Risk of hepatitis B virus reactivation in patients with resolved infection on therapy with corticosteroids and conventional synthesis immunosuppressants for kidney disease — a single-centre analysis of 258 patients

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Research Article

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Abstract

Background

The risk of hepatitis B virus (HBV) reactivation in patients with a previously resolved HBV (prHBV) infection on therapy with corticosteroids and conventional synthesis immunosuppressants (csISs) for kidney disease has not been well described.

Methods

We performed a retrospective study on the risk of HBV reactivation (HBVr) in patients with a prHBV infection on therapy with corticosteroids and csISs for kidney disease between January 2012 and December 2021 in the Department of Nephrology at Ruijin Hospital.

Results

A total of 258 patients with a prHBV infection (all treated with high-dose corticosteroids, of whom 192 were receiving a corticosteroid combined with csISs therapy, including cyclophosphamide (155), cyclosporine A (14), mycophenolate mofetil (14), and tacrolimus (9)) were enrolled. During a mean follow-up time of 21.66 months (range: 9–70 months), HBVr were not observed in these patients.

Conclusions

Among patients with a prHBV infection on therapy with corticosteroids and csISs for kidney disease, HBVr was not common and severe, suggesting that universal prophylaxis may not be justified or cost-effective in this clinical setting.

Background

In patients with chronic hepatitis B virus (HBV) infection and/or those who are inactive HBsAg carriers treated with immunosuppressants, such as rituximab or prednisone ≥ 20 mg/day for at least four weeks, HBV reactivation (HBVr), as defined by standard criteria [1], has been well recognized [2–3]. Prophylactic nucleoside analogue therapy has been shown to reduce the incidence of HBVr in HBsAg-positive patients and is recommended in current treatment guidelines [4]. In patients with a previously resolved HBV (prHBV) infection (HBsAg-negative/anti-HBc-positive, undetectable serum HBV DNA), HBVr has also been reported, mainly occurring in those receiving anti-CD20 agents (e.g., rituximab) or bone marrow/haematopoietic stem cell transplantations [5–6]. Among patients with a prHBV infection who were treated with corticosteroid monotherapy or corticosteroid in combination with conventional synthesis immunosuppressants (csISs) therapy, HBVr has also been reported, but there are limited data to

classify the risk [7]. The prevalence of a prHBV infection is very common, with a high seroprevalence of anti-HBc in East Asia (estimated between 13.5% and 40.9%) [8–10]. There is a pressing need to define the risk of HBVr during immunosuppressive therapy in these populations. The risk of HBVr in patients with a prHBV infection on corticosteroid monotherapy or corticosteroid in combination with csISs therapy for kidney disease has not been well described. Herein, we performed a retrospective study to assess the risk of HBVr in these patients.

Methods

Study design and setting

The study was a retrospective observational study. We included patients who had a prHBV infection on therapy with corticosteroids and csISs for kidney disease in Department of Nephrology at Ruijin Hospital from January 2012 to December 2021. The international medical association code of ethics was followed in all aspects of the study protocol, including access to and use of patients' clinical information. This study was approved by the Ruijin Hospital Ethics Committee at the Shanghai Jiao Tong University School of Medicine (2010 No.29) in agreement with the Declaration of Helsinki.

Study population

The inclusion criteria of the patients were as follows: (1) patients with kidney disease who needed high-dose (prednisone or equivalent ≥ 20 mg/day) corticosteroid monotherapy or high-dose corticosteroid in combination with csISs therapy for at least 3 months; (2) a prHBV infection was identified by serum HBV markers (HBsAg, anti-HBs, anti-HBc) before immunosuppressive therapy; and (3) reexaminations of liver function monthly and/or serum HBV markers every one to three months were performed after the initiation of immunosuppressive therapy and lasted at least 6 months after the completion of immunosuppressive therapy. The exclusion criteria were as follows: (1) patients with positive-HBsAg or positive-anti-HCV; (2) patients with abnormal liver function before the immunosuppressive therapy; and (3) patients with therapies of rituximab or other biological agents. As a result, a total of 258 patients with a prHBV infection were enrolled (all of whom were anti-HBc-positive, and of whom 175 were simultaneously anti-HBs-positive). All HBV virus markers were tested in our hospital.

HBV reactivation

The definitions of HBVr and seroconversion are summarized in Table 1. Hepatitis flare is frequently determined to be present when there is at least a two- to three-fold elevation in ALT above the patient's baseline. In patients with resolved infection, reactivation has been considered to occur upon the demonstration of reverse seroconversion to HBsAg-positive status [1].

Table 1
Definitions

HBV reactivation	**Abrupt, marked increase in HBV replication (HBV DNA levels) usually accompanied by elevations in serum aminotransferase levels**
Reverse seroconversion	Reappearance of HBsAg in a person who was HBsAg-negative, anti-HBc-positive
Recovered hepatitis B (prHBV infection)	Seropositivity for anti-HBc without detectable HBsAg (with or without anti-HBs)
Current HBV infection	Seropositivity for HBsAg

Data collection

All patient data were collected from individual electronic patient records. This included: patient demographics, diagnosis, drug regimen, serologic HBV markers and liver function indicators of pre-, intra- and post-treatment.

Data analysis

IBM® SPSS® Statistics Version 21 and Microsoft® Excel® 2010 were used for the statistical analysis. Quantitative data were analyzed by t test for comparison of mean values of two independent samples, and qualitative data were analyzed by Chi-square test for comparison of two or more constituent ratios. For all tests, the two-tailed significance level α was set 0.05.

Results

Characteristics of enrolled patients

In this group of patients, the most common kidney disease was primary nephrotic syndrome (53.9%) with membranous nephropathy (MN, 34.5%) as the main pathological type, followed by IgA nephropathy (21.3%) and anti-neutrophilic cytoplasmic antibody (ANCA)-associated glomerulonephritis (14.0%). The demographic characteristics of the 258 patients are summarized in Table 2.

Table 2
Demographic characteristics of the 258 patients with a prHBV infection.

	Number (%)
Age (mean)	18–87 (52)
Sex (f/m)	109/149
Diseases	
Nephrotic syndrome	139 (53.9)
MN	89 (34.5)
FSGS	14 (5.4)
MCD	13 (5.0)
IgAN	9 (3.5)
MPGN	8 (3.1)
Lupus nephritis	6 (2.3)
IgAN	55 (21.3)
ANCA associated glomerulonephritis	36 (14.0)
Lupus nephritis	10 (3.9)
Primary chronic glomerulonephritis	8 (3.1)
Anti-GBM disease	5 (1.9)
Others	5 (1.9)

IgAN: IgA nephropathy; MN: membranous nephropathy; FSGS: focal segmental glomerulosclerosis; MCD: minimal change nephropathy; MPGN: membranoproliferative glomerulonephritis; GBM: glomerular basement membrane.

Overall, all patients (100%) received a high-dose corticosteroid therapy (prednisone 20 ~ 60 mg/d, mean: 42.57 mg/d) for a mean time of 6.11 months (range: 3 ~ 24 months), of whom 192 patients (74.4%) received corticosteroid in combination with csISs therapy. The most commonly used csIS was cyclophosphamide (60.1%). Twenty-six patients (10.1%) received a methylprednisolone pulse therapy (11 patients with 200 mg/d and 15 patients with 500 mg/d) for three days before routine dosages. The treatment conditions are summarized in Table 3.

Table 3
Types of drug treatment, dosages and treatment durations of the 258 patients.

Drugs	Number (%)	Dosage (mean)	Treatment duration (months, mean)
Prednisone (Pred)	258 (100)	20 ~ 60 (42.57) mg/d	3 ~ 24 (6.11) [a]
Cyclophosphamide (with Pred)	155 (60.1)	1.8 ~ 11.2 (4.86) g [b]	3 ~ 14 (6.87)
Cyclosporin A (with Pred)	14 (5.4)	150–250 (194.12) mg/d	3–29 (8.6)
Mycophenolate mofetil (with Pred)	14 (5.4)	0.5–1.5 (1.0) g/d	3–29 (15.4)
Tacrolimus (with Pred)	9 (3.5)	4–7 (5.25) mg/d	3–23 (11.56)

a: treatment duration with prednisone ≥ 20 mg/d, including 11 and 15 patients accepted a methylprednisolone pulse therapy of 200 mg/d ×3d and 500 mg/d ×3d initially; b: total cumulative dosages.

Incidence of HBVr

Before receiving immunosuppressive therapy, the 258 patients were all positive for serum anti-HBc, including 175 patients (67.8%) who were simultaneously positive for serum anti-HBs. All patients were negative for serum anti-HCV and anti-HBc-IgM. All the 258 patients (100%) underwent regular reexaminations of liver function monthly and 106 of them (41.1%) also reexamined for serum HBV markers every one to three months after the initiation of immunosuppressive therapy, and the reexamined time lasted at least 6 months after the completion of immunosuppressive therapy. HBV DNA was detected in 33 patients before treatment and in 19 patients after treatment, all with negative results. The total reexamination time of liver function fluctuated between 9 and 70 months (mean: 17.33 months). No hepatitis flare were observed during and after the treatment.

No negative-to-positive HBsAg reverse seroconversion was observed in the 106 patients who underwent reexaminations for serum HBV markers, and the total reexamination time for them fluctuated between 9 and 70 months (mean: 21.66 months). However, some changes in serum HBV markers were observed, including 8 patients with anti-HBc seroconversion from positive to negative, 14 patients with anti-HBs seroconversion from positive to negative, and 9 patients with anti-HBs seroconversion from negative to positive (Table 4).

Table 4
The HBV markers before and after immunosuppressive treatment in the 106 patients. No serum reversion of HBsAg was observed in a mean observation time of 21.66 months.

	Before treatment		After treatment	
	Number (%)	Value (mean)	Number (%)	Value (mean)
Anti-HBs [a]				
Pos.	73 (68.9)	10.4 ~ 970.0 (144.7), with 3 > 1000	68 (64.2)	10.4 ~ 986.6 (126.6), with 3 > 1000
Neg.	33 (31.1)	< 10	38 (35.8)	< 10
HBs-Ag [b]				
Neg.	106 (100)	≦ 0.05	106 (100)	≦ 0.05
HBe-Ag[c]				
Neg.	106 (100)	< 1	106 (100)	< 1
Anti-HBe [c]				
Pos.	38 (35.8)	0.02 ~ 0.99 (0.51)	31 (29.2)	0.02 ~ 0.99 (0.55)
Neg.	68 (64.2)	> 1	75 (70.8)	> 1
Anti-HBc [c]				
Pos.	106 (100)	1.03 ~ 12.53 (5.91)	98 (89.9)	1.26 ~ 11.73 (5.52)
Neg.	0	< 1	8	< 1
Test of HBV DNA [d]	22 (20.7)	< 20 or < 500	19 (17.9)	< 20 or < 500

a: The unit was mIU/ml; b: The unit was IU/ml; c: The unit was S/CO; d:The unit was U/mL; Pos.: positive; Neg.: negtive.

There were no statistically significant differences in the clinical features and immunosuppressive therapies between patients with (group A, n = 106) and without (group B, n = 152) reexaminations for serum HBV markers after the treatment (Table 5).

Table 5
Comparison of the clinical features and immunosuppressive therapies between patients with (group A) and without (group B) reexaminations for serum HBV markers after the treatment.

	Group A (N = 106)	Group B (N = 152)	P values
Clinical features			
Age (mean)	25–87 (50.64)	18–84 (52.31)	0.367
Sex (f/m)	40/66	69/83	0.220
Disease (%)	106 (41.09)	152 (58.91)	0.625
Nephrotic syndrome	62	77	/
IgAN	19	36	/
ANCA associated GN	14	22	/
Others	11	17	/
Therapies			
Prednisone (Pred)			
Number (%)	106 (100%)	152 (100%)	/
Dosage (mg/d, mean)	20–60 (43.06)	20–60 (42.24)	0.579
Treatment duration (M, mean)	3 ~ 24 (6.12)	3 ~ 14 (5.86)	0.159
Cyclophosphamide (with Pred)			
Number (%)	67 (63.21)	88 (58.00)	0.414
Dosage (mean)	1.8 ~ 10.6 (4.94)	1.8 ~ 11.2 (4.80)	0.660
Treatment duration (M, mean)	3 ~ 14 (7.02)	3 ~ 14 (6.76)	0.829
Others			
Number (%)	16 (15.10)	25 (16.45)	0.770
Treatment duration (M, mean)	3 ~ 23 (11.44)	3 ~ 29 (8.31)	0.205
M: months, GN: glomerulonephritis, Others: including cyclosporin A, mycophenolate mofetil, and tacrolimus.			

Discussion

In clinical practice, a variety of primary or secondary autoimmune kidney diseases, including nephrotic syndrome, IgA nephropathy, ANCA-associated glomerulonephritis or lupus nephritis, usually require high-dose corticosteroid monotherapy or corticosteroid in combination with csISs therapies. Combination

therapy with corticosteroid and monthly cyclophosphamide pulse therapy is a commonly used treatment regimen. Other csISs, including mycophenolate, cyclosporine A, and tacrolimus are also used frequently.

In the past decade, a large number of studies have reported the occurrence of HBVr in patients receiving immunosuppressive therapy. The reactivation of hepatitis B in the context of immunosuppressive therapy may be severe and potentially fatal. HBVr mainly occurs in HBsAg- and anti-HBc-positive patients, but it also occurs in individuals with a prHBV infection [11]. Among patients with a prHBV infection, HBVr mainly occurred in patients receiving rituximab-containing regimens with or without haematological diseases. In contrast, patients with non-haematological diseases or receiving rituximab-free regimens, including nonbiologic or biologic disease-modifying antirheumatic drugs (DMARDs), had a low risk of HBVr and may not require anti-HBV prophylaxis [12–14]. Some studies reported that in anti-HBc-positive patients with rheumatic diseases treated with conventional synthetic DMARDs, including methotrexate, tacrolimus, and azathiopurine, the risk of HBVr was also very low [15–16]. Risk factors for HBVr in these patients may include negative or low titres of HBsAb, advanced age, and a history of the use of ≥ 3 classes of immunosuppressants [14–16].

In 2015, according to patients' HBsAg status and clinical treatment plans, the risk of HBVr was divided into 5 levels by the American Society for the Study of Liver Diseases [1]. In patients with a prHBV infection who received high-dose corticosteroid therapy (e.g., ≥ 20 mg/day), the risk of HBVr was low (< 1%). For those treated with corticosteroid-free cytotoxic chemotherapy, anti-TNF therapy, methotrexate, or azathioprine, the risk was considered to be very low. For patients with a low and a very low risk for reactivation, it was recommended that regular monitoring should be carried out, and antiviral treatment should be started if HBVr occurred. However, the recommendations were considered to be weak and based on evidence of moderate quality. Our research is consistent with the literature. In this study, all the 258 patients received prednisone ≥ 20 mg/day for at least 3 months with a mean treatment time of 6.11 months (range: 3 ~ 24 months). Of these patients, 74.4% of them received corticosteroid in combination with csISs therapy, with cyclophosphamide as the most commonly used agent, followed by mycophenolate mofetil and calcineurin inhibitors. No hepatitis flare and reverse seroconversion to positive HBsAg status were observed during a mean follow-up time of 21.66 months.

The precise mechanism by which HBVr occurs is unclear, and the initial event is thought to be a disruption in the ability of the host immune system to control HBV replication [17]. Among HBsAg-positive patients receiving corticosteroids, HBVr has occurred both with high-dose, rapidly tapered regimens and moderate-dose, prolonged regimens [3]. The increased viral replication may be due, in part, to a corticosteroid responsive element in the HBV genome that stimulates viral replication and transcriptional activity [18].

HBVr refers to a sudden and significant increase in HBV replication (HBV DNA level), usually accompanied by an increase in serum transaminase levels. In patients with resolved infection, reactivation has been considered to occur upon the demonstration of reverse seroconversion to HBsAg-

positive status [1]. In our 258 patients, no hepatitis flare was observed in the course of regular and continuous monitoring of liver functions during and after the immunosuppressive therapy. 41.09% of them also reexamined HBV markers regularly and reverse seroconversion to positive HBsAg status was not observed. Meanwhile, there were no statistically significant differences in the clinical features and immunosuppressive therapies between patients with and without reexaminations for the serum HBV markers.

However, as our research was a retrospective study and some patients did not undergo regular monitoring of serum HBV markers, the actual incidence of HBVr may be underestimated. The actual rate of HBVr in this group of patients and whether the common preventive anti-HBV treatment is needed still needs prospective studies for confirmation.

Conclusions

In summary, in patients with a prHBV infection on therapy with high-dose corticosteroids (prednisone or equivalent ≥ 20 mg/day) in combination with/without csISs for kidney disease, HBVr and hepatitis flare were not observed, suggesting that HBVr is not common and severe in this disease entity, and the common preventive anti-HBV treatment may be unreasonable and not have economic benefits.

Abbreviations

HBV: hepatitis B virus; prHBV infection: previously resolved HBV infection; csISs: conventional synthesis immunosuppressants; HBVr: HBV reactivation; MN: membranous nephropathy; ANCA: anti-neutrophilic cytoplasmic antibody; DMARDs: disease-modifying antirheumatic drugs.

Declarations

Ethics approval and consent to participate

All procedures performed in this study complied with the institutional and/or national research committee ethical standards and the 1964 Helsinki declaration and subsequent amendments or equivalent ethical standards. This study was approved by the Ruijin Hospital Ethics Committee at the Shanghai Jiao Tong University School of Medicine (2010 No.29). The Institutional Review Board of Shanghai Jiao Tong University School of Medicine waived informed consent because the study used secondary data. Participants' data confidentiality was ensured, and all of the data collected were used for the research purpose only.

Consent for publication: Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests, including financial and non-financial interests.

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Authors' contributions

PYH and ZHW participated in research design and data analysis. PYH performed data collection and drafted the manuscript. ZHW revised the manuscript. ZQW, PYS, WZ, and HR contributed to the data collection or the writing of the manuscript. PYH had primary responsibility for final content. All authors read and approved the final manuscript.

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