Editorial

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Editorial

Individualizing hepatitis B infection prophylaxis in liver transplant recipients

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Globally, chronic infection with hepatitis B virus (HBV) remains a leading cause of liver related mortality [1]. Liver transplantation (LT) provides a life saving therapy for HBV-infected patients with complications of end stage liver disease and hepatocellular carcinoma (HCC). Although chronic HBV infection is a declining indication for LT in the United States, chronic HBV remains the leading indication for LT in Asia [2,3]. Prior to the early 1990's, reinfection with HBV after transplantation occurred in greater than 80% of graft recipients and the 5-year graft and patient survival rates were only 50%. However, over the past two decades, significant advances in both prevention and treatment of recurrent HBV disease have resulted in improved survival, such that patients transplanted for chronic HBV now have comparable or superior outcomes compared to recipients transplanted for other chronic liver diseases [4].

Hepatitis B immune globulin (HBIG) has been central to prevention strategies since the early 1990s. Although its mechanism of action is incompletely understood, HBIG likely acts by binding to and neutralizing circulating virions and by inhibiting cell-to-cell infection [5]. The landmark study by Samuel and colleagues in 1993 demonstrated that the use of prolonged high dose HBIG was associated with a significant reduction in HBV recurrence and improved survival [6]. This finding revolutionized post transplant outcomes for those with HBV infection. The next major advance came with the approval of lamivudine, the first nucleoside analogue for HBV, with a safety and tolerability profile well-suited to cirrhotics and transplant recipients [7,8]. Lamivudine alone, however, was limited by a high rate of viral resistance and, consequently, prophylactic strategies rapidly evolved to a combination of HBIG and lamivudine. Although antiviral drugs have improved over the years, with current entecavir and tenofovir having very low rates of drug resistance, most transplant programs in North America and Europe still utilize a combination of HBIG and a nucleoside analogue for prophylaxis and this combination prevents HBV recurrence in ⩾90% of transplant recipients [9,10].

The major shortcoming of HBIG therapy has been its prohibitive cost. For this reason alone, prophylactic strategies using lower doses or limited duration of HBIG have evolved. "HBIG minimization" strategies, using low dose or limited duration HBIG in combination with nucleoside analogues have been shown to be highly effective in preventing HBV recurrence. The Australasian Liver Transplant Study Group reported HBV recurrence rates were only 4% at 5 years with use of low dose intramuscular HBIG (400–800 IU monthly) in combination with lamivudine. Moreover, this regimen was less than 10% of the cost of high dose intravenous HBIG plus lamivudine [11]. Buti and colleagues evaluated short-term (1 month) HBIG in combination with lamivudine, and among 29 patients, no recurrences were seen after 18 months [12], and a long-term follow-up study of 14 of these patients identified only one patient with HBV recurrence at 48 months post-LT [13]. It is noteworthy that in both these studies, the majority of patients received antiviral therapy at initial assessment and HBV DNA was suppressed to undetectable levels prior to transplantation. The efficacy of antiviral therapy in patients with cirrhosis is likely an important element of the success of prophylactic regimens using either reduced dosing or duration of HBIG.

The strategy of active immunoprophylaxis with HBV vaccination as an alternative to HBIG in the post transplant setting has yielded conflicting results [14–17]. Sanchez-Fueyo and colleagues reported success of achieving protective anti-HBs titres (>10 IU/L) with active immunization in 14 of 17 (82%) low risk patients [14]. In contrast, Angelico et al. reported success rates of only 18% [15]. Other data have emerged that suggest administration of either booster doses or double dose third generation recombinant vaccines may enhance the vaccination response and decrease formation of escape mutants [16,17]. However, pending additional studies with long-term follow-up, vaccination cannot be recommended as an alternative to passive immunoprophylaxis.

Studies have consistently shown that the risk of recurrent HBV infection is highest in those with HBe antigen positivity or >100,000 copies/ml of HBV DNA present at the time of transplantation [6,11,18]. Conversely, the risk is significantly lower in those who are HBe antigen negative and/or have low or negative HBV DNA levels at transplantation. With current potent antiviral therapies, most patients can achieve undetectable HBV DNA levels at the time of transplantation, and thus be at low risk for recurrent HBV. These patients are ideally suited for prophylactic strategies that minimize HBIG use. This low risk group – HBe antigen negative and HBV DNA undetectable – was the target

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group for withdrawal of prophylaxis in the study by Lenci and colleagues [19].

With the availability of potent antiviral drugs with a high genetic barrier to resistance, one may argue that HBIG is unnecessary. There are no published data on the use of drugs such as tenofovir and entecavir as monotherapy to prevent HBV recurrence from the time of transplantation, but limited studies have evaluated use of these drugs after discontinuation of HBIG in patients initially treated with combined HBIG and nucleoside analogues therapy and high efficacy is reported (only 3% HBV recurrence) with average follow-up periods of 1.5 years [20,21]. Other studies using less potent nucleoside analogues combinations (lamivudine and adefovir predominantly) but with follow-up periods of up to 4 years report high efficacy with rates of recurrent HBV of <10% [22,23]. Interestingly, in some patients, non-compliance rather than viral resistance was the reason for the failure of prophylaxis. Indeed, one reason for the high efficacy of combination therapy of HBIG and nucleoside analogues may be the ability to monitor adherence to the receipt of HBIG.

The study by Lenci et al. focused upon whether it was possible to define a subgroup of transplant recipients who are not at risk for HBV recurrence and in whom prophylactic therapy can be discontinued [19]. In a cohort of 30 subjects, all of whom were at a low risk for recurrence (HBsAg positive, HBeAg antigen negative and HBV DNA negative at transplant) and treated with combination HBIG and lamivudine (± adefovir) for at least 3 years, sequential liver biopsies were performed and evaluated for the presence of intrahepatic HBV DNA total and cccDNA. Using the absence of intrahepatic total HBV DNA and cccDNA as a guide, HBIG and then antiviral therapy was withdrawn in a stepwise fashion. After a median of 28.7 months off all prophylactic therapy, 83% of the cohort remained without serologic recurrence of HBV infection. Five patients had HBV DNA recurrence but only one patient manifested evidence of HBV disease (high HBV DNA levels plus increased ALT activity). While the findings of this study suggest that a rigorous assessment of HBV in the liver may provide a mechanism of identifying transplant recipients in whom HBV prophylaxis may be safely withdrawn, additional prospective studies are needed to confirm these results.

In a previously published study, Lenci and colleagues studied 44 patients, from which the present cohort was derived, and found only three (7%) patients tested positive for total intrahepatic HBV DNA and only one (2%) was positive for cccDNA [24]. These results contrast sharply with the results of other studies that found that the majority of serologically HBsAg-negative liver transplant recipients on prophylactic therapy have HBV DNA or cccDNA detectable in liver and/or peripheral blood mononuclear cells (PBMCs). The high prevalence of detectable virus in these sites has supported the use of indefinite HBV prophylaxis. Roche et al. found that 20 out of 44 (45%) patients on long-term HBIG (with and without nucleoside analogue) had persistence of HBV DNA in the serum (18/20), PMBC (13/20), or liver (10/20) [25]. Cheung et al. found that 67% and 33% of 12 HBsAg-negative recipients on nucleoside analogue prophylaxis had intrahepatic HBV DNA and cccDNA detectable, respectively [26]. Coffin et al. reported that among 10 patients on combined HBIG plus nucleoside analogue therapy followed for median 16 months post-transplantation, 90% and 23% had HBV DNA detectable in the liver and PBMCs, respectively [27]. Finally, the NIH-HBVLT study of 25 patients on long-term prophylaxis, found that 84% and 44% of liver biopsies were positive for total HBV DNA and cccDNA, with up to 48 months follow-up post-

LT [28]. The significant differences in the prevalence of cccDNA and intrahepatic HBV DNA across studies may reflect differences in patient population (HBV DNA levels at transplant, presence of HCC), sampling variability, or the sensitivity and reliability of the molecular techniques used in quantifying residual HBV burden.

Practically, the utility of HBV DNA and cccDNA measurements in the liver to determine suitability for withdrawal of prophylaxis has limitations. Repeated liver biopsies are burdensome and assays for quantitation of intrahepatic HBV DNA and cccDNA are not standardized. As mentioned, sampling error and variable assay accuracy may contribute to disparities in detection of liver HBV DNA and cccDNA across studies and highlight the challenges in using these measurements in managing HBV transplant recipients. Indeed, the study's authors acknowledge that their molecular approach is not clinically applicable. Whether measurement of HBV DNA in PBMCs may be an alternative means of assessing suitability for prophylaxis withdrawal is unknown. Future studies will need to identify alternative biomarkers to identify those patients who are candidates for withdrawal of prophylactic therapy. The lessons learned regarding HBV prophylaxis from the Lenci study and others is that an individualized approach for the prevention of HBV recurrence can and should be utilized. Low and high-risk groups can be defined primarily by HBV DNA levels at transplantation. Other potential factors influencing prophylaxis choices may be the presence of HDV coinfection (no effective antiviral drugs), HIV coinfection (high prevalence of lamivudine resistance), presence of drug-resistant HBV, and the risk of HCC recurrence (as this is a risk for recurrent HBV) [29]. The findings of the present study support the notion that low-risk patients – those with undetectable HBV DNA at transplant – may be candidates for withdrawal of HBIG and, more provocatively, may possibly be candidates for withdrawal of all prophylactic drugs. Conversely, higher risk patients – all other groups – are better served by long-term combination low dose HBIG plus nucleoside analogues. Certainly, the availability of effective antiviral "rescue" therapy makes reduction or elimination of prophylactic drugs more feasible to consider. However, close monitoring for recurrence of HBV is essential during and after minimization or withdrawal of prophylactic drugs to insure prompt initiation of antiviral therapy to prevent significant graft damage. Although our ability to control recurrent HBV disease is greater today than it was a decade ago, the treatment options for chronic HBV are not infinite and multidrug-resistant HBV has been described in transplant recipients exposed to multiple sequential HBV therapies [30]. Thus, while we should continue to refine prophylactic algorithms to reduce drug costs and increase patient and provider convenience, the current high efficacy in preventing HBV should not be compromised. Prevention of HBV infection is still the preferred strategy over managing recurrent chronic disease.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris) 2010;58:273–277.

[2] Kim WR, Terrault NA, Pedersen RA, Therneau TM, Edwards E, Hindman AA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology 2009;137:1680–1686.

[3] Lo CM, Fan ST, Liu CL, Lai CL, Wong J. Prophylaxis and treatment of recurrent hepatitis B after liver transplantation. Transplantation 2003;75:S41–S44.

[4] Kim WR, Poterucha JJ, Kremers WK, Ishitani MB, Dickson ER. Outcome of liver transplantation for hepatitis B in the United States. Liver Transpl 2004;10:968–974.

[5] Terrault NA, Vyas G. Hepatitis B immune globulin preparations and use in liver transplantation. Clin Liver Dis 2003;7:537–550.

[6] Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993;329:1842–1847.

[7] Grellier L, Brown D, McPhillips P, Burroughs A, Rolles K, Dusheiko G. Lamivudine prophylaxis: a new strategy for prevention of reinfection in liver transplantation for hepatitis B DNA positive cirrhosis. Hepatology 1995;22:224A.

[8] Nery JR, Weppler D, Rodriguez M, Ruiz P, Schiff ER, Tzakis AG. Efficacy of lamivudine in controlling hepatitis B virus recurrence after liver transplantation. Transplantation 1998;65:1615–1621.

[9] Terrault N, Roche B, Samuel D. Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. Liver Transpl 2005;11:716–732.

[10] Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. Liver Int 2009;29:1294–1305.

[11] Gane EJ, Angus PW, Strasser S, Crawford DH, Ring J, Jeffrey GP, et al. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology 2007;132:931–937.

[12] Buti M, Mas A, Prieto M, Casafont F, Gonzalez A, Miras M, et al. A randomized study comparing lamivudine monotherapy after a short course of hepatitis B immune globulin (HBIg) and lamivudine with long-term lamivudine plus HBIg in the prevention of hepatitis B virus recurrence after liver transplantation. J Hepatol 2003;38:811–817.

[13] Buti M, Mas A, Prieto M, Casafont F, Gonzalez A, Miras M, et al. Adherence to lamivudine after an early withdrawal of hepatitis B immune globulin plays an important role in the long-term prevention of hepatitis B virus recurrence. Transplantation 2007;84:650–654.

[14] Sanchez-Fueyo A, Rimola A, Grande L, Costa J, Mas A, Navasa M, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. Hepatology 2000;31:496–501.

[15] Angelico M, Di Paolo D, Trinito MO, Petrolati A, Araco A, Zazza S, et al. Failure of a reinforced triple course of hepatitis B vaccination in patients transplanted for HBV-related cirrhosis. Hepatology 2002;35:176–181.

[16] Gunther M, Neuhaus R, Bauer T, Jilg W, Holtz JA, Bienzle U. Immunization with an adjuvant hepatitis B vaccine in liver transplant recipients: antibody decline and booster vaccination with conventional vaccine. Liver Transpl 2006;12:316–319.

[17] Lo CM, Lau GK, Chan SC, Fan ST, Wong J. Efficacy of a pre-S containing vaccine in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. Am J Transplant 2007;7:434–439.

[18] Marzano A, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transpl 2005;11:402–409.

[19] Lenci I, Tisone G, Di Paolo D, Marcuccilli F, Tariciotti L, Ciotti M, et al. Safety of complete and sustained prophylaxis withdrawal in patients liver transplanted for HBV-related cirrhosis at low risk of HBV recurrence. J Hepatol 2011;55:587–593.

[20] Saab S, Desai S, Tsaoi D, Durazo F, Han S, McClune A, et al. Posttransplantation hepatitis B prophylaxis with combination oral nucleoside and nucleotide analog therapy. Am J Transplant 2011;11:511–517.

[21] Karlas T, Hartmann J, Weimann A, Maier M, Bartels M, Jonas S, et al. Prevention of lamivudine-resistant hepatitis B recurrence after liver transplantation with entecavir plus tenofovir combination therapy and perioperative hepatitis B immunoglobulin only. Transpl Infect Dis 2010.

[22] Wong SN, Chu CJ, Wai CT, et al. Low risk of hepatitis B virus recurrence after withdrawal of long-term hepatitis B immunoglobulin in patients receiving maintenance nucleos(t)ide analogue therapy. Liver Transpl 2007;13:374–381.

[23] Angus PW, Patterson SJ, Strasser SI, et al. A randomized study of adefovir dipivoxil in place of HBIG in combination with lamivudine as post-liver transplantation hepatitis B prophylaxis. Hepatology 2008;48:1460–1466.

[24] Lenci I, Marcuccilli F, Tisone G, Di Paolo D, Tariciotti L, Ciotti M, et al. Total and covalently closed circular DNA detection in liver tissue of long-term survivors transplanted for HBV-related cirrhosis. Dig Liver Dis 2010;42:578–584.

[25] Roche B, Feray C, Gigou M, Roque-Afonso AM, Arulnaden JL, Delvart V, et al. HBV DNA persistence 10 years after liver transplantation despite successful anti-HBS passive immunoprophylaxis. Hepatology 2003;38:86–95.

[26] Cheung CK, Lo CM, Man K, Lau GK. Occult hepatitis B virus infection of donor and recipient origin after liver transplantation despite nucleoside analogue prophylaxis. Liver Transpl 2010;16:1314–1323.

[27] Coffin Carla S, Mulrooney-Cousins Patricia M, van Marle Guido, Roberts John P, Michalak Tomasz I, Terrault Norah A. Hepatitis B Virus (HBV) quasispecies in hepatic and extrahepatic viral reservoirs in liver transplant recipients on prophylactic therapy. Liver Transpl 2011.

[28] Hussain M, Soldevila-Pico C, Emre S, Luketic V, Lok AS. Presence of intrahepatic (total and ccc) HBV DNA is not predictive of HBV recurrence after liver transplantation. Liver Transpl 2007;13:1137–1144.

[29] Faria LC, Gigou M, Roque-Afonso AM, Sebagh M, Roche B, Fallot G, et al. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. Gastroenterology 2008;134:1890–1899, [quiz 2155].

[30] Yim HJ, Hussain M, Liu Y, Wong SN, Fung SK, Lok AS. Evolution of multi-drug resistant hepatitis B virus during sequential therapy. Hepatology 2006;44:703–712.

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