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INVITED COMMENTARY

Lamivudine combined with hepatitis B immunoglobulin in for prophylaxis of hepatitis B recurrence after liver transplantation: time for a change?

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Without appropriate prophylaxis, high rates of hepatitis B virus (HBV) infection occur after orthotopic liver transplantation (OLT). There is controversy regarding the optimal therapy to prevent recurrence of HBV infection after OLT. Rao *et al.* [1] have studied the efficacy of both lamivudine monotherapy and lamivudine combined with hepatitis B immunoglobulin (HBIG) in the prophylaxis of recurrence of hepatitis B viral infection after liver transplantation. Their meta-analysis model examines the effects of both these treatments on outcomes post-OLT. The authors observe that a combination of lamivudine and HBIG reduces recurrence of hepatitis B compared with lamivudine monotherapy. The trials analysed in the model included different regimens of HBIG, ranging from 400–800 IU intramuscularly (i.m.) per month, to 10 000 IU i.m. per month. Statistically significant differences were observed between lamivudine monotherapy versus lamivudine and HBIG combination therapy in hepatitis B recurrence, hepatitis B recurrence in HBV DNA positive patients and the development of lamivudine resistance. The authors conclude that high levels of HBV replication and poor antiviral strategies, including the selection of lamivudine-resistant mutations, were the main factors for disease progression post-OLT. Patient- and graft survival tended to be higher after the combination therapy than the same after lamivudine therapy.

Another recent meta-analysis also supports the use of a combination strategy to prevent recurrence. Katz *et al.* [2] found no significant difference between HBIG and lamivudine, when these treatments were given alone, in all measured outcomes. However, combination treatment was superior to HBIG alone in all outcomes measured, i.e. the combination therapy resulted in reduced overall mortality, hepatitis B-related mortality, hepatitis B-related active liver disease and HBsAg recurrence post-OLT.

Probably the majority of patients transplanted worldwide for end-stage hepatitis B are treated with HBIG and antiviral therapy to prevent recurrence, although HBIG regimens vary considerably and may not affect the outcome. A multivariate analysis of an NIH OLT cohort transplanted between 2001 and 2007 assessed recurrence rates in patients given high-dose IV, lower-dose IV, lower-dose IM maintenance, and in patients who discontinued HBIG (12%) [3]. These data show that HBeAg positivity at listing, HBV DNA concentrations of >5 $\log_{10}$ and Caucasian race were associated with HBV recurrence. Many US centres continue to use indefinite high-dose IV HBIG, even though the cumulative 5-year HBV recurrence was not significantly different between HBIG regimens.

Thus, combination therapy with lamivudine and HBIG is superior to monotherapy. There is, however, a need to scrutinize the appropriate place of HBIG in prophylaxis,

and the necessity for high-dose long-term (or lifelong) HBIG use. It may be possible to discern cohorts of patients in whom antiviral therapy can be continued without long-term HBIG, particularly given the advent of new antiviral agents, which are less prone to lead to resistance in the short term.

Hepatitis B virus DNA in liver and extrahepatic tissues may provide some clues to management. Lenci *et al.* [4] have studied HBV ccc DNA in liver years after continued prophylaxis in HBsAg-negative transplant recipients. In a cohort of transplant recipients at low risk of HBV recurrence who received HBV prophylaxis for a minimum of 5 years and who did not exhibit viral breakthrough, no evidence of intrahepatic cccDNA was found in the liver. HBIG and lamivudine were sequentially withdrawn. Whilst careful further follow-up is required in these patients, the authors suggest that patients without detectable HBV DNA in the liver are unlikely to undergo HBV recurrence and could be cautiously considered for complete withdrawal of prophylaxis.

Alternatively, the absence of HBV DNA may identify those in whom prophylaxis can be minimized and HBIG stopped. Although serum HBV DNA is used as the main predictor of HBV recurrence post-OLT, evaluation of viral reservoirs may be more important in the current era of highly effective antiviral therapy.

Strategies to prevent recurrent hepatitis B will be enhanced by the use of more potent agents than lamivudine. These agents include tenofovir and entecavir. There is strong clinical evidence of the efficacy of tenofovir in chronic hepatitis B, with less nephrotoxicity. The drug is active against wild type and precore mutant hepatitis B, as well as lamivudine resistant-HBV *in vitro* [5–7]. Entecavir inhibits all three activities of the HBV polymerase/reverse transcriptase: base priming, reverse transcription of the negative strand from the pregenomic messenger RNA and synthesis of the positive strand of HBV DNA [8]. The mean change in HBV DNA from baseline after 1 year of treatment in entecavir- or tenofovir-treated patients is typically of the order of 6.5 log in HBeAg-positive patients. Although a complex picture of tenofovir- and entecavir resistance may yet emerge, initial results suggest that cumulative resistance rates in naïve patients with these agents remain low. Thus, these agents are likely to play an important role in the treatment of end-stage liver disease, although additional safety data in these patients is still being collected.

Vaccination strategies may also improve. New 3-deacylated monophosphoryl-lipid-A (MPL) recombinant S vaccine vaccines have significantly increased successful anti-HBs seroconversion rates in patients with HBV cirrhosis and may provide protective anti-HBs titres [9].

Thus, although HBIG use remains important as an adjunct to lamivudine prophylaxis, the advent of more potent nucleosides and nucleotides without high rates of resistances suggests that HBV recurrence rates can be influenced by appropriate antiviral therapy and short-term HBIG use. Clearly, preventing recurrent hepatitis B is of pivotal importance in patients transplanted for HBV-associated liver disease, but applying effective suppression pre- and post-transplant and more limited use of HBIG post-transplant, with careful monitoring for (and avoidance of) resistance and effective suppression of HBV replication in the graft.

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