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Novel Hepatitis B Virus Reactivation Monitoring Strategies for Kidney Transplant Patients

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INTRODUCTION

Hepatitis B virus reactivation (HBVr) is common in patients infected with hepatitis B virus (HBV) who are receiving immunosuppressive therapy.[1] High-dose steroids or rituximab increase the incidence of HBVr in kidney transplant patients with cured HBV infection (HBsAg-negative and anti-HBsAg-positive).[2] However, there is little evidence about how to monitor the risk of HBVr in these patients.[3] The recent Asian-Pacific guidelines indicate that HBV DNA monitoring-guided preemptive antiviral therapy for HBV is effective for preventing HBV-related hepatitis in these patients.[4] Furthermore, international guidelines define HBVr based on the presence of HBV DNA and seropositive conversion of hepatitis B surface antigen (HBsAg).[4,5] However, all recommendations are primarily focused on patients receiving high-risk immunosuppressive agents such as rituximab with high dose steroid therapy. There is no shared opinion regarding HBV DNA monitoring for HBVr in patients receiving moderate-risk agents such as tacrolimus therapy for renal transplantation.

In clinical practice, DNA screening is not recommended for all patients. We need innovative biomarkers to identify HBVr in kidney transplant patients and improve monitoring strategies.

Hepatitis B core-related antigen (HBcrAg) and highly sensitive HBsAg (HBsAg-HS) are considered early markers for the translation activity of covalently closed circular DNA.[6] The reappearance of HBV DNA and positive conversion of both markers seem to be early signs of HBVr in patients with resolved HBV infection. In contrast, antihepatitis surface antibody (anti-HBsAb) titers seem to play an important role in predicting HBVr in patients with resolved HBV who are receiving immunosuppressive therapy.[7,8]

Thus, the purpose of this study was to determine the effectiveness and safety of monitoring for HBVr using HBcrAg, anti-HBs Ab, HBsAg-HS, and HBV DNA (Supplementary Methods) for kidney transplant recipients with resolved HBV infection receiving long-term tacrolimus-based therapy.

RESULTS

Twenty-five patients were initially included. After excluding 2 patients with previous nucleoside analogue experience for HBVr and 2 patients with acute graft rejection who resumed hemodialysis and ceased immunosuppressive therapy, 21 kidney transplant recipients were included. As shown in Table 1, all included patients had resolved HBV infection and were in chronic stable condition for the tacrolimus plus mofetil mycophenolate therapy for a mean of 7.4 ± 1.2 years. Very low dose (0–2.5 mg/d) prednisolone were also combined for treatment. The induction agents in these patients were by IL-2 receptor antagonist therapy. However, no patient experienced HBVr during induction treatment. The mean age of the patients was

Table 1. Baseline characteristics of 21 kidney transplant recipients with resolved HBV receiving long-term tacrolimus-based antirejection therapy

Factors	Data ($N = 21$)
Age, yrs (mean ± SD)	55.7 ± 10.4
Gender, male/female	10/11
Anti-HBc, positive/negative	21/0
HBV DNA, IU/ml	
≥10 / <10	0 / 21
Anti-HBs Ab, mIU/ml	
>100 / 10–99 / <10	10 / 10 / 1
HBcrAg, log IU/ml	
≥3 / <3	0 / 21
HBsAg-HS, IU/ml	
≥0.005 / <0.005	0 / 21
Tacrolimus-based therapy, yrs (mean ± SD)	7.4 ± 1.2
Tacrolimus level, ng/ml (mean ± SD)	5.68 ± 0.59
ALT, U/l (mean ± SD)	22.7 ± 13.8
AST, U/l (mean ± SD)	20.4 ± 6.7
Total bilirubin, mg/dl (mean ± SD)	0.5 ± 0.3
Albumin, g/dl (mean ± SD)	4.2 ± 0.2
Platelet count, × 1000 cumm (mean ± SD)	244.8 ± 63.2
Creatinine, mg/dl (mean ± SD)	1.41 ± 0.43

ALT, alanine aminotransferase; Anti-HBc, antihepatitis B core antibody; anti-HBs Ab, antihepatitis B surface antibody; AST, aspartate aminotransferase; HBcrAg, hepatitis B core-related antigen; HBsAg-HS, highly sensitive hepatitis B surface antigen; HBV, hepatitis B virus.
The induction therapy: IL-2 receptor antagonist.
The maintenance therapy: tacrolimus plus mofetil mycophenolate with very low dose prednisolone (0–2.5 mg/d).

55.7 ± 10.4 years, and 10 (48%) were male. At the beginning of the enrollment, all patients had normal liver biochemistry and were negative for HBV DNA, HBcrAg, and HBsAg-HS, and only 1 patient was anti-HBs Ab-negative (<10 mIU/ml). The serum levels of tacrolimus were 5.68 ± 0.59 (range: 4.80–7.30) ng/ml. None of the patients had received an HBV vaccination, and all were naïve of anti-HBV therapy.

After mean follow-up of 39.4 ± 3.6 months, 5 patients (23.8%) experienced 8 episodes of seropositive reversion (SR) of markers. The cumulative rates of SR based on the markers were 4.8%, 19%, and 23.8% at 1, 2, and 3 years of follow-up, respectively (Figure 1). As shown in Table S1 (Supplementary References), SR based on HBcrAg, HBV-DNA, HBcrAg and HBsAg-HS, and HBcrAg and HBV-DNA were seen in 2, 1, and 1 patient, respectively. The serum levels of tacrolimus on SR were within therapeutic levels (5.0–6.0 ng/ml). However, all the SR markers spontaneously converted to negative after 1 month of follow-up. In addition, all these patients had low levels of HBcrAg (3.1–3.6 log IU/ml), HBsAg-HS (0.008 mg/dl), and HBV DNA (24–26 IU/ml) on SR. All the patients, except 1, exhibited anti-HBs Ab-positivity; the 1 patient was anti-HBs Ab-negative at baseline and remained negative (Case 2).

Three of 20 (15%) recipients converted from anti-HBs Ab-positive to -negative during follow-up.

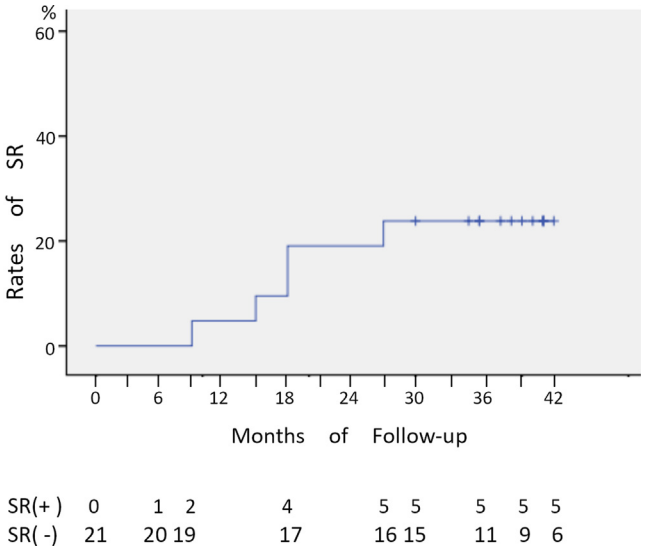

Figure 1. The cumulative incidence of seropositive reversion (SR), based on the 3 markers in 21 kidney transplant recipients on tacrolimus-based therapy. SR was defined as any one of the following: HBcrAg ≥3 log IU/ml, HBsAg-HS ≥ 0.005 IU/ml, or HBV DNA ≥ 10 IU/ml.

However, the 3 patients were not positive for any of the SR markers, and anti-HBs Ab returned to positive thereafter. With respect to anti-HBs Ab, 17 of 20 patients (85%) had persistent anti-HBs Ab-positivity during follow-up. None of them experienced HBVr, although 4 recipients experienced SR. Finally, there were no cases of HBVr using a monitoring frequency of every 3 months.

DISCUSSION

The present study is the first to evaluate a novel monitoring strategy for patients with resolved HBV infection who are receiving immunosuppressive agents and are at moderate risk for HBVr. Our results showed that SR based on levels of HBcrAg, HBsAg-HS, or HBV DNA occurred in about 23% of patients over 3 years of follow-up. There were no patients who experienced HBVr from the relatively low levels of the SR markers. It is understandable that these novel markers were tested by very sensitive methods, and they may be detected at low levels without clinical meanings. Even though we cannot conclude that persistent anti-HBs Ab-positivity was predictive of spontaneous remission of SR and absence of HBVr because of no comparison group; regular monitoring of anti-HBs Ab might be useful for patients with baseline anti-HBs Ab-positivity because the persistent anti-HBs Ab-positivity during follow-up suggests absence of HBVr.[9]

In Taiwan, the national health insurance pays for antiviral prophylaxis for the recipients with HBV carrier (HBsAg-positive) rather than resolved HBV

(HBsAg-negative) during the induction therapy by using immunosuppressive agents (such as rituximab or high dose steroid) before 2019. Therefore, our patients were not on anti-HBV prophylaxis. The research found no HBVr in the patients. The major reason is that all patients were in good immune control and patients were not in acute stage for antirejection induction therapy and were stable on their immunosuppressive regimen for a mean of 7.4 ± 1.2 years. Furthermore, most patients remained persistently anti-HBs Ab-positive. Other recent reports have indicated the incidence of HBVr is 0% at 10 years of follow-up in patients who were anti-HBs Ab-positive and were not treated with high-dose steroids.[8] In addition, the change of anti-HBs Ab from positive to negative in patients treated similarly is reported to be about 14% at 93 months of follow-up.[7] Results of the present study are comparable with those previous results. Notably, in the present study, SR based on HBcrAg, HBsAg-HS, or HBV DNA at low levels combined with anti-HBs Ab-positivity may predict spontaneous remission without progression to HBVr. This implies that regular monitoring of anti-HBs Ab may be an effective method for recipients who are anti-HBs Ab-positive at baseline.

There are some limitations to this study. First, the predictive value of the markers for HBVr cannot be evaluated because there were no cases of HBVr. A larger study can potentially discern the ability of these markers to predict true HBVr. Second, patients who were persistently anti-HBs Ab-negative or were transiently anti-HBs Ab-negative, did not develop HBVr, which might be attributed to the limited number of patients. There was no information in the literature for the HBVr in resolved HBV recipients on the time of study designed. It was hard to perform a power analysis for the appropriate sample size, which significantly limits the findings of the study. In addition, we excluded the patients who had acute rejection episodes in the past or during the study period. Therefore, the enrollment of study patient was not easy. However, a sample size of 21 would not be powered appropriately. Finally, we did not perform HBV RNA testing, although HBV RNA is correlated with HBV activity.

Conclusions

Using HBcrAg and HBsAg-HS levels, combined with HBV DNA and anti-HBs Ab levels is a novel method for monitoring kidney transplant recipients who are at moderate risk for HBVr.

DISCLOSURE

All the authors declared no conflicting interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

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DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article and its supplementary information files.

ETHICAL STATEMENT

This study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (Number: VGHKS 19-CT8-14).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Supplementary References

Table S1. Seropositive reversion (SR) of HBcrAg, HBsAg-HS or HBV DNA in 5 kidney transplant recipients receiving long-term tacrolimus-based antirejection therapy.

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