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Outcomes of Entecavir Prophylaxis in Hepatitis B Immune Patients Receiving Hepatitis B Infected Kidneys: A Single Center Experience

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Abstract

Purpose of Review Hepatitis B (HBV) vaccinated patients have mixed responses with regard to antibody titers and subsequent level of immunity. This review aims to examine the diverse strategies employed by transplant centers for infection prevention when utilizing HBV-infected kidneys, including our own center's practice.

Recent Findings Transplant centers have implemented varied prophylaxis approaches based on recipients' anti-HB titers for utilizing HBV-infected kidneys. We retrospectively reviewed ten recipients who received kidneys from HBV-positive donors at our center. Recipients with anti-HBs titers above 100 mIU/mL received entecavir prophylaxis, while those with lower titers received perioperative HBIG. Throughout the follow-up, all patients remained negative for HBV NAT and HBsAg. Six patients experienced asymptomatic anti-HBc seroconversion, of which two patients cleared anti-HBc within 1 year. One patient experienced a decline in anti-HBs titers below 100 mIU/mL but remained free of HBV infection.

Summary The utilization of Hepatitis B-infected kidneys for transplantation in HBV-immunized recipients is safe. Asymptomatic seroconversion is frequent, but viremia is prevented by immunization and/or entecavir. The role of HBIG prophylaxis is unclear. Most patients with preoperative anti-HBs titer > 100 mIU/mL maintain those titers during the first-year post-transplant.

Keywords Kidney transplant · Hepatitis B infected donors · Seroconversion · HBV immunization · Entecavir

Introduction

Currently, over 100,000 patients are on the kidney transplant wait list in the USA. Transplant wait list times remain long and are associated with poor outcomes; 3 years after being placed on wait list, 34.6% of patients were still waiting for transplant and 26.4% had died or were removed from wait list [1]. The use of kidneys from hepatitis B (HBV)-positive donors has been proposed as a solution to increase the donor pool. Unlike hepatitis C viremic kidneys that have shown recent increased utilization due to the data from trials like EXPANDER-1 and THINKER showing excellent safety and success by utilizing direct-acting antiviral (DAA) therapies [2], HBV viremic organs' utilization is not widespread. This could be explained by the lack of consensus on its management. Also, current anti-HBV treatments, although have a good viral biochemical response rate (81%, 95%, and 99.5% at 1, 3, and 5 years, respectively), they are not curative [3]. Hepatitis B is the leading cause of hepatitis, cirrhosis, and hepatocellular carcinoma [4]; therefore, transplantation from HBV-positive donors to HBV naïve recipients poses the significant challenge of preventing de novo HBV infection in this severely immunocompromised population. This is further complicated by the variability of ESRD patients' response to vaccination as well as their rapid decline in vaccine-induced antibody titers compared to the general population [5].

In 2015, a multidisciplinary expert panel convened by the American Society of Transplantation developed consensus recommendations regarding the use of organs from HBV-positive donors in solid organ transplantation. There were no direct recommendations on how to utilize HBV viremic (HBV +) donors into HBV seronegative (HBV −) recipients due to the lack of evidence on the safety and effectiveness of

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HBV Nucleic acid test positive (HBV NAT +) organs [6•]. This paper did reference published experiences from mainly East Asia with variable prophylactic and treatment measures that had a combination of hepatitis B immunoglobulin (HBIG) and/or highly potent anti-virals like entecavir and tenofovir or in some cases no treatment (depending on recipient hepatitis B surface antibody titer levels).

After a careful review of the available literature, we created a single-center protocol for prophylaxis for HBV − recipients who receive HBV + donor kidneys. The goal of this study is to assess the safety and effectiveness of the use of HBV + viremic donors in HBV NAT − recipients using our protocol.

Methods

All patients received kidney transplant education on the implications of using hepatitis B viremic kidneys. Informed consent was obtained prior to enrollment. Additionally, as part of the transplant evaluation process, candidate's immunization history was reviewed, and HBV vaccination was administered if not previously received. Per our protocol, recipients with HBV surface antibody (anti-HBs) titer > 100 mIU/mL were selected for transplantation with HBV + kidneys. Recipients that are expected to receive higher immunosuppressive therapy like those with a history of prior transplant, high calculated panel reactive antibody (cPRA ≥ 80), and pre-existing donor-specific antibodies (DSA) were not eligible to receive HBV + kidneys per our protocol. At the time of admission for transplant, if patients were found to have anti-HBs titers < 100 mIU/mL they were given a dose of HBIG. Our protocol requires HBIG administration preoperatively if readily available, otherwise administered in the immediate post-operative period as soon as available.

Patients received standard induction of a cumulative dose of thymoglobulin 4.5 mg/kg or 2 doses of Basiliximab 20 mg each depending on their immunological risk profile. A tapering regimen of methylprednisolone 500 mg, 250 mg, 125 mg, and 60 mg were administered on post-operative day (POD) 0 through 3, respectively, followed by prednisone 20 mg daily which is further tapered to 5 mg daily over 6–12 weeks. Patients were started on mycophenolate sodium 720 mg twice daily on POD 0. Patients were also started on tacrolimus on POD 1 or 2 based on allograft function. Renally dosed entecavir was initiated on POD 0 and continued for 1 year. Recipients' liver function tests are tested daily while inpatient and on each outpatient clinic visit. Hepatitis B serologies including anti-HBs, hepatitis B surface antigen (HBsAg), HBV core antibody (anti-HBc), and HBV NAT were tested at 6 weeks, 6 months, and 1 year post-transplant. If HBsAg and/or HBV NAT are detected positive, our protocol requires referral to hepatology for further evaluation and treatment. We performed a retrospective chart review to evaluate donor and recipient characteristics, recipient preoperative and post-operative HBV serologies, and kidney transplant outcomes.

Results

Donor Characteristics

We identified ten transplants performed utilizing kidneys from HBV NAT or HBsAg positive donors. The baseline characteristics of donors are outlined in Table 1. Donors had a mean age of 43.3 years (range 28–59) with a mean KDPI of 54.6% (range 24–90). Six out of ten donors were

Table 1 Baseline characteristics of donors

Donor characteristics	Donors ($n = 10$)
Age, years, mean	43.3
Sex, male, *n* (%)	8 (80%)
Kidney donor profile index (%) mean	54.6 (%)
Race, *n* (%)	
Non-Hispanic White	6(60%)
African American	3(30%)
Hispanic	1(10%)
Asian	0(0%)
Donor blood group, *n* (%)	
O	8(80%)
A	2(20%)
B	0(0%)
AB	0(0%)
Organ location, *n* (%)	
Local	2(20%)
Regional	2(20%)
National	6(60%)
Body mass index (kg/m^2), mean	27.8
Donation after circulatory death, *n* (%)	3(30%)
Cold ischemic time, h, mean	18.6 h
Terminal creatinine, mean	1.0
Donor peak AST/ALT, mean	178/133
Hepatitis C testing, *n* (%)	
HCV NAT (−), HCV AB (−)	7(70%)
HCV NAT (+), HCV AB (+)	1(10%)
HCV NAT (−), HCV AB (+)	2(20%)
Hepatitis B serologies, *n* (%)	
HBV NAT (+), HBsAg (+)	6(60%)
HBV NAT (+), HBsAg (−)	3(30%)
HBV NAT (−), HBsAg (+)	1(10%)
Anti-HBc (+)	6(60%)

non-Hispanic white and eight out of ten were males. Most of the donors were blood group O [7]. The mean donor terminal creatinine was 1.0 (range 0.61–1.6). The mean cold ischemia time was 18.6 h (range 12–23 h) with 6 being national offers. Seventy percent of the donors were brain-dead donors. Six donors were both HBsAg and HBV NAT positive. The rest were either HBV NAT + only (3 of 10) or HBsAg + (1 of 10). One donor was co-infected with hepatitis C (HCV) NAT +, while two other donors were HCV NAT − but anti-HCV +.

Recipient Characteristics

Recipient characteristics are described in Table 2. The mean recipient age was 53.9 years. Ninety percent of recipients were male. The mean estimated post-transplant survival (EPTS) score was 55%. Racial/ethnic composition was African American (40%), non-Hispanic white (30%), and Hispanic (30%). The mean time from the wait list to transplant was 296 days (range 9–1085 days). Nine patients have an anti-HBs titer > 100 with a mean titer of 516 mIU/mL. The one patient who had an anti-HBs titer of 68 mIU/mL at the time of transplant admission was given a single HBIG dose perioperatively.

Table 2 Baseline characteristics of recipients

Recipient characteristics	Recipients ($n = 10$)
Age, years, mean	53.9
Sex, *n* (%)	
Male	9(90%)
Female	1(10%)
Estimated post-transplant survival, (%) mean	55
Mean calculated panel reactive antibody (cPRA), (%)	0
Race, *n* (%)	
African American	4(40%)
Non-Hispanic White	3(30%)
Hispanic	3(30%)
Asian	0(0%)
Blood group, *n* (%)	
O	8(80%)
A	2(20%)
B	0(0%)
AB	0(0%)
Body mass index (kg/m^2), mean	30.6
Waitlist duration, days, mean	296
Anti-HBs preoperative titers mIU/mL	
Mean	516.6
N (%) > 100 mIU/mL	9 (90%)
N (%) < 100 mIU/mL	1(10%)
Etiology of end-stage renal disease, *n* (%)	
Diabetes	5(50%)
Hypertension	3(30%)
Glomerular disease	2(20%)

Post-transplant recipient HBV serological changes and outcomes

All recipients remained HBV NAT and HBsAg negative at 6 weeks, 6 months, and 12 months. Nine recipients maintained anti-HBs titers > 100 mIU/mL at 6 weeks, 6 months, and 12 months, with one patient dropping to a titer of < 100 mIU/mL (47.4 mIU/mL) at the 12-month visit. Six patients developed asymptomatic seroconversion anti-HBc + during their 6 weeks post-transplant serology check. Two of the six patients who had asymptomatic seroconversion to anti-HBc were negative at 12 months. The mean serum creatinine post-transplant in recipients was 1.58 mg/dL (range 0.9–2.4) at 12 months follow up. All patients had excellent outcomes with 100% graft and patient survival at 12 months. These results are summarized in Table 3.

Discussion

Several studies reported promising transplant outcomes from utilization of organs from HBV-positive donors. Various prophylactic regimens and serial monitoring strategies are proposed. Jiang et al. used weekly HBIG for 3 months and lamivudine treatment for 6 months, which resulted in transient de novo HBV infection in 2 of 65 recipients. However, neither patient developed liver dysfunction or adverse graft outcomes [8]. Tuncer et al. did not incorporate any prophylaxis in their study of 35 recipients who all had anti-HBs > 100 mIU/mL. None of the recipients in this study developed no de novo HBV infection postoperatively [7]. Chancharoenthana et al. transplanted recipients with anti-HBs titers > 100 mIU/mL. Lamivudine was given in 23 of 43 of the recipients. HBIG was also given in 2 of 43 patients because the donor was HBV DNA positive and recipients developed immediate post-transplant AMR requiring plasmapheresis-based treatments. The recipients' anti-HBs range was 385.7 to > 1000 mIU/mL. There were no asymptomatic seroconversion or de novo HBV infections reported [9]. Wang et al. described their experience with living donor kidney transplantation from HBsAg + donors to HBsAg − recipients regardless of recipient anti-HBs status. Positive HBsAg and HBV NAT were noted in 2.41% of recipients [10]. In contrast, Delman et al. performed 56 kidneys using HBV viremic organs. All recipients received entecavir regardless of their anti-HBs status which was started on day 0 and continued for a year. Nine of 56 recipients had a transient

Table 3 Post-transplant recipient HBV serological changes and outcomes

Post-transplant serological changes and graft outcomes	Recipients ($n=10$)
HBV NAT + or HBsAg + at any post-op visit (%)	0%
Patients whose ant-HBs titers dropped < 100 over the 1st year visits, *n* (%)	1(10%)
Mean anti-HBs titers at end of 1-year post-op mIU/mL	523
Recipients that showed anti-HBc + serological change at any stage, *n* (%)	6 (60%)
Percentage of patients at the end of first year post-transplant who were: HBsAg −, HBV NAT − and Anti-HBc −	60%
1st year patient survival (%)	100%
1st year graft survival (%)	100%
Mean creatinine at the end of first post-transplant year visit	1.58
No. of patients who had significant perioperative transaminitis (2 × upper limit of normal AST/ALT)	3
Percentage of patients who had delayed graft function	20%

detectable HBV DNA postoperatively which resolved, and all recipients were HBV NAT negative at their last follow up [11•].

Our study demonstrates that hepatitis B viremic kidney utilization is safe with none of our recipients being HBV NAT positive and no significant alteration of liver function tests (LFTs) during their first post-transplant year. Although nine of ten patients had preoperative anti-HBs titers > 100 mIU/mL, six of nine patients had anti-HBc seroconversion suggesting resolved HBV infection with adequate anti-HBs titers (> 100 mIU/mL) and having entecavir prophylaxis during the first post-transplant year. The elevated asymptomatic seroconversion noted in our study (66.67%) could be related to our monitoring of all HBV serologies, unlike other studies that monitored only HBV NAT. The clinical relevance of the anti-HBc seroconversion seems insignificant as patients were asymptomatic and no alteration of LFTs was noted.

We were also able to trend the anti-HBs titers over time. This has allowed us to observe changes in our patients' anti-HBs with polyclonal antibody induction treatment. Only one of the nine patients who had anti-HBs titers > 100 mIU/mL preoperatively dropped their titers below 100 despite the use of polyclonal antibody induction. Although this is reassuring that patients at that titer threshold are good responders and have a good chance of maintaining their titers with time, it did not necessarily confirm enhanced immunity as two-thirds of them showed serological changes confirming resolved infection. In fact, four of six patients who did have seroconversion had anti-HBs > 200 mIU/mL and their mean titer was 1359 mIU/mL at the time of seroconversion. On the other hand, one of nine patients had anti-HBs titer dropped to 47.4 at the 1-year post-transplant visit (most likely related to immunosuppression) but that patient remained HBsAg and HBV NAT negative.

All of our recipients received entecavir with 100% success in preventing HBV infection. This also did not prevent the asymptomatic seroconversion in the six patients, which may signify that despite antiviral therapy, some degree of HBV infectivity still occurs. Two of the six patients who seroconverted were no longer anti-HBc positive at 1 year follow up visit. Whether entecavir had a role in clearing the seroconversion in these two patients remains unclear. Both patients also notably had anti-HBs > 900 mIU/mL. Whether the patients that remain anti-Hbc positive at the end of 1 year follow up need longer entecavir prophylaxis needs to be investigated.

One of our recipients received HBIG treatment in addition to entecavir prophylaxis as anti-HBs titers were below 100 mIU/mL at the time of transplant. This patient did not show any seroconversion and maintained anti-HBs titers > 700 mIU/mL at the end of 1 year. The utility of HBIG remains very controversial in kidney transplant. While some studies reported usage of HBIG, Delman et al. did not use HBIG and relied solely on entecavir regardless of their patient population's anti-HB titers with excellent outcomes. It is important to consider that patients who are poor responders to HBV vaccination will drop their anti-HB titers and will likely not maintain titers for long. of HBIG passive prophylaxis is likely to give some protection in the short term, but its long-term efficacy is unclear, and leads to an additional cost.

Furthermore, the results of our study do not demonstrate a clear correlation between donor age, donor serologies, donor HBV NAT status, donor PHS increased risk factors, or donor HCV status on recipient seroconversion. Similarly, studies by Chancharoenthana et al. and Jiang et al. also did not observe a significant relationship between donor baseline characteristics or donor serologies and recipient asymptomatic anti-HBc seroconversion [8, 9].

It is also evident that the use of HBV viremic kidneys allows patients to be transplanted quickly. On average, our recipients were on the waitlist for 296 days (range 9–1085 days). This donor pool can allow faster transplant rates and has the potential to mitigate the waitlist morbidity and mortality at a low risk. Limitations of our study include a retrospective study at a single institution, a shorter follow-up, and a small sample size.

Conclusions

Effectiveness of entecavir prophylaxis in HBV immune patients receiving HBV-infected kidneys has been well described by several studies in keeping HBV dormant and preventing acute fulminant HBV hepatitis but the need for lifelong prophylaxis can challenge its cost-effectiveness. Patients with anti-HBs titers > 100 mIU/mL preoperatively tend to maintain their titers. HBIG prophylaxis's role in non-immune or poor responders is unclear and will need to be further investigated. Similarly, the duration of prophylaxis with entecavir while utilizing organs from HBV-infected donors will need to be investigated in a prospective randomized controlled trial.

Author Contribution Authors S. M., A. R., and N. R. wrote the manuscript. All authors reviewed the manuscript.

Data Availability Direct URL citations appear in the printed text. Supporting information can be found online in the supporting information section at the end of this article.

Declarations

Ethics Approval and Consent to Participate This study was approved by Medical City Healthcare Institutional Review Board as part of Master Retrospective Protocol Medical City Outcomes Research (MCOR-01). Informed consent from patients was not obtained as this was a retrospective study using deidentified data.

Competing Interests The authors declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Lentine KL, Smith JM, Hart A, et al. OPTN/SRTR 2020 Annual data report: kidney. Am J Transplant. 2022;22(Suppl 2):21–136. https://doi.org/10.1111/ajt.16982.
2. Sise ME, Strohbehn IA, Bethea E, Gustafson JL, Chung RT. Balancing the risk and rewards of utilizing organs from Hepatitis C viremic donors. Curr Opin Organ Transplant. 2019Jun;24(3):351–7.
3. Cho JY, Sohn W, Sinn DH, Gwak GY, Paik YH, Choi MS, Kohl's KC, Paik SW, Yoo BC, Lee JH. Long-term real-world entecavir therapy in treatment-naïve hepatitis B patients: baseline hepatitis B virus DNA and hepatitis B surface antigen levels predict virological response. Korean J Intern Med. 2017;32(4):636–46.
4. Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci. 2017 Oct 19;372(1732):20160274. https://doi.org/10.1098/rstb.2016.0274. (Erratum.In:PhilosTransRSocLondBBiolSci.2018 Jan5;373(1737)).
5. Zitt E, Hafner-Giessauf H, Wimmer B, et al. Response to active hepatitis B vaccination and mortality in incident dialysis patients. Vaccine. 2017;35(5):814–20. https://doi.org/10.1016/j.vaccine.2016.12.032.
6.• Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. Am J Transplant. 2015;15(5):1162–72. https://doi.org/10.1111/ajt.13187. **Provides a foundation for the transplant centers to develop HBV prophylaxis protocols when starting to utilize hepatitis B infected organs.**
7. Tuncer M, Tekin S, Yücetin L, Şengül A, Demirbaş A. Hepatitis B surface antigen positivity is not a contraindication for living kidney donation. Transplant Proc. 2012;44(6):1628–9. https://doi.org/10.1016/j.transproceed.2012.04.015.
8. Jiang H, Wu J, Zhang X, et al. Kidney transplantation from hepatitis B surface antigen positive donors into hepatitis B surface antibody positive recipients: a prospective nonrandomized controlled study from a single center. Am J Transplant. 2009;9(8):1853–8. https://doi.org/10.1111/j.1600-6143.2009.02707.x.
9. Chancharoenthana W, Townamchai N, Pongpirul K, et al. The outcomes of kidney transplantation in hepatitis B surface antigen (HBsAg)-negative recipients receiving graft from HBsAg-positive donors: a retrospective, propensity score-matched study. Am J Transplant. 2014;14(12):2814–20. https://doi.org/10.1111/ajt.12921.
10. Wang XD, Liu JP, Song TR, et al. Kidney transplantation from HBsAg+ living donors to HBsAg- recipients: clinical outcomes at a high volume center in china. Clin Infect Dis. 2021;72:1016–23.
11.• Delman AM, Turner KM, Safdar K, Anwar N, Silski LS, Lee TC, Luckett K, Cuffy MC, Quillin RC, Schoech M, Kaiser TE, Govil A, Bari K, Shah SA. Expanding the donor pool: first use of hepatitis B virus NAT positive slid organ allografts into seronegative recipients. Annals of Surg. 2021;274(4):556–64. **This is the largest series describing the transplantation of HBV NAT + kidney and liver allografts into HBV seronegative recipients.**