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EDITORIAL

HBV prophylaxis after liver transplantation: close to the full success but at the price of long-term prophylaxis adapted to the risk of HBV recurrence

Bruno Roche[1,2] · **Didier Samuel**[1,2,3]

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In western countries, 5–10% of liver transplantation (LT) are performed for hepatitis B virus (HBV)-related liver diseases, while it is a main indication in Asia. The outcome has improved markedly over the past three decades.

In the early 1990s, long-term intravenous hepatitis B immunoglobulin (HBIG) use was associated with improved graft and patient survival and with a significant reduction of the rate of HBV recurrence [1]. HBIG is thought to bind to circulating viral particles and to prevent their attachment at the hepatocyte membrane. Also, antibody-dependent cell-mediated cytotoxicity could be enhanced by binding to infected hepatocytes expressing HBsAg [2].

In the late 1990s, the management of post-LT prophylaxis has been modified by the advent of low genetic barrier nucleos(t)ide analogs (lgbNA) such as lamivudine (LAM) pre- and post-transplantation in combination with post-transplant prophylaxis with HBIG. The goal of antiviral treatment before LT is to inhibit HBV replication to improve liver function, and also to reduce the risk of post-LT HBV recurrence. It has been shown that the risk of HBV recurrence after transplantation is related to the level of HBV DNA with a cut-off of 10^4–10^5 copies/ml. The combination of HBIG and lgbNA expressed better results than HBIG or lgbNA alone in improving overall HBV-related post-LT mortality and in preventing HBV recurrence [3]. However, the use of long-term lgbNA was limited by the emergence of HBV resistance due to YMDD mutations.

✉ Didier Samuel
didier.samuel@aphp.fr

1 AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Inserm Research Unit 1193, Université Paris-Saclay, 94800 Villejuif, France

2 FHU Hepatinov, 94800 Villejuif, France

3 Assistance Publique-Hôpitaux de Paris, Hôpital Paul Brousse, Centre Hépato-Biliaire, 12 av P.V. Couturier, 94804 Villejuif, France

High genetic barrier nucleos(t)ide analogs (hgbNA) such as entecavir (ETV) or tenofovir disoproxil fumarate (TDF) are now recommended as first-line HBV therapy. Combination prophylaxis using HBIG with a hgbNA pre- and post-transplant is currently the standard of care for the prophylaxis of HBV recurrence post-LT. The total amount of HBIG needed can be reduced by the combined synergistic effect of HBIG which neutralizes circulating virions allowing HBsAg negativation and of hgbNA which inhibits viral replication. The combination of HBIG with hgbNA was shown to be superior to HBIG plus LAM with a rate of HBV recurrence of 1 vs 6.1% ($p < 0.001$), respectively [3]. It will be difficult to further reduce the rate of HBV recurrence. The aim is now to reduce the overall cost of HBV prophylaxis and to improve the compliance with a similar efficacy.

IV HBIG limits are: a high cost, parenteral administration, limited supply, and the need for anti-HBs monitoring. Therefore, alternative prophylactic strategies have been developed such as the use of intramuscular or subcutaneous HBIG, the switch to antiviral monotherapy, or monoprophylaxis with antiviral from the start [2, 4–6]. Combination prophylaxis with low-dose IM HBIG decreases costs by more than 90% with a recurrence rate of 4% at 4 years [5]. The 3-year post-LT HBV recurrence with lamivudine (LAM) monoprophylaxis from the start was 41% mainly due to an escape mutant in the YMDD motif of the polymerase gene [2].

There is no randomized study evaluating HBV recurrence in patients receiving hgbNA monotherapy vs. hgbNA combination with HBIG.

The study by Sheng et al. is a systematic review and meta-analysis of 41 studies involving 9435 patients, comparing hgbNA with or without HBIG for HBV prophylaxis after LT [7]. A similar cumulative HBV recurrence rate and overall survival at 1, 3, 5 and 10 years post-LT was observed: 0.3, 0.9, 1.2, 1.7% and 95.6, 89, 86.4, 86.4% in the combination prophylaxis group vs. 0.6%, 0.6%; 1.2%, 1.7% and 94.5%,

86.8%, 84.1%, 81.2% in the antiviral monotherapy group. Cumulative incidence of HBV recurrence was significantly lower using hgbNA with HBIG as compared with lgbNA with HBIG (HR of 0.23; 95% CI 0.13–0.39; $p < 0{,}0001$). HBV recurrence rate at 5 years post-LT was 1.2 vs. 5.4% using hgbNA with HBIG as compared with lgbNA with HBIG. As previously reported, these results confirmed the superiority of hgbNA over lgbNA in combination prophylaxis with HBIG [4]. The study of Sheng et al. has several limitations: studies included heterogeneous population at variable risk of HBV recurrence, all studies except one were retrospective, unmatched, non-blinded, and therefore prone to biases. Modalities of HBIG administration such as route of administration, dose or duration are heterogeneous in the different studies. Covariates such as hepatocellular carcinoma recurrence, quantification of HBV DNA at the time of LT, were not analyzed.

The definition of HBV recurrence is commonly based on the reappearance of circulating HBsAg with or without detectable HBV DNA. However, a clinically significant HBV recurrence evaluated on an increase in aminotransferase levels and acute or chronic hepatitis is only observed for patients with persistently detectable HBV DNA. In patients receiving hgbNA monoprophylaxis, persistence or reappearance of HBsAg positivity is not associated with graft hepatitis when serum HBV DNA is not detectable. The presence of serum HBsAg without HBVDNA is due to the production of sub-viral HBsAg particles not blocked by nucleoside analogs [2] while HBsAg particles are blocked by HBIG in immune complexes.

The findings of the present study contrast with those of a recently published meta-analysis [8]. In the latter one, Li et al. included 25 studies, with a pooled HBV recurrence rate of 1.01% (95% CI 0.53–1.59%). The recurrence rate under an indefinite combination of hgbNA and HBIG was lower than that under hgbNA monotherapy ($p = 0.000$) and similar to that under hgbNA plus a finite course of HBIG ($p = 0.48$). The difference between the results of the two studies could be related to a difference in the definition of HBV recurrence. Conversely to the study of Sheng et al., in the study of Li et al., HBsAg reappearance was treated as a true HBV recurrence. In addition, in the study by Sheng et al., it is impossible to know if patients at higher risk of recurrence did receive the combination HBIG + hgbNA or the hgbNA monotherapy which might include a bias in the result.

Currently, only few studies have administered hgbNA to more than ten patients. The largest study, reported by Fung et al., reported the long-term outcome of 265 liver transplant recipients treated with ETV monotherapy [9]. At the time of transplant, 26% of the patients had HBV DNA level more than 4 log IU/ml. The median duration of follow-up was 59 months. Fifty patients (18.8%) had persistent HBsAg positivity either without seroclearance ($n = 14$) or reappearance of HBsAg after initial seroclearance ($n = 36$). The pre-transplant quantitative HBsAg level (i.e., < 3 log IU/ml) was shown to be a predictor of a low HBV recurrence risk. At 1, 3, 5, and 8 years post-LT, 95%, 99%, 100%, and 100% had undetectable HBV DNA, respectively. Liver graft stiffness measurements after LT were similar between those who had durable HBsAg seroclearance compared to those who remained HBsAg positive. This was associated with an overall 85% 9-year survival, without any graft loss or death due to HBV recurrence.

Several studies have identified patients at low and high risk of HBV recurrence post-LT [2]. Patients who have undetectable HBV DNA levels at LT are at low recurrence risk. Factors associated with a high risk of HBV recurrence are: pre-transplant HBeAg positivity, pre-transplant HBV DNA levels > 10^5 copies/mL or 20,000 IU/mL, preexisting drug resistance, those with a high risk of HCC recurrence and drug non-compliance. Most patients could achieve undetectable HBV DNA levels at LT with a treatment with hgbNA. However, patients with life-threatening HBV reactivation are frequently transplanted with a persistent viral load due to lack of time. The study by Sheng et al. by its retrospective nature does not bring enough definite answer to the question of the type of prophylaxis. Therefore, we should still stick to the below guidelines [10].

At the present time, patients at low risk of HBV recurrence are the best candidates for protocols with hgbNA and HBIG minimization or HBIG-free prophylaxis. The high efficacy of current prophylaxis protocols should be preserved using a combination prophylaxis with hgbNA and low-dose HBIG for patients at high risk for HBV recurrence. A close monitoring for HBV recurrence is crucial during and after minimization or discontinuation of prophylaxis while rescue antiviral therapies for HBV reinfection are limited. The main objective of prophylaxis is prevention of HBV graft reinfection and not management of HBV recurrence.

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