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Liver Transplantation in Chronic Hepatitis B – A New Era?

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Chronic hepatitis B is a serious liver disorder that can lead to acute liver failure, liver cirrhosis or hepatocellular carcinoma (HCC) with a risk of death from HCC and/or cirrhosis of between 40% to 50% for men and about 15% for women[1]. Worldwide, there are an estimated 300 million chronic hepatitis B carriers, and in Singapore, about 5% to 7% of the population are carriers.

Liver transplantation is the established treatment for life-threatening liver disease. It has been performed in Singapore since 1990 with 26 transplants carried out to date. Earlier worldwide attempts at transplanting hepatitis B patients were plagued with reinfection, leading to recurrence of cirrhosis and in some cases, to rapid liver failure. This was particularly the case for patients who were HBeAg or HBV DNA positive. These findings, coupled with the scarcity of liver donors, led to a moratorium on transplanting hepatitis B patients.

Elsewhere, continued attempts at liver transplantation for such patients were performed with immunoprophylaxis (anti-HBs immunoglobulin – HBIG). The results from a European study were encouraging. It showed that HBIG reduced the risk of HBV recurrence to 36 ± 4% from 75 ± 6% for those patients treated for 6 months or longer[2].

Survival rate also improved in those that remained HBsAg-negative (3-year survival of 83%). Such treatment however, is prohibitively expensive, costing about S$5,000 for each 5000 IU, and the patient would require approximately 15 doses in the first year (S$75,000). Furthermore, since HBIG is produced from pooled human blood, the risk of transmission of other known or unknown viruses is real. In addition, poisoning by mercury, which is employed to preserve the antibody, has also been reported[3].

New hope arrived with the development of novel agents. Lamivudine is an oral 2' - deoxy - 3, - thiacytadine which was initially used in HIV patients, and it was noticed that HBV co-infected patients had suppression of their HBV DNA levels. In a preliminary double-blind randomised trial involving 32 patients with chronic hepatitis B, 12 weeks of lamivudine therapy at daily doses of 100 mg and 300 mg reduced HBV DNA to undetectable levels[4]. Lamivudine use was extended to patients undergoing liver transplantation for hepatitis B with heartening results. Grellier et al treated the patients with oral lamivudine (100 mg daily) for at least 4 weeks before transplantation and continued for at least one year after transplantation[5]. During follow-up, the liver biochemistry was normal in 9 out of the 12 patients. Furthermore, all 9 demonstrated loss of both HBsAg as well as HBV DNA (using Chiron branched-chain DNA assay) and biopsy specimens showed no evidence of recurrent hepatitis B. The use of lamivudine in chronic hepatitis B, however, is not without its problems. It is known that in the majority of patients, virus replication returns to former levels when treatment is withdrawn. Continued treatment may be the answer but the long-term effects of lamivudine treatment have yet to be documented. Furthermore, despite the continued administration of lamivudine, there is a small risk of viral mutation that leads to viral replication[6,7].

Famciclovir, another nucleoside analogue, has also been used in Pittsburgh. Early results demonstrated HBV DNA suppression but the suppression appeared to be less thorough[8]. Other known anti-viral drugs, including α-interferon, ganciclovir, prostaglandin E, foscarnet, have also been investigated in the prevention of recurrent hepatitis B after liver transplants. These drugs proved to have very limited efficacy and their use was complicated by side effects[4].

The current protocol of the National University Hospital employs lamivudine pretreatment until the patient is HBV DNA negative before liver transplantation. With this protocol, we have transplanted 4 patients with hepatitis B cirrhosis (one had associated hepatocellular carcinoma). So far, all 4 patients are HBV DNA negative and two of them have also shown negative HBsAg with weak positive HBsAb (> 20 mIU/mL).

In conclusion, in the light of recent evidence, chronic hepatitis B carriers complicated by liver failure should be considered for liver transplantation. Encouraging results have been reported with the introduction of passive immunoprophylaxis with HBIG and lamivudine. This will bring renewed hope to a large number of local and regional sufferers and promises a new era in liver transplantation for hepatitis B patients.

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