Bahrain Medical Bulletin, Volume 18, Number 4, December 1996

Editorial

LIVER TRANSPLANTATION FOR HEPATITIS B VIRUS END-STAGE LIVER DISEASE: IS IT JUSTIFIABLE ?

Abdul-Wahed Nasir Meshikhes, FICS, FRCSI*

Although hepatitis B virus (HBV) infection occurs sporadically in Europe and North America, affecting mainly drug abusers and homosexuals, it is endemic in certain areas of the world.

HBV is a DNA virus causing silent infection in 90 % of patients and jaundice in the remaining 10 %. Patients presenting with acute hepatitis are at 1 % risk of developing fulminant hepatic failure. Ten percent of patients will develop chronic active hepatitis and have a high risk of developing cirrhosis within 10-30 years and are at higher risk of developing hepatocellular carcinoma1. Liver transplantation is now well accepted as the treatment of choice for a wide variety of end-stage liver diseases[2].
However, its role in the treatment of patients with HBV related liver cirrhosis remains controversial. This is mainly due to the high morbidity and mortality associated with hepatic graft reinfection and subsequent failure[3,4].

The first patient with HBV cirrhosis was transplanted in Denver in 1970 and he died 20 months later with disease recurrence[5]. In 1986, eight patients transplanted for HBV cirrhosis developed reinfection despite receiving perioperative immunoprophylaxis[6]. Patients with HBV infection are considered immunologically impaired which may explain the high mortality associated with liver transplantation in these patients[7]. This high morbidity and mortality made many centres consider the presence of HBsAg in the serum as a relative contraindication and the presence of active viral replication, indicated by HBeAg seropositivity, as an absolute contraindication to liver transplantation[8]. Recent evidence suggests that patients who are HBeAg-negative and HBe antibody-positive may have replicating HBV in their serum and therefore, absence of HBeAg does by no means exclude presence of viral replication[9].

---

* Consultant Surgeon
Dammam Central Hospital
Dammam, Eastern Province
Saudi Arabia

The improvements in survival after liver transplantation as a result of better donor selection criteria, improvements in organ procurement, preservation and immunosuppression, refinement in surgical techniques, better postoperative intensive care and the widespread application of liver transplantation as a treatment modality for end-stage liver diseases in areas where HBV infection is prevalent led to wider acceptance of patients with HBV cirrhosis for liver transplant assessment.

The high risk of graft reinfection may be attributed to facilitated viral replication as a result of immunosuppression10. The reinfection rate in patients with active viral replication at the time of transplantation (indicated by positive HBV DNA) approaches 96 % at 2 years compared to 29 % in HBV DNA-negative patients10. Therefore, to reduce the risk of reinfection following liver transplantation, most centres now consider the presence of active viral replication (HBV DNA-positivity) at the time of transplantation as an absolute

contraindication[10,11] and to improve results, HBV replication must be arrested prior to transplantation. This can be achieved by the administration of long term passive immunoprophylaxis[10] which has been shown to reduce the incidence of graft reinfection and significantly improves patient survival.

There are various immunoprophylactic protocols which are adopted by different centres. Lauchart et al reported very low one and 2- year reinfection rates (17 % and 29 % respectively) by the administration of 10,000 units of anti-HBs immunoglobulin during the anhepatic phase and 10,000 units daily for the first 6 postoperative days[4]. Anti-HBs titres are checked weekly and anti-HBs immunoglobulin is given whenever the titre falls below 100 iu/ml. A similar protocol is adopted by the Birmingham group however, the dose is halved and is given daily for the first 3 postoperative days only1[1]. Anti-HBs titres are then checked weekly during the inpatient stay and later monthly at each outpatient visit and a further dose (5000 units) is administered whenever the titres fall below 100 units / ml. Although reappearance of HBsAg in the serum after transplantation indicates recurrence, it does not correlate with recurrence of liver disease or survival[12] and is considered an indication to stop immunoprophylaxis. The Paris group gives 10,000 units during the anhepatic phase and daily until HBsAg disappears from the serum or daily for the first 6 postoperative days and further doses if the anti-HBs titre is less than 100 units / ml during follow up[10].

Short term immunoprophylaxis (less than 6 months) is shown to delay the appearance of reinfection but does not prevent it[4], since graft reinfection occurs as a result of viral replication in the serum and other extrahepatic sites especially peripheral mononuclear cells13. Failure to control HBV replication at these sites after liver transplantation will ultimately lead to allograft reinfection.

Early experience with polyclonal anti HBs immunoprophylaxis was disappointing[14-16] as it was administered in small doses with the aim to neutralise all circulating HBsAg without taking into account the extrahepatic sites of viral existence and was very expensive. It is now widely replaced by the much cheaper monoclonal anti HBs immunoglobulin. Low risk of reinfection was reported in patients transplanted for fulminant hepatic failure secondary to HBV infection and similarly in patients with hepatitis delta coinfection as presence of hepatitis delta virus has an inhibitory effect on HBV replication[10,15,17]. Eason et al reported no survival advantage for patients with fulminant HBV over those with chronic HBV and noted higher mortality in patients with chronic HBV in presence of an associated hepatocellular carcinoma[12].

The effect of HBV reinfection on liver allograft is quite variable and some patients will have normal liver functions despite reinfection and as many as 50 % will have a slowly progressive disease allowing them to have a prolonged period of rehabilitation for more than 5 years after reinfection[11,14]. At the other end of the spectrum, some patients will develop an aggressive clinical and histological syndrome called fibrosing cholestatic hepatitis (FCH). This syndrome is characterised by periportal fibrosis, cellular cholestasis, ballooning degeneration of the hepatocytes, extensive viral expression and rapid progression to cirrhosis, allograft dysfunction and death if retransplantation is not undertaken[14]. The liver function tests abnormalities associated with FCH are rapidly rising bilirubin, prolonged prothrombin time, near normal alkaline phosphatase and relatively low level of transaminases[14]. Nevertheless some patients with FCH may lead normal lives with reasonable liver functions for more than 12 months after transplantation[11]. Some authors argue against regrafting patients who develop graft failure as a result of HBV reinfection since reinfection of the second graft is usually faster and more aggressive[7,15].

Long term passive immunoprophylaxis administering anti HBs immunoglobulin is now widely practiced in many centres and is currently the best method available for

the prevention of HBV reinfection after liver transplantation. However, the question remains as for how long it has to be administered to confer the required protection. Furthermore, it is administered intravenously and this is quite expensive and may be associated with some side effect such as anaphylactic reactions11. Clinical trials involving a safer antiviral drug; nucleoside analogue called lamivudine (3'-thiacytidine) is now underway in Europe and North America. It is hoped that it will reduce the incidence of graft reinfection and therefore, will improve the patient survival dramatically. In the mean time, hepatitis B vaccine remains the most effective method of prevention which will subsequently reduce the incidence of cirrhosis with its associated risk of hepatocellular carcinoma and this in turn will reduce the need for liver transplantation.

CONCLUSION

Although there is a high reinfection rate in transplanted patients with HBV infection, there have been recent improvements in survival due to better anaesthetetic, surgical and postoperative care. Furthermore, the introduction of long term immunoprophylaxis may reduce reinfection rate and improves patient and graft survival. This and the fact that great number of reinfected individuals can experience prolonged period of rehabilitation with reasonable liver functions, argue strongly against denying patients with HBV - related end stage liver disease the enormous benefits of liver transplantation.

REFERENCES

1. Beasly RP, Hwang LY. Overview on the epidemiology of the hepatocellular carcinoma. In: Hollinger FB, Leman SM, Margolts HS, eds. Viral hepatitis and liver disease. Baltimore:Williams and Wilkins, 1991:532-5.

2. Gordon R, Shaw B, Iwatsuki S, et al. Indications for liver transplantation in the cyclosporine era. Surg Clin North Am 1986;66:541-6.

3. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation. N Engl J Med 1989;321:1094-9.

4. Lauchart W, Muller R, Pichlmayr R. Immunoprophylaxis of hepatitis B virus reinfection in recipients of human liver allografts. Transplant Proc 1987;19:2387-9.

5. Orman JR, Putnam CW, Iwatsuki S, et al. Liver allograft: Its use in chronic active hepatitis with macronodular cirrhosis, hepatitis B surface antigen. Arch Surg 1979;114:75-8.

6. Demetris AJ, Jaffe R, Sheahan DG, et al. Recurrent hepatitis B in liver allograft recipients. Differentiation between viral hepatitis B and rejection. Am J Surg Pathol 1986;125:161-72.

7. Iwatsuki S, Starzl TE, Todo S, et al. Experience in 1000 liver tansplants under cyclosporine-steroid therapy: A survival report. Transplant Proc 1988;20[suppl 1]:498-504.

8. Van Thiel DH, Schade RR, Gavaler JS, et al. Medical aspects of liver transplantation. Hepatology

1984;4:79S-83S.

9. Matsuyama Y, Omata M, Yokosuka O, et al. Discordance of hepatitis B e antigen / antibody and hepatitis B virus deoxyribonucleic acid in serum. Analysis of 1063 specimens. Gasteroenterology 1985;89:1104-8.

10. Samuel D, Bismuth A, Mathieu D, et al. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. Lancet 1991;337:813-5.

11. Meshikhes AN, Ferraz-Neto BH, Ahmed M, et al. Orthotopic liver transplantation for hepatitis B and hepatitis C virus related Liver diseases [in preparation].

12. Eason JD, Freeman RB, Rohrer RJ, et al. Should liver transplantation be performed for patients with hepatitis B ? Transplantation 1994;11:1588-93.

13. Feray C, Zignego AL, Samuel D, et al. Persistent hepatitis B virus infection of mononuclear cells without concomitant liver infection. The liver transplantation model. Transplantation 1990;449:1155-8.

14. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatol 1992;14:104-11.

15. Todo S, Demetris AJ, Van Thiel D, et al. Orthotopic liver transplantation for patients with hepatitis B virus-related liver diseases. Hepatology 1991;13:619-26.

16. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993;329:1842-7.