Safety of Complete and Sustained Prophylaxis Withdrawal in Patients Liver-transplanted for Hepatitis B Virus-related Cirrhosis at Low Risk of Hepatitis B Virus Recurrence

Lenci I, Tisone G, Di Paolo D, 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;55:587–93.

Abstract

Background: HBV (hepatitis B virus) reactivation after liver transplantation may be related to persistence of covalently closed circular (ccc) DNA. We investigated the safety of HBV prophylaxis withdrawal in selected HBV transplanted patients. **Methods:** Thirty patients transplanted 64–195 months earlier (23 males, median age 56 years), HBsAg-positive, HBeAg, and HBV-DNA-negative at transplant (43% HCV/HDV coinfecting), with undetectable intrahepatic total and ccc-DNA were enrolled. All patients underwent HBIG withdrawal and continued lamivudine with monthly HBsAg and HBV-DNA monitoring and sequential liver biopsies. Those with confirmed intrahepatic total and ccc-DNA undetectability 24 weeks after stopping HBIG also underwent lamivudine withdrawal and were followed up without prophylaxis. **Results:** Twenty-five patients did not exhibit signs of HBV recurrence after prophylaxis withdrawal (median follow-up 28.7 months, range 22–42). Five patients became HBsAg-positive: one early after HBIG withdrawal, the other four after HBIG and lamivudine withdrawal. None of these patients experienced clinically relevant events. In the first patient, HBIG were reinstituted with prompt HBsAg negativization. Of the

other four, one remained HBsAg-positive with detectable HBV-DNA and mild alanine transaminase elevation and was successfully treated with tenofovir. In the remaining three, HBsAg positivity was transient and followed by anti-HBs seroconversion; thus no antiviral treatment was needed. **Conclusion:** Patients with undetectable HBV viremia at transplant and no evidence of intrahepatic total and ccc-DNA may safely undergo cautious weaning of prophylaxis, showing the low rate of HBV recurrence after a 2-year follow-up. Undetectability of intrahepatic ccc-DNA may help to identify patients at low risk of recurrence; yet studies with longer follow-up are needed.

Comment

In spite of the availability of potent antiviral drugs such as entecavir and tenofovir, most liver-transplant programs still use a combination of hepatitis B immunoglobulin (HBIG) and lamivudine or adefovir for prophylaxis and this combination prevents HBV recurrence in >90% of transplant recipients.¹ To cut down the cost of HBIG, various strategies including lower doses or limited duration of HBIG have been studied and in combination with nucleoside analogs have been shown to be effective in preventing HBV recurrence.²

Overall, the risk of recurrence of HBV infection post-transplant is dependent on the replicative status of the virus and is the highest in those with HBe antigen positivity or high viral load (HBV-DNA > 10⁵ copies/mL) present at the time of transplantation. The risk of recurrence of HBV infection is low if patients are able to achieve the negative HBV-DNA status with antiviral drugs prior to liver transplantation. 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 group for withdrawal of prophylaxis in the study by Lenci et al.³

Lenci et al³ evaluated a subgroup of transplant recipients who are not at risk for HBV recurrence and in whom prophylactic therapy can be discontinued. All 30 patients included in the study were at a low risk for recurrence (HBsAg-positive, HBe-antigen-negative, and HBV-DNA-negative at transplant) and treated with combination HBIG and lamivudine ($\pm$ adefovir) for at least 3 years. Patients underwent sequential liver biopsies for the presence of total intrahepatic HBV-DNA and ccc-DNA. Using the absence of intrahepatic total HBV-DNA and ccc-DNA as a guide, HBIG and then antiviral therapy were 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.

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Abbreviations: DAMP: damage-associated molecular patterns; FFA: free fatty acid; HBV: hepatitis B virus; HFD: high-fat diet; NAFLD: non-alcoholic fatty liver disease; PAMP: pathogen-associated molecular patterns; TLR: toll-like receptors

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Though quite encouraging, the results by Lenci et al are in contrast 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 ccc-DNA detectable in liver and/or peripheral blood mononuclear cells.^{4,5} The high prevalence of detectable virus in these sites (up to 23–90%) in previous studies has supported the use of indefinite HBV prophylaxis. In addition, the repeated use of HBV-DNA and ccc-DNA measurements in the liver as a guide to withdrawal of prophylaxis has its own limitations. Repeated liver biopsies are burdensome, are not free of complications, and assays for quantitation of intrahepatic HBV-DNA and ccc-DNA are not standardized. Sampling error and the variable accuracy of the assay may further add to the disparities in detection of intrahepatic HBV-DNA and ccc-DNA.

In spite of the limitations, study by Lenci et al³ suggests that a special approach can be taken in a select group of patients at low risk of re-infection depending on the HBV-DNA at the time of transplantation. Those with undetectable HBV-DNA at transplant can be candidates for withdrawal of HBIg or possibly be candidates for withdrawal of all

prophylactic drugs. Whereas those at a higher risk are treated by long-term combination low-dose HBIg plus nucleoside analogs. Though potent drugs with high genetic barrier are available to treat the recurrent HBV infection, the focus should still be on prevention of re-infection rather than on the treatment of recurrent infection.

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Nuclear Factor High-mobility Group Box1 Mediating the Activation of Toll-like Receptor 4 Signaling in Hepatocytes in the Early Stage of Non-alcoholic Fatty Liver Disease in Mice

Li L, Chen L, Hu L, et al. Nuclear factor high-mobility group box1 mediating the activation of toll-like receptor 4 signaling in hepatocytes in the early stage of nonalcoholic fatty liver disease in mice. *Hepatology* 2011, July 11.

Abstract

One of the challenges surrounding nonalcoholic fatty liver disease (NAFLD) is to discover the mechanisms that underlie the initiation of it. The aim of this study was to elucidate the effects of toll-like receptor 4 (TLR4) signaling in liver parenchymal cells during the early stage of NAFLD. Male TLR4-wildtype, TLR4-knockout, TLR2-knockout, MyD88-knockout, and TRIF-knockout mice were fed a normal diet or high-fat diet (HFD). Liver steatosis, alanine aminotransferase levels, nuclear translocation of nuclear factor kappa B (NF- κ B) (P65), macrophage accumulation, and neutrophil infiltration were assessed. Using Kupffer cell depletion or bone-marrow transplantation, we examined the potential role

of Kupffer cells and myeloid infiltrating cells during the initiation of NAFLD. Immunohistochemistry and western blotting were implemented to determine the release of high-mobility group box1 (HMGB1). The neutral antibody against HMGB1 was used to block the activity of free HMGB1. Here, we report that the activation of TLR4 signaling in hepatocytes, accompanied with the relocation of P65 in nucleus, was proven to play an important role during the initiation of NAFLD. Importantly, HMGB1 releasing from hepatocytes in response to free fatty acid (FFA) infusion was first reported as the key molecule for the TLR4/MyD88 activation and cytokines expression in vitro and in vivo. Treatment with neutralizing antibody to HMGB1 protects against FFA-induced tumor necrosis factor alpha and interleukin-6 production. **Conclusion:** Our study supports the notion that TLR4/MyD88 signaling in liver parenchymal cells plays a pivotal role during the early progression of HFD-induced NAFLD, in which free HMGB1 served as a positive component mediating TLR4 activation.

Comment

Pathogenesis of non-alcoholic fatty liver disease (NAFLD) is still ill understood. Insulin resistance, oxidative stress, endotoxemia, and gene polymorphism are thought to be involved in the pathogenesis of NAFLD. Gut-derived portal endotoxins contribute to the overactivation of Kupffer cell through toll-like receptors (TLRs) and therefore aggravate liver inflammation and cell injury which may lead