophysiological basis of pharmacotherapy in the hepatoreal syndrome Scandinavian Journal of Gastroenterology 2005: 40: 491-500
8. Russo M, Brown R Adult Living Donor Liver Transplantation, American Journal of Transplantation 2004; 4: 458-465
9. Everhart JE, Lombarderro M, Detre KM et al. Increase waiting time for liver transplantation results in higher mortality. Transplantation 1997, 67: 1300-1306.
10. Resuccia T, Ortega R et al. Effects of treatment of hepatorenal syndrome before transplantation on post-transplantation outcome. A case control study. Journal of Hepatology 2004 40: 140-146
11. Jassem W et al Cadaveric versus Living- Donor Lovers: Differences in Inflammatory Markers After Transplantation. Transplantation 3003 76(11): 1599-1603