Prevention of de novo Hepatitis B Virus Infection in Recipients of Hepatitis B Core Antibody-Positive Donor Graft Using Lamivudine or Combination of Lamivudine and Hepatitis B Immune Globulin: A Retrospective Study

Cui Li Lin, PGY2

A. Study Purpose and Rationale

Liver transplantation remains the major treatment for patients with end-stage liver disease. Since 1988 more than 79,496 liver transplantations were performed nationwide and despite overall increase in the number transplants since that time the availability of organs have remained stagnant in recent years. Due to increasing shortage of organs the waiting time for liver transplant has been increasing. As of January 2006 more than 17,000 patients have been wait-listed for liver transplant and so far this year only about 4500 patients have been transplanted.[1] Due to shortage of grafts for transplant this has led to increasing use of Hepatitis B core antibody-positive surface-antigen negative, hence forward referred to hepBcore+, donor grafts. These grafts were originally used in patients with end-stage liver disease secondary to hepatitis B virus (HBV) infection particularly in areas of the world where HBV is endemic and where more than 80% of adults are hepBcore+.[2] Transplantation of hepBcore+ donor grafts to HBV recipients are known to have a high recurrence rate without anti-viral prophylaxis against HBV and HBV recurrence has a major impact on graft and patient survival. Multiple small retrospective studies have reported HBV recurrence rate of 22.6%-50%[3] over a 1-2 year follow-up period while on lamivudine prophylaxis and <10% recurrence on combination of lamivudine and hepatitis B immunglobulins (HBIG). Currently, at our institution (Center for Liver Disease and Transplantation of the NewYork-Presbyterian Transplant Institute) all patients with end-stage liver disease due to HBV infection who received hepBcore+ donor grafts are maintained on anti-viral prophylaxis with lamivudine plus HBIG. However, over the recent years these hepBcore+ donor grafts are increasingly being used on HBV naïve recipients and it is known that these recipients are at risk for de novo HBV infection without anti-viral prophylaxis. However, optimal prophylaxis regimens and rates of de novo HBV in these recipients are still not yet known. Multiple small retrospective studies involving 7-22 patients have been performed using either lamivudine or lamivudine plus Hepatitis B immunoglobulins (HBIG) showed no development of de novo HBV infection. Therefore, the true rate of de novo hepatitis B infection with prophylaxis is still unknown and the comparison efficacy of the two prophylaxis regimen is unclear. The use of HBIG however, is expensive and constraining due to the need for close monitoring of the level of anti-HepB surface-antibodies(anti-HBs) and frequent re-injection requirement.[4] It is hoped that if lamivudine proves to be as

---

[1] The Organ Procurement and Transplantation Network (www.UNOS.org)

[2] Chen YS, Wang CC, de Villa VH, Wang SH, Cheng YF, Huang TL, Jawan B, Chiu KW, Chen CL. Prevention of de novo hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transplant. 2002 Dec;16(6):405-9.

[3] Busuttil R.W., Klintmalm G.B., Transplantation of the Liver[2nd ed.]: New York, Elsevier Health Sciences, Page 119

[4] Busuttil R.W., Klintmalm G.B., Transplantation of the Liver[2nd ed.]: New York, Elsevier Health Sciences, Page 117

effective as lamivudine plus HBIG for HBV prophylaxis the cost of anti-viral prophylaxis for this population can be greatly reduced and the potential number of patients who would be subjected to the side effects of HBIG could be minimized.

B. Study Design and Statistical Procedures

The initial pool of candidates will come from multi-center retrospective chart review of non-HBV recipients of hepBcore+ grafts placed on lamivudine or lamivudine plus HBIG for anti-viral prophylaxis against de novo hepatitis B infection. Pre-transplant hepatitis B viral serology will be determined by chart review as will other relevant information including pre-transplant diagnoses, age, gender, date of transplant, and type of liver transplant. As the true rate of de novo HBV infection on prophylaxis is unknown this study will assume that this rate is equal if not less then 22.6% in 1 year (HBV recurrence rate of HBV recipients of hepBcore+ grafts on lamivudine monotherpy). Inclusion criteria into the study include pre-transplant diagnoses not related to HBV infection, age>=18, transplanted between January 2000 to December 2005 with at least 1 year viral serology follow-up and negative HIV status. Exclusion criteria includes multiple organ transplant

The primary endpoint will be looking for the rate of de novo hepatitis B infection using hepatitis B viral serology which include hepatitis B surface-antibody, hepatitis B surface-antigen, and hepatitis b core-antibody in patients on either lamivudine or lamivudine plus HBIG prophylaxis.

The number of patients necessary for this trial was determined by a power analysis with a Chi-square test for categorical outcome. Based on the HBV recurrence data of 22.6% on lamivudine monotherapy and <10% on lamivudine plus HBIG this study is powered in order to detect a 12.5% difference in the two groups as this is the additional amount of benefit patients on combination prophylaxis derived from the HBV recurrence prevention data. From this analysis it is calculated that 149 patients are needed in each prophylaxis group in order to achieve a power of at least 80%. Between January 2000 to December 2005 33,799[5] patients received a liver transplant nationwide. Only a small percentage, ~5% based on chart reviews for this period at this institution, will meet the criteria of this study. Therefore, about 1690 potential candidates nationwide would be available for this study.

C. Study Procedures: None

D. Study Devices: None

E. Study Drugs

<u>Lamivudine:</u>

[5] The Organ Procurement and Transplantation Network (www.UNOS.org)

Lamivudine(Epivir) is an anti-viral agent originally developed for use in patients with human immunodeficiency virus (HIV) infection and subsequently found to be effective in inhibiting HBV replication. Lamivudine is a cytosine analog that competes with dCTP for incorporation into growing DNA chains causing chain termination which leads to suppression of HBV replication.

Lamivudine is generally well tolerated and has proven efficacy as monotherapy in de novo HBV prevention. However, HBV recurrence rate on lamivudine monotherapy is still unacceptably high and is thought secondary to development of escape mutant. Although rare, potential serious adverse effects of lamivudine include pancreatitis and lactic acidosis. Lamivudine is metabolized by the kidneys and dosed at 100mg daily.

Hepatitis B immunoglobulins (HBIG):

HBIG is a polyclonal preparation of human anti-HBs purified from pooled donor plasma. Its use in de novo HBV prophylaxis is based on the rationale that passive immunization of anti-HBs will bind to and neutralize circulating virions and therefore prevent graft infection. Anti-HBs also decrease HBsAg secretion via its interaction with HBsAg within hepatocytes after endocytosis.

HBIG is usually given intravenously as a 10,000U bolus during the anhepatic phase of liver transplantation. Subsequent dosing schedule varies by institution but can be either given monthly or guided by anti-HBs titers (trough titers needs to be at least 100 IU/l).

The major serious complications of HBIG administration are due to immune-mediated reactions and anaphylaxis attributed to the protein content in HBIG. In addition, concern for mercury toxicity from long-term intravenous use of HBIG has been raised due to the small amount of a mercury-containing preservative (thimerosal) that are present in older formulation. These problems have been remedied by newer formulations that do not contain thimerosal and lower protein content.

HBIG monotherapy is proven beneficial for prevention of de novo and recurrent HBV infection but in the case of recurrent HBV infection combination prophylaxis with lamivudine and HBIG is still superior to either medication alone.

F. Study Questionnaires: None

G. Study Subjects

Chart review of patients with end-stage liver disease of all etiologies except for HBV infection who received a hepBcore+ graft.

H. Study Locations

Major liver transplantation centers nationwide.

I. Recruitment: None

J. Potential Risks: None

K: Potential Benefits:

Patients will most likely not derive any direct benefit from this study but results of the study may help elucidate what the optimal de no HBV infection prophylaxis regimen aught to be for future HBV naïve recipients of hepBcore+ grafts.

L. Alternatives: None

M. Compensation: None

N. Costs to Subjects: None

O. Minors as Research Subjects: None

P. Radiation or Radioactive Substances: None

References:

- The Organ Procurement and Transplantation Network (www.UNOS.org)

- Busuttil R.W., Klintmalm G.B., Transplantation of the Liver[2nd ed.]: New York, Elsevier Health Sciences, Page 117

- Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, Hashimoto K, Mochida Y, Maehara Y, Kuwano H. Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int. 2005 Dec; 25(6):1169-74.

- Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW. Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. Clin Transplant. 2006 May-Jun;20(3):369-73.

- Chen YS, Wang CC, de Villa VH, Wang SH, Cheng YF, Huang TL, Jawan B, Chiu KW, Chen CL. Prevention of de novo hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transplant. 2002 Dec; 16(6):405-9.

- UpToDate (www.uptodate.com) “Liver Tranplantation for Chronic HBV Infection”