Surveillance of Liver Function in Uveitis with or without Chronic HBV Infection

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Keywords
Uveitis · Hepatitis B · Liver damage · Corticosteroids

Abstract

Introduction: Immunosuppressive therapy for uveitis may cause liver damage. Methods: To investigate incidence of liver damage during uveitis treatment, we compared serological Hepatitis B core antibody (HBcAb) status with risk of liver dysfunction in all participants (n = 992), in anterior uveitis (AU) (n = 489), and combined of intermediate, posterior, or panuveitis (IPPU) patients (n = 503). The primary endpoint was incidence of elevated serum alanine aminotransferase level above 2-fold upper limits of normal within 6 months. Results: The incidence rate of primary endpoint for HBcAb-negative and HBcAb-positive patients was 65 and 212 per 1,000 person years, respectively. The absolute rate difference was 147 (95% confidence interval [CI], 80–213) per 1,000 person years. HBcAb positivity was associated with a higher risk for primary endpoint in all participants (adjusted hazard ratio [aHR], 3.53; 95% CI, 1.79–6.99; p value = 2.8 × 10⁻⁴) and in IPPU (aHR, 3.80; 95% CI, 1.61–9.01; p value = 0.002). No significant association with primary endpoint was observed for HBcAb positivity in AU (aHR, 3.21; 95% CI, 0.94–10.95; p value = 0.063). AU was mainly treated with topical eye drops (74.0%), whereas IPPU cases received systemic therapy including prednisone (94.0%), cyclosporine (80.9%), or other additionally combined immunomodulatory agents (14.9%). Conclusion: Noninfectious uveitis cases with HBcAb positivity have an increased risk of liver damage. This association was predominantly driven by IPPU but was not significant in AU, suggesting that the association is mediated by systemic therapy.

Introduction

Uveitis is an intraocular inflammatory disorder, which can be caused by infectious or noninfectious triggers [1, 2]. Noninfectious uveitis entities are related to an aberrant autoimmune or autoinflammatory response [2, 3]. Immunosuppressive treatments such as corticosteroids and immunomodulatory agents have been the mainstay of therapy for noninfectious uveitis [4]. To prevent visual impairment and achieve remission of the disease, uveitis patients and especially those with a chronic course, posterior segment involvement, or an associated systemic
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Among the known safety profiles, liver damage is one of the most common adverse events, which may lead to drug withdrawal and treatment failure for uveitis [6].

Hepatitis B virus (HBV) infection is a life-threatening problem, whereby about 30% of the world’s population has serological evidence of current or past infection [7]. In China, the prevalence of HBV infection is still at a higher intermediate level (5.0–7.9% Hepatitis B surface antigen [HBsAg] positive rate), although this number has declined over the past 10 years due to HBV vaccination [8]. Treatment for HBV infection is limited and only suppresses replication but may not be able to eradicating the virus [7]. Patients with chronic HBV infection are threatened by liver damage and are also at high risk of liver cirrhosis or hepatocellular carcinoma even in a resolved phase [7]. In terms of side effects of corticosteroids and immunosuppressants, it is not clear whether or which special care should be implemented for patients with uveitis or certain uveitis subtypes who have a positive HBV status. The current practice is primarily derived from experience on patients with rheumatoid diseases or malignancies receiving chemotherapy [9–11], for which the medications and durations may differ substantially from that in uveitis. There is insufficient clinical evidence on how to properly manage these uveitis patients during the treatment of their ocular disease. In this study, we performed a scheduled monitoring of liver function in non-infectious uveitis patients and compared the risk of liver impairment with regard to their HBV status.

Materials and Methods

Study Design and Procedures

This prospective, 26-week, active surveillance study was conducted at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Eligible patients were 18 years of age or older, presenting as noninfectious uveitis (unilateral or bilateral) and requiring topical, local, or systemic treatment with corticosteroids or immunosuppressive agents. Key exclusion criteria included treatment with anti-tumor necrosis factor (TNF) antibodies; treatment with more than one immunosuppressive agent (other than corticosteroids) within the last two months before baseline; past or concurrent infection with Hepatitis C or Hepatitis D virus; having received antiviral therapy or having an indication for antiviral therapy immediately according to international guidelines [7]; serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations above normal; evidence of or already diagnosed with liver cirrhosis; concomitant other chronic liver diseases; and other severe health problems.

Treatment for Uveitis

All patients were treated for uveitis based on the recommendations of current guidelines [4, 5]. In general, in order to achieve a quiescent disease, patients were treated with topical corticosteroid drops, periocular injection of corticosteroid preparations, or oral corticosteroid and immunosuppressive drugs, as appropriate; and if suppression of uveitis was achieved and maintained, an attempt would be made to taper these treatments according to the patient’s ocular condition and the nature of the specific type of uveitis. In particular, for patients with anterior uveitis (AU), corticosteroids were mainly administered topically, although some patients were treated systemically at a low dose for a short time period when having an acute or episodic disease. If indicated, according to guidelines [5], such as those associated with a systemic disease, an additional immunosuppressive drug would be administrated orally. For patients with intermediate, posterior, or panuveitis (IPPU), oral corticosteroids were used as the primary option; and if necessary, periocular injection of corticosteroid preparations would be implemented. In addition, one immunosuppressive agent would be introduced to control persistent or severe inflammation or to prevent ocular structural complications, based on either the uveitis type and severity or therapeutic needs [12]. If adding one immunosuppressive agent was not adequately effective, several approaches would be considered based upon clinical judgment, including dose escalation, transition to an alternative drug, or combined with an additional agent. In this study, the preferred immunosuppressive drug was cyclosporine (2–5 mg/kg/day), a T-cell inhibitor. If adding cyclosporine was not able to control inflammation, other immunomodulatory agents including the antimetabolites mycophenolate mofetil (0.5–2 g/day) and the alkylating agents, cyclophosphamide (1–2 mg/kg/day) and chlorambucil (0.1 mg/kg/day), and interferon alfa-2a (3 MIU/day), were permitted to initiate additionally after

The complete list of inclusion and exclusion criteria is provided in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000520835).

Hepatitis B serological biomarkers including HBsAg, Hepatitis B surface antibody (HBsAb), Hepatitis B e antigen, Hepatitis B e antibody, and Hepatitis B core antibody (HBcAb) were assayed at the first visit of the patient to our clinic. HBV DNA level was measured for HBsAb-positive patients at baseline. Participants were divided into two groups according to their HBcAb status at baseline. The HBcAb positivity indicates an exposure of HBV infection, which may be presented in association with HBsAg positivity in chronic infection or in association with HBsAb positivity after recovery from acute infection [7]. According to our monitoring plan, all participants undertook liver function tests on predetermined follow-up visits after 1 week, 2 weeks, 4 weeks, 2 months, 4 months, and 6 months (Fig. 1). Normal ranges of laboratory tests and name of medical device used were provided in online supplementary Table 2. For each visit, we performed routine ophthalmic examinations including visual acuity, intraocular pressure, slit-lamp microscopy, and ophthalmoscopy for all participants. Auxiliary examinations such as ultrasound biomicroscopy, B-scan ultrasonography, fundus fluorescein angiography, and optical coherence tomography were performed based on clinical needs. The institutional review board at the First Affiliated Hospital of Chongqing Medical University approved the study. The procedures were performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolling.

DOI: 10.1159/000520835
baseline. Patients receiving TNF inhibitors were excluded from the study in the light of existing reports on liver-related adverse events in HBV-infected individuals [13, 14].

Outcome Measures

The primary endpoint was the incidence of an elevated serum ALT level above the 2-fold upper limit of normal (ULN) within 6 months after baseline. Those patients reaching the primary endpoint would receive immediate best medical judgment and treatment, including but not limited to close monitoring, measuring HBV DNA level, dose reduction or withdrawal of drugs for uveitis, commencement with hepatoprotectors, and antiviral therapy which was performed by colleagues at the department of infectious diseases of our hospital. The secondary endpoints included abnormalities in serum ALT, AST, total bilirubin, creatinine, albumin concentrations, and platelet counts. In addition to comparing the endpoint events between the HBcAb-positive and HBcAb-negative groups in the entire cohort, comparisons were also performed in patients with AU and in those with a combined group of IPPU patients.

Statistical Analysis

Assuming an approximately equal enrollment of HBcAb-positive and HBcAb-negative participants (available data showed an HBcAb positive rate of 50.04% in China) [15] and an overall withdrawal rate of 10%, this study was designed to target a minimum recruitment of 488 persons for each stratification. This sample size would have 80% power to detect a clinically meaningful hazard ratio (HR) of 2.0, at a two-sided significance level of 0.017 (0.05 ÷ 3), would have 80% power to detect a clinically meaningful hazard ratio (HR) of 2.0, at a two-sided significance level of 0.017 (0.05 ÷ 3), after Bonferroni adjustment for 3 multiple comparisons), as compared with the HBcAb-negative group in which the annual incidence rate of the primary endpoint was estimated to be about 10% [16]. Therefore, a minimum enrollment of 976 patients would be accrued for two stratifications (AU vs. a combined IPPU group).

Descriptive data are presented as numbers and percentages for categorized variables, as means and standard deviations (SD) for normally distributed data, and as medians and interquartile ranges (IQR) for skewed data. Normality was evaluated by using the Shapiro-Wilk test. Crude incidence rates were compared by using the χ² test. The main analysis was based on the time from baseline to the first occurrence of endpoint event. The Kaplan-Meier curve was plotted to display the time-to-event data. Participants without an endpoint event had their data censored on the last visit. We used the Cox proportional-hazards regression models to estimate HRs and 95% confidence intervals (CIs) for endpoints. The proportional-hazards assumption was tested by Schoenfeld residuals. The crude HRs were estimated in the univariate Cox model. In the main analysis, we estimated the adjusted HRs by using the Cox regression conditioned on matching major confounders including age, sex, body mass index, smoking status, drinking alcohol, baseline daily dose of prednisone and cyclosporine, HBsAg and HBsAb status, and baseline serum ALT and AST levels.

We assessed the robustness of our primary findings in several sensitivity analyses. First, we constructed a separate Cox model in which HRs were further adjusted for potential confounders including residence, education level, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, and the best corrected visual acuity (BCVA) in the worse-seeing eye. Second, in order to deal with the outcomes of participants who withdrew or were lost to follow-up early and were excluded from the primary analysis, we performed a multiple imputation based on the baseline characteristics, with statistical coefficients obtained from 10 imputed datasets, pooled using the Rubin’s rule. The primary endpoint was therefore reassessed in the full dataset. Third, although most of the patients in this cohort were treated exclusively with corticosteroids and cyclosporine, we compared the risk for the primary endpoint in the datasets after exclusion of other drug users. In addition, we attempted to perform several exploratory analyses with the use of multivariate Cox regression to predict other potential risk factors associated with the primary endpoint.

To preserve an overall type I error rate of 5% for the primary outcome in the study, the p value should be interpreted in the context of the threshold of 0.017 (0.05 ÷ 3) after Bonferroni adjustment. We did not plan for adjustment for multiple comparisons in

![Fig. 1. Schedule of liver function surveillance in uveitis. HBcAb, Hepatitis B core antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.](image-url)
secondary outcomes, sensitivity analyses, and exploratory estimates, and therefore, the results are reported with point estimates and 95% CIs descriptively and no clinical inferences can be drawn from these results. All analyses were performed with IBM SPSS Statistics version 25.

**Results**

**Study Participants**

Between July 29, 2019, and April 1, 2020, a total of 1,357 consecutive patients underwent screening, and 992 eligible noninfectious uveitis patients with a normal liver function were enrolled for the study (Fig. 2). This study was completed on October 11, 2020, when the last participant was seen at the 6-month visit. Ninety-four (9.5%) patients withdrew or were lost to follow-up before the 2-week visit, and therefore, a total of 898 individuals were included in the primary analysis.

Baseline demographic and clinical characteristics are shown in online supplementary Table 3. For the entire cohort at enrollment, the median (IQR) age of patients was 43 (32–53) years. Men (503 patients) accounted for 50.7% of the participants. There were 488 patients in the HBcAb-negative group, of which 247 were diagnosed
with AU and 241 with IPPU. In the HBcAb-positive group, 504 patients were included, which consisted of 242 patients with AU and 262 patients with IPPU. At baseline, according to the severity of the ocular condition, patients in the HBcAb-negative group were treated with prednisone in a median daily dose of 20 (IQR, 20–20) mg and cyclosporine in 100 (IQR, 0–0) mg, respectively. Similar doses were used for the HBcAb-positive group (median daily doses of prednisone and cyclosporine were 20 [IQR, 15–20] mg and 100 [IQR, 0–100] mg, respectively). During the follow-up period, 50/488 (10.2%) patients in the HBcAb-negative group and 45/504 (8.9%) patients in the HBcAb-positive group were treated with additional immunomodulatory agents other than cyclosporine. AU patients were mainly treated with topical eye drops (74.0%) and shortly tapered systemic corticosteroids. Patients with IPPU received systemic therapy including prednisone (94.0%), cyclosporine (80.9%), or other additionally combined immunomodulatory agents (14.9%). Patients with IPPU had a higher portion of bilateral involvement and poorer BCVA in the worse-seeing eye at baseline, as compared with those with AU. But overall, the severity of uveitis, the treatment for uveitis, as well as the baseline serum ALT and AST levels did not differ between the HBcAb-positive and HBcAb-negative groups, regardless of the anatomical diagnosis of uveitis (online suppl. Table 3).

### Primary Outcome

In the primary analysis, during a mean (SD) follow-up time of 5.3 (1.6) months, a total of 55 individuals reached the primary endpoint of an elevated serum ALT level above the 2-fold ULN. In the HBcAb-negative group, 13 patients had the primary endpoint within a mean (SD) follow-up of 5.3 (1.7) months, of which five patients were diagnosed with AU and eight were IPPU. In the HBcAb-positive group, 42 primary endpoint events occurred after a mean (SD) follow-up of 5.4 (1.6) months, whereby 10 were diagnosed with AU and 32 belonged to the combined IPPU group (Table 1). Overall, for patients with a negative HBcAb status, the incidence rate of the primary endpoint was 65 per 1,000 person years. A relatively higher incidence of 212 per 1,000 person years was noted in HBcAb-positive patients (p value = 2.2 × 10−4), with an absolute increase of 147 (95% CI, 80–213) per 1,000 person years. In the time-to-event analysis, a sustained separation of Kaplan-Meier curves regarding HBcAb status was observed before the 1-month visit in the entire cohort as well as those with IPPU (Fig. 3). After adjustment for potential major confounders, the HBcAb positivity was significantly associated with a higher risk of reaching the primary endpoint (HR, 3.53; 95% CI, 1.79–6.99; p value = 2.8 × 10−4). In patients with IPPU, the HBcAb positivity was also a significant risk factor for having the primary endpoint (HR, 3.80; 95% CI, 1.61–9.01; p value = 0.002). No significant association with the primary end-

| Table 1. Primary outcome in the prospective study |
|--------------------------------------------------|
| HBcAb status | N | n | Primary analysis |
|---------------|---|---|-----------------|
|               | endpoint within 6 months‡ | no endpoint within 6 months | aHR (95% CI)† | p value |
| All participants |  | | | |
| HBcAb (−) | 440 | 13 | 427 | 1 [reference] | 2.8 × 10−4 |
| HBcAb (+) | 458 | 42 | 416 | 3.53 (1.79–6.99) | |
| AU | | | | |
| HBcAb (−) | 216 | 5 | 211 | 1 [reference] | 0.063 |
| HBcAb (+) | 213 | 10 | 203 | 3.21 (0.94–10.95) | |
| IPPU | | | | |
| HBcAb (−) | 224 | 8 | 216 | 1 [reference] | 0.002 |
| HBcAb (+) | 245 | 32 | 213 | 3.80 (1.61–9.01) | |

HBcAb, Hepatitis B core antibody; ULN, upper limit of normal; ALT, alanine aminotransferase; HBsAg, Hepatitis B surface antigen; HBsAb, Hepatitis B surface antibody; AST, aspartate aminotransferase; aHR, adjusted hazard ratio; CI, confidence interval; IPPU, intermediate, posterior, or panuveitis; AU, anterior uveitis. ‡The primary endpoint was the serum ALT level greater than the 2-fold ULNs. †Data were adjusted for age, sex, body mass index, smoking, drinking, dose of prednisone and cyclosporine per day, HBsAg status, HBsAb status, and the baseline serum ALT level and AST level by using the multivariate Cox regression analysis.
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**Fig. 3.** Kaplan-Meier analysis of the cumulative incidence of primary endpoint in the HBcAb-negative or HBcAb-positive participants. Comparisons are shown for the entire cohort (a), in AU (b), and in the combined group of IPPU patients (c). HBcAb, Hepatitis B core antibody; HR, hazard ratio; aHR, adjusted hazard ratio; IPPU, intermediate, posterior, or panuveitis; AU, anterior uveitis.

| Months since baseline | Number at risk |
|----------------------|----------------|
| <sup>a</sup> HBcAb (+) | 458 | 440 | 411 | 388 | 374 |
| HBcAb (–) | 440 | 422 | 412 | 397 | 385 |
| <sup>b</sup> HBcAb (+) | 213 | 205 | 192 | 182 | 171 |
| HBcAb (–) | 216 | 206 | 199 | 191 | 186 |
| <sup>c</sup> HBcAb (+) | 245 | 235 | 219 | 206 | 203 |
| HBcAb (–) | 224 | 216 | 213 | 206 | 199 |

Crude hazard ratio = 3.19 (1.88–5.42)
Adjusted hazard ratio = 3.53 (1.79–6.99)
p value = 2.8 × 10⁻⁴

Crude hazard ratio = 2.07 (0.75–5.71)
Adjusted hazard ratio = 3.21 (0.94–10.95)
p value = 0.063

Crude hazard ratio = 3.78 (2.03–7.02)
Adjusted hazard ratio = 3.80 (1.61–9.01)
p value = 0.002
point was observed for HBcAb positivity in AU (HR, 3.21; 95% CI, 0.94–10.95; p value = 0.063) (Table 1; Fig. 3). In addition, sensitivity analyses of primary outcome with the use of a further adjustment model, multiple imputation, and exclusion of other immunomodulatory agent users showed similar results as compared with the primary analysis in the entire cohort and in subgroups stratified by uveitis anatomical diagnosis, respectively (Fig. 4).

Secondary Outcomes

During the follow-up period, an increased serum ALT level above the ULN occurred in 33/440 (7.5%) HBcAb-negative patients and 67/458 (14.6%) HBcAb-positive patients in the entire cohort, while 20/440 (4.5%) HBcAb-negative patients and 39/458 (8.5%) HBcAb-positive patients developed an elevated AST level above the ULN. After adjusted for major covariables, patients with a positive HBcAb status were found to have a higher risk of liver dysfunction in serum ALT levels (HR, 1.93; 95% CI, 1.22–3.08) and AST levels (HR, 1.81; 95% CI, 1.00–3.28). After stratification according to uveitis anatomical diagnosis, the HRs for elevated ALT and AST levels remained largely similar, but with relatively wider confidence intervals. This study did not detect robust associations of HBcAb status with the time to an elevated AST level above the 2-fold ULN, an elevated level of total bilirubin and creatinine above the ULN, and a decreased platelet count and albumin level below the lower limits of normal, respectively.

Exploratory Analyses

Besides the HBcAb status, we further evaluated other potential risk factors predicting the primary endpoint in an exploratory and hypothesis-generating analysis (Table 2). With adjustment for covariables, the diagnosis of IPPU (HR, 2.00; 95% CI, 1.02–3.91), poorer BCVA in the worse-seeing eye (HR, 1.65; 95% CI, 1.20–2.26), baseline daily prednisone dose (HR, 1.06; 95% CI, 1.02–1.09), and serum ALT levels (HR, 1.06; 95% CI, 1.03–1.09) were found to be independently associated with the primary endpoint in the entire cohort. Further analyses in HBcAb-positive individuals showed similar estimates for these variables and also indicated male sex as a potential risk factor (adjusted HR, 2.80; 95% CI, 1.17–6.70).

Discussion

In this study, we show that uveitis patients with a pre-existing chronic HBV infection, despite presenting a normal liver function, have a higher risk of developing liver function abnormalities as shown by an elevated ALT level during the treatment of uveitis. This association was especially apparent in the combined group of IPPU patients but was not observed in AU cases. AU patients are mainly treated with topical eye drops whereas the other group often receives systemic therapy, which strongly suggests that systemic therapy in HBV-positive uveitis patients is linked to better outcomes.
cases may lead to liver damage. This subject has not received much attention until now, even though monitoring of liver function in these uveitis patients can easily be done by testing their serum ALT.

ALT is a specific cytoplasmic enzyme produced by hepatocytes. Although the concentration of serum ALT can fluctuate, its elevation over the 2-fold ULN is considered as a reliable marker of liver damage [17]. In AU, despite the fact that the incidence of an elevated serum ALT level above the ULN in HBcAb-positive individuals is of potential concern, the observed difference in the risk for serum ALT level above the 2-fold ULN was not significant between HBcAb-positive and HBcAb-negative patients. Because AU patients are usually treated with topical medications and are not dependent on long-term systemic immunosuppressive therapies [18], the treatment for AU is safe and does not cause a substantial risk for those with a history of HBV infection.

Our findings show that there is a higher risk of liver damage associated with HBcAb positivity in the treatment of noninfectious IPPU. This higher risk was even apparent in cases where conventional immunosuppressive therapies were used, instead of TNF inhibitors. As mentioned earlier, we excluded uveitis cases that were treated with TNF inhibitors in or current study. These findings extend previous data regarding the safety of immunosuppressive therapy in chronic HBV infection [19–21] and linked the risk to a specific subgroup of patients with IPPU. Therefore, for this subgroup, we recommend screening for HBV and periodic monitoring of liver function. Our prospective study suggests that HBcAb may be a more rational indicator than HBsAg for the risk assessment among patients with normal ALT and AST levels. If the result for HBcAb is positive, the patient will be recommended for a close (every 4–6 weeks) monitoring of liver function during systemic therapy. In this study, the median time (IQR) to reaching an increase above a 2-fold ULN of their ALT level was 1.5 (1–4) months for those HBcAb-positive patients that had fulfilled our primary endpoint criterium. Currently, a risk-based screening and monitoring of liver function is not included in the guidelines for the use of immunosuppressive medication in uveitis [4, 5], and it is unclear how often these tests are being done in the eye clinic. Nevertheless, surveys in the field of rheumatology, hematology, and gastroenterology have shown that actual screening and monitoring for liver function is performed infrequently [22–24]. No studies have been reported on prophylactic antivirus therapy in uveitis, and there is no consensus on whether or when prophylactic antivirus therapy should particularly be initiated, which warrants further investigation.

Table 2. Exploratory multivariate analysis of risk factors associated with the primary endpoint

| Baseline variables | aHR (95% CI) in the entire cohort ‡ | aHR (95% CI) in individuals with HBcAb (+) ‡ |
|--------------------|-------------------------------------|-----------------------------------------------|
| Male, sex          | 2.02 (0.98–4.14)                  | 2.80 (1.17–6.70)                             |
| Age§               | 0.99 (0.97–1.02)                  | 0.99 (0.96–1.02)                             |
| IPPU†              | 2.00 (1.02–3.91)                  | 2.12 (0.96–4.64)                             |
| HBsAg serological positivity | 0.84 (0.31–2.32)   | 0.85 (0.29–2.52)                             |
| HBsAb serological positivity | 1.09 (0.60–1.97)   | 1.12 (0.55–2.30)                             |
| LogMAR BCVA in the worse-seeing eye§ | 1.65 (1.20–2.26) | 1.56 (1.08–2.27)                             |
| Daily prednisone dose§ | 1.06 (1.02–1.09)   | 1.06 (1.02–1.10)                             |
| Daily cyclosporine dose§ | 0.99 (0.99–1.00)   | 1.00 (0.99–1.10)                             |
| Serum ALT level§   | 1.06 (1.03–1.09)                  | 1.05 (1.02–1.09)                             |
| Serum AST level§   | 1.01 (0.97–1.04)                  | 1.02 (0.97–1.06)                             |

HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HBsAb, Hepatitis B surface antibody; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aHR, adjusted hazard ratio; CI, confidence interval; IPPU, intermediate, posterior, or panuveitis; AU, anterior uveitis. ‡Data were estimated in the multivariate Cox regression model with adjustment for covariables including age, sex, body mass index, uveitis anatomical diagnosis, uveitis laterality, BCVA in the worse-seeing eye, smoking, drinking, residence, educational level, self-reported hypertension, diabetes, coronary heart disease and malignancies, dose of prednisone and cyclosporine per day, HBcAb status, HBsAg status, HBsAb status, and the baseline serum ALT level and AST level. †As compared with AU. ‡For these continuous variables, HRs were expressed as per unit increase in the level of the variable.
We observed a positive correlation between prednisone daily dose and risk of liver dysfunction as shown by increased serum ALT levels in preliminary analyses (Table 2). The correlation for the dose of cyclosporine and liver function was not as strong as that for prednisone dose after multivariable adjustment. Owing to power concerns and multiple comparisons, these exploratory estimates require further validation. Nevertheless, previous studies showed that HBV DNA contains a transcriptional enhancer sequence and glucocorticoids can stimulate HBV replication by activating the enhancer element [12, 25]. Based on these studies, it appears that glucocorticoids may have a stronger potential to elevate HBV DNA level than cyclosporine. These observations suggest that it may be safer to start treatment in HBCAb-positive uveitis patients with a low dose of prednisone in combination with corticosteroid-sparing agents. Our previous studies have shown that a reduced dose of corticosteroids (initial dose: 20–30 mg/day) combined with immunosuppressive drugs could also effectively control the intraocular inflammation and improve visual acuity in most Chinese patients [26–28].

We acknowledge several limitations in our study. First, given the fact that the treatment for uveitis is largely individualized and is not fixed during treatment [5], we could not compare the risk of liver dysfunction stratified by treatment doses and regimens. We evaluated the risk based on the anatomical diagnosis of uveitis, which permitted a sufficient sample size in each stratification. Further studies are needed to investigate whether certain uveitis subtypes as based on their etiology might be more prone to liver damage in HBV-positive cases. Second, the interpretation of results should be limited by eligibility criteria. For example, owing to ethical considerations, we only enrolled eligible participants with normal serum ALT and AST concentrations. Therefore, our findings, especially the observed lower risk in AU, may not be extrapolated to more severe cases such as those with decompensated cirrhosis, Hepatitis B e antigen-positive chronic HBV infection, or acute exacerbation of chronic HBV infection. Third, given that changes in biomarkers such as AST, bilirubin, and albumin would be delayed as compared to ALT levels during the progression of liver function impairment and that participants reaching the primary endpoint had been immediately subjected to the best medical judgment and treatment, this study might not be powered for detecting these secondary endpoints. Fourth, this study mainly focused on the investigation of the effect of prednisone and cyclosporine, and we were unable to estimate the effect of other drugs due to limit of the number of other drug users. In sensitivity analyses, exclusion of other drug users or inclusion of them did not affect the study conclusions. In addition, this study focused on the outcome on liver function impairment, which may be attributed not only to HBV status but may also be caused directly by certain systemic drugs (or combinations thereof). Further prospective studies are therefore warranted to precisely investigate the effect of dose and duration of systemic therapy on liver damage in HBV-infected individuals. In our study, we did not include specific markers of HBV DNA levels [29] for all participants during follow-up due to financial constraints and this should be included in future studies to definitely conclude that the abnormal liver function observed was caused by this virus.

Conclusions

In conclusion, among patients with noninfectious uveitis, all of whom had a normal liver function at baseline, a positive HBV status is associated with an increased risk of developing an elevated ALT during the treatment for uveitis. This association was most pronounced among patients with IPPU, which highlights the need for HBV screening and routine liver function monitoring during treatment in these patients.

Statement of Ethics

The study was reviewed and approved by the Ethical Committee of the First affiliated Hospital of Chongqing Medical University (20195001), adhered to the tenets of the Declaration of Helsinki and was registered at Chinese Clinical Trial Register, ChiCTR1900023955. Written informed consent was obtained from all participants before enrolling.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

The work was supported by the Chongqing Key Laboratory of Ophthalmology (CSTC, 2008CA5003), Chongqing Outstanding Scientists Project (2019), Chongqing Chief Medical Scientist Project (2018), Chongqing Science & Technology Platform and Base Construction Program (cstc2014pt-sy10002).
Author Contributions

P.Y., Z.Z., and W.L. conceived and designed the study. W.L., G.S., X.F., L.D., F.L., and L.D. collected clinical data. W.L. and Z.Z. analyzed and interpreted the data. Z.Z. wrote the first draft of the article. P.Y., W.L., and K.A. reviewed and edited the manuscript. All authors provided a final review and approved the manuscript before submission.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplemental information. Further enquiries can be directed to the corresponding author.

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