CLINICAL SCIENCE

Average corticosteroid dose and risk for HBV reactivation and hepatitis flare in patients with resolved hepatitis B infection

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Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-221650).

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Received 10 October 2021
Accepted 3 December 2021
Published Online First 21 December 2021

To cite: Zhong Z, Liao W, Dai L, *et al*. *Ann Rheum Dis* 2022;**81**:584–591.

ABSTRACT

Objectives Corticosteroids remain the mainstay of treatment for rheumatic diseases but can cause hepatitis B virus (HBV) reactivation in patients with resolved HBV infection. Risk assessment and stratification are needed to guide the management of these patients before corticosteroid therapy.

Methods We prospectively enrolled patients with negative hepatitis B surface antigen positive Anti-hepatitis B core status with or without corticosteroid use and determined corticosteroid exposure by calculating cumulative dose and time-weighted average daily dose of prednisone. The primary outcome was the time to a composite of HBV reactivation, hepatitis flare or severe hepatitis.

Results Among 1303 participants, the median of cumulative dose and time-weighted average dose of prednisone used in this cohort was 3000 mg (IQR: 300–6750 mg) and 15 mg/day (IQR: 10–20 mg/day), respectively. In multivariable analyses, cumulative dose showed inverted V-shaped relationship with primary events, which peaked at a cumulative dose of 1506 mg (HR: 3.72; 95% CI, 1.96 to 7.08). Quartiles of time-weighted average dose were independently associated with a monotonic increase in event risk (HR per quartile increase: 2.15; 95% CI, 1.56 to 2.98), reaching an HR of 49.48 (95% CI, 6.24 to 392.48) in the top quartile. The incidence of primary outcome was 16.67 per 100 person-years in the top quartile of time-weighted average dose (Q4>20 mg/day). Other quartiles all had an incidence of primary outcome less than 10 per 100 person-years.

Conclusion Patients with time-weighted average prednisone dose greater than 20 mg/day would be classified as the high risk for HBV reactivation or hepatitis flare. Prophylactic Anti-HBV therapy may be needed for these high-risk patients.

Trial registration number ChiCTR1900023955.

Key messages

What is already known about this subject?

- Corticosteroids remain the mainstay of treatment of musculoskeletal conditions, arthritic disease and connective tissue disorders.
- Guidelines are currently in consensus on recommending the use of anti-hepatitis B virus (HBV) prophylaxis in patients with positive hepatitis B surface antigen (HBsAg) before corticosteroid therapy, but such a consensus has not been reached in the management of patients with resolved HBV infection with an HBsAg-negative Anti-hepatitis B core positive status.
- Due to the lack of systemically collected data, reliable risk assessment and stratification of HBV reactivation in corticosteroid users with resolved HBV infection are lacking.

What does this study add?

- This study proposed a time-weighted average dose of prednisone to quantify corticosteroid exposure, and this indicator, instead of cumulative dose, positively predicted the risk of HBV reactivation or hepatitis flare in patients with resolved HBV infection.
- Use of prednisone with a time-weighted average dose greater than 20 mg/day resulted in an incidence of HBV reactivation or hepatitis flare more than 10 per 100 person-years in patients with resolved HBV infection, and prophylactic Anti-HBV therapy may therefore be needed for these high-risk patients.

How might this impact on clinical practice or future developments?

- Assessment of time-weighted average prednisone dose, instead of the peak dose, treatment duration and cumulative dose, would allow for the risk stratification for HBV reactivation in patients with resolved HBV infection treated with corticosteroids for a variety of rheumatic diseases.

INTRODUCTION

Corticosteroids currently remain the mainstay of treatment of musculoskeletal conditions, arthritic disease and connective tissue disorders. However, given the fact that hepatitis B is a common comorbidity among rheumatic patients, improper use of corticosteroids may cause hepatitis B virus (HBV) reactivation or hepatitis flare. HBV reactivation and hepatitis flare are a potentially serious disorder, which may lead to fulminant hepatic failure and death.[1] A prevailing opinion on the prevention of HBV reactivation is to initiate prophylactic antiviral therapy according to risk stratification instead of universal prophylaxis before corticosteroid therapy.[2 3] HBV reactivation more frequently occurs in patients with positive hepatitis B surface

antigen (HBsAg), and guidelines are currently in consensus on recommending the use of Anti-HBV prophylaxis in HBsAg-positive patients.[4] HBV reactivation may also occur in patients with resolved HBV infection with an HBsAg-negative and antibody against hepatitis B core (Anti-HBc) positive status; however, guidelines are not always in agreement on the initiation of Anti-HBV prophylaxis in these patients.[4] Reliable risk assessment and stratification are, therefore, needed to guide the management of these patients.

Most of existing studies concerning HBV reactivation focused on novel biological drugs, such as rituximab, abatacept and anti-TNF agents.[5 6] Due to the lack of systemically collected data, there is difficulty in estimating the precise risk of HBV reactivation in corticosteroid users with resolved HBV infection. Currently, these patients are usually categorised by prednisone or equivalent dose (low dose: <10 mg/day; moderate dose: 10–20 mg/day; high dose: >20 mg/day) and treatment duration (<4 weeks vs ≥4 weeks).[7] Nevertheless, according to the dose and duration of corticosteroids used, the estimated risk levels are not always consistent among several guidelines.[7–9] Furthermore, corticosteroids are often used in a tapering or pulse manner, which may have an impact on the course of HBV reactivation,[7] but these situations have not been considered in the current risk assessment. As medication patterns may vary markedly in different rheumatic diseases, the reported incidence of HBV reactivation was largely distinct,[10–12] and a more generalised tool may be needed to quantify the risk of HBV reactivation in various rheumatic diseases when given a corticosteroid therapy.

In the prospective study, we perform a continuous monitoring of corticosteroid medication and HBV reactivation in patients with resolved HBV infection with uveitis. This condition is in a wide association with a variety of acute or chronic autoimmune and autoinflammatory diseases, such as ankylosing spondylitis, Behçet's disease, inflammatory bowel disease, psoriasis and sarcoidosis,[13 14] and corticosteroids currently remain the mainstay of treatment.[15] We assess the association of the cumulative dose and the time-weighted average dose of prednisone use with the risk of HBV reactivation in the analysis of different corticosteroid medication patterns for these immune-related diseases. We hypothesise that such indicators would be most likely to characterise the extent of corticosteroid exposure and to quantify the risk of HBV reactivation.

METHODS

Study design and participants

This was a prospective observational study conducted at Uveitis Centre of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. We enrolled consecutive uveitis patients who had an HBsAg-negative Anti-HBc-positive status and would receive systemic corticosteroids or not according to their ocular and systemic conditions to observe whether these patients would have a composite endpoint event of HBV reactivation, hepatitis flare or severe hepatitis. Those patients reaching the endpoints received immediate best medical judgement and proper antiviral therapy, and observation for the study purpose would be terminated. Evidence suggested that the deferred preemptive use of antiviral agents would be feasible to control HBV reactivation,[16 17] and, therefore, entecavir (0.5 mg/day) was initiated in patients when HBV reactivation was encountered. In this study, eligible participants were aged 18 years or older, seropositive for Anti-HBc and negative for HBsAg. Key exclusion criteria included past or concurrent infection with hepatitis C or hepatitis D virus; being receiving antiviral therapy; serum alanine aminotransferase (ALT) concentrations above normal; high HBV DNA level ($\geq 1\times10^7$ IU/mL); evidence of liver cirrhosis; concomitant other chronic liver diseases or other severe health problems. Online supplemental table S1 shows a complete list of inclusion and exclusion criteria. This cohort study is prospectively registered with Chinese Clinical Trial Register.

Study procedures and clinic visits

Treatment was generally implemented based on the recommendations of current guidelines.[15 18] In this study, according to the severity of ocular and systemic condition, patients received either different doses of oral prednisone or not, in combination with or without cyclosporine (2–5 mg/kg/day) as a corticosteroid-sparing immunosuppressive agent. In addition to systemic therapies, patients were also allowed to use any forms of topical treatments as a complementary therapy. Those patients in no need for systemic corticosteroids and cyclosporine only received topical therapies or even observation. To preclude other drug effects, additional systemic immunosuppressive agents, non-steroidal anti-inflammatory drugs and antiviral therapy were prohibited, otherwise observation would be terminated with data censored. Clinic visits were scheduled at baseline, at the end of 2 weeks, 4 weeks and 8 weeks, and approximately every 2 months thereafter. For each visit, we performed HBV DNA quantification and biochemical measures (serum ALT, aspartate aminotransferase (AST) and bilirubin) for all participants. HBV serology makers, including HBsAg, antibody against HBsAg (Anti-HBs), hepatitis B e antigen (HBeAg), antibody against HBeAg (Anti-HBe) and Anti-HBc, were measured every 6 months since baseline (see laboratory tests in online supplemental table S2). If suppression of disease was achieved and maintained, an attempt would be made to taper oral prednisone according to the patient's ocular and systemic conditions. Patients' conditions were evaluated until the occurrence of study endpoints, initiation of other treatments (eg, adding another immunosuppressant), withdrawal or loss to follow-up, or the completion of study. Corticosteroid tapering to discontinuation was not part of reasons for termination of evaluation, and the observation would continue.

Definitions, measurements and outcomes

The primary exposure factor was corticosteroid use, characterised by two continuous variables, cumulative dose and time-weighted average daily dose of prednisone, calculated as follows. We first determined the prednisone duration–dose curve for each participant based on the daily dose of prednisone over time from baseline to prednisone discontinuation if occurred during the study period, or to the termination of evaluation as mentioned before (online supplemental figure S1). During the period from baseline to the last evaluation, we performed interpolation over the days of missing data on daily dose, if any, by using the last observation carried forward. The cumulative dose was, therefore, defined as the total dose of prednisone accumulated over the duration interval measured as area under the curve. The time-weighted average dose was calculated by dividing the cumulative dose by the drug duration (days). In this study, the primary outcome was the time to a composite of HBV reactivation, hepatitis flare or severe hepatitis. Endpoint events were adjudicated by two independent clinicians who were unknown of the treatment assignment according to the AASLD recommended criteria (online supplemental table S3).[19]

Covariates

Covariates prospectively measured in this study included the dose of cyclosporine used, age, sex, body mass index, residence (rural vs urban), educational level (primary school and less, middle school, high school, and college and higher), smoking (none, past and current), drinking (none, past and current), presence of hypertension, diabetes, coronary heart disease or malignancy, uveitis affected eye (one eye vs both eyes), best corrected visual acuity in the worse-seeing eye (logarithm of the minimum angle of resolution (logMAR) transformed; a higher logMAR score indicates a worse visual acuity), Anti-HBs status, ALT level, AST level, total bilirubin level and creatinine level.

Statistical analyses

Data are expressed as numbers and percentages for categorised variables, as means and SD for normally distributed data, and as medians and IQRs for skewed data. Normality was evaluated with the Shapiro-Wilk test. Data on cumulative dose and time-weighted average dose were categorised into each quartile. Incidence rates of study endpoints for each quartile were calculated as events per 100 person-years. To account for potential confounders, we used the propensity score-based inverse probability weighting to obtain incidence estimates, in which each observation was weighted by the inverse of the probability of a patient being in each quartile. The propensity scores based on the probability of being in each quartile were generated using the multinomial logistic regression with the full set of covariates as independent variables. This approach produced a pseudopopulation, where incidence rates were estimated to represent the population-average treatment effects of each quartile independent of measured covariates.[20] We used the Cox proportional hazards regression model to estimate adjusted HRs with 95% CIs for endpoint events. Participants without an endpoint event had their data censored on their last evaluation. Schoenfeld residuals indicated no violations of the proportional hazards assumption. All multivariable models adjusted for the full set of covariates measured at baseline unless stated otherwise. A linear trend was estimated by modelling the factor as a continuous variable. Non-linear relationship was explored by remodelling the Cox regression equation with restricted cubic splines. To examine the subgroup effects, we additionally used a multivariable Cox regression model, including the interaction between each subgroup variable and time-weighted average prednisone dose quartiles as a factor. A p value of <0.05 on the Wald χ^2 test was considered to indicate statistical significance for the interaction term. In a sensitivity analysis, HRs for the primary composite outcome were estimated with a multivariable Cox model adjusted for suitable minimally sufficient adjustment sets that were identified by a directed acyclic graph (DAG). The DAG is composed of nodes representing variables and arrows showing associations between these variables, and produces the minimum number of covariates required to account for confounding.[21] The DAG was generated with the use of DAGitty V.3.0.[22] All tests were two-sided. No adjustments were made for multiple comparisons. Statistical analyses were performed with SPSS Statistics V.25 or R V.3.5.0.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

Study population and events

From July 2019 through March 2021, a total of 2996 consecutive patients underwent eligibility assessment, and 1303 HBsAg-negative Anti-HBc-positive patients were enrolled (online supplemental figure S2). The median age of our cohort was 47.5 (IQR: 38–56) years, and 47.5% were female. Participants had a median ALT level of 18 (IQR: 14–24) U/L, 842 (64.6%) patients were Anti-HBs-positive and all had an undetectable HBV DNA level ($<1\times10^2$ IU/mL) at enrolment. Other baseline demographic and clinical characteristics are summarised according to the cumulative dose and time-weighted average dose quartiles in tables 1 and 2. Oral prednisone was initiated in 77.8% of participants at a median dose of 20 mg/day (IQR: 15–20 mg/day), and cyclosporine in 56.3% at 100 mg/day (IQR: 100–125 mg/day). The median of cumulative prednisone dose and time-weighted average prednisone dose used in this cohort was 3000 mg (IQR: 300–6750 mg) and 15 mg/day (IQR: 10–20 mg/day), respectively. This study was completed on 31 March 2021, which provided a median follow-up of 10 months (IQR: 4–16 months) for participants. There were 70 participants initiating other systemic therapies than prednisone and cyclosporine, for whom the evaluation was terminated and data were censored. During the study period, a total of 51 participants had the incident HBV reactivation or hepatitis flare, reaching the primary composite endpoint. The mean detectable HBV DNA level was 1.81×10^3 IU/mL at the first sign of HBV reactivation. No severe hepatitis occurred in the cohort.

Cumulative dose

A higher incidence of primary outcome was not seen in patients with a higher cumulative prednisone dose (table 3). After inverse probability weighting, patients in the top quartile of cumulative dose had the lowest incidence rate of primary endpoint events (0.17 per 100 person-years), while those in the second quartile had the highest incidence (48 per 100 person-years). In Cox regression analysis with the fully adjusted model, as compared with the bottom quartile, the highest risk of primary endpoint events was detected in the second quartile of cumulative dose (HR: 6.03; 95% CI, 2.60 to 14.01) and the lowest risk in the top quartile (HR: 0.06; 95% CI, 0.01 to 0.49) (table 4). In linear remodelling, there seemed to be an inverse association between cumulative dose and event risk (HR per quartile increase: 0.46; 95% CI, 0.33 to 0.65). In cubic spline analyses, cumulative dose showed an inverted V-shaped relationship with the event risk, which peaked at a cumulative dose value of 1506 mg (HR: 3.72; 95% CI, 1.96 to 7.08) (figure 1 and online supplemental table S4).

Time-weighted average dose

Participants using a higher time-weighted average prednisone dose had a higher incidence of HBV reactivation or hepatitis flare, and the relationship between the time-weighted average dose and event risk appeared to be dose dependent (table 3). After inverse probability weighting, the incidence rate of primary endpoint events was 16.67 per 100 person-years in the top quartile of time-weighted average dose (Q4: >20 mg/day). All other quartiles (Q1: ≤10 mg/day; Q2: >10 mg/day but ≤15 mg/day; Q3: >15 mg/day but ≤20 mg/day) had a lower incidence of primary endpoint

Table 1 Baseline demographic and clinical characteristics according to cumulative prednisone dose categories

Characteristics	Cumulative prednisone dose*			
	Q1	Q2	Q3	Q4
No. of participants	383	269	328	323
Age, median (IQR), years	47.5 (40–56)	48 (38–57)	47.5 (37–56)	47.5 (36–56)
Female, no. (%)	182 (47.4)	121 (45.1)	173 (52.7)	170 (52.6)
BMI, median (IQR), kg/m^2	23.2 (22.1–24.2)	23.2 (21.5–25.4)	23.2 (22.0–24.6)	23.2 (22.2–24.4)
Rural residents, no. (%)	120 (31.3)	113 (42.2)	146 (44.5)	197 (61.0)
Education level, no. (%)				
Primary school and less	93 (24.2)	69 (25.7)	94 (24.6)	84 (26.0)
Middle school	91 (23.7)	77 (28.7)	107 (32.6)	119 (36.8)
High school	68 (17.7)	61 (22.8)	72 (22.0)	71 (22.0)
College and higher	132 (34.4)	61 (22.8)	55 (16.8)	49 (15.2)
Smoking status, no. (%)				
None	275 (71.6)	180 (67.2)	211 (64.3)	173 (53.6)
Past	44 (11.5)	35 (13.1)	50 (15.2)	74 (22.9)
Current	65 (16.9)	53 (19.8)	67 (20.4)	76 (23.5)
Drinking alcohol, no. (%)				
None	251 (65.4)	171 (63.8)	196 (59.8)	178 (55.1)
Past	68 (17.7)	50 (18.7)	68 (20.7)	80 (24.8)
Current	65 (16.9)	47 (17.5)	64 (19.5)	65 (20.1)
Hypertension, no. (%)	29 (7.6)	34 (12.7)	32 (9.8)	37 (11.5)
Diabetes, no. (%)	21 (5.5)	11 (4.1)	11 (3.4)	14 (4.3)
Coronary heart disease, no. (%)	3 (0.8)	9 (3.4)	6 (1.8)	3 (0.9)
Malignancy, no. (%)	4 (1.0)	4 (1.5)	3 (0.9)	0 (0.0)
Dose of cyclosporine used, median (IQR), mg/day	0 (0–0)	100 (0–125)	100 (0–100)	100 (75–125)
Uveitis affected eye, no. (%)				
One eye	254 (66.1)	144 (53.7)	211 (64.3)	166 (51.4)
Both eyes	130 (33.9)	124 (46.3)	117 (35.7)	157 (48.6)
BCVA in the worse-seeing eye, median (IQR), LogMAR	0.10 (0–0.52)	0.22 (0–1.0)	0.15 (0–0.70)	0.30 (0–0.82)
Anti-HBs (+), no. (%)	248 (64.6)	166 (61.9)	213 (64.9)	215 (66.6)
ALT level, median (IQR), U/L	18 (13–23)	18 (14–24)	18 (13–23)	18 (14–24)
AST level, median (IQR), U/L	18 (15–21)	18 (15–22)	17 (14–22)	18 (14–22)
Total bilirubin level, median (IQR), µmol/L	9.9 (7.7–12.9)	9.9 (7.3–12.6)	9.9 (7.6–12.6)	9.4 (7.2–12.4)
Creatinine level, median (IQR), µmol/L	70 (61–81)	70 (63–80)	70 (59–76)	70 (60–76)

*Values are reported according to the quartile (Q) of cumulative prednisone dose. The cumulative prednisone dose was categorised as: Q1 ≤300 mg; Q2 >300 mg but ≤3000 mg; Q3 > 3000 mg but ≤6750 mg; Q4 > 6750 mg.
ALT, alanine aminotransferase; Anti-HBs, antibody against hepatitis B surface antigen; AST, aspartate aminotransferase; BCVA, best corrected visual acuity; BMI, body mass index; LogMAR, logarithm of the minimum angle of resolution (higher logMAR scores indicate a worse visual acuity).

events than 10 per 100 person-years. After multivariable adjustment, quartiles of time-weighted average dose were independently associated with a monotonic increase in the event risk (HR per quartile increase: 2.15; 95% CI, 1.56 to 2.98), reaching an HR of 49.48 (95% CI, 6.24 to 392.48) in the top quartile as compared with the bottom one (table 4). There tended to be a stepwise increase in the event risk when given an increase in time-weighted average dose, whereby the risk was marginally higher at time-weighted average dose values of 21 mg/day (HR: 4.37; 95% CI, 1.00 to 19.06) or greater (figure 1 and online supplemental table S5). As the time-weighted average dose increased, a similar increasing trend in event risk and incidence rate was seen in subgroup analyses comparing patients with or without Anti-HBs positivity, using cyclosporine or not, and with baseline ALT level of ≤20 U/L or >20 U/L (online supplemental figure S3 and online supplemental table S6). Results indicated no effect modification according to Anti-HBs status (p=0.42 for interaction), use of cyclosporine (p=0.47 for interaction) and baseline ALT levels (p=0.82 for interaction) (online supplemental table S6). After adjustment for the full set of covariates, a significant protective effect in HBV reactivation or hepatitis flare was not observed for Anti-HBs positivity (HR: 0.99; 95% CI, 0.54 to 1.80), Anti-HBs level of ≥20 mIU/mL (HR: 0.82; 95%, 0.47–1.45) and even ≥100 mIU/mL (HR: 0.83; 95% CI, 0.44 to 1.55) (online supplemental table S7). The DAG identified several suitable minimally sufficient adjustment sets of covariates needed to account for confounding (online supplemental figure S4 and online supplemental table S8). Results of the sensitivity analysis with adjustment for these sets did not differ substantially from that of the primary analysis, where HRs were adjusted for the full set of covariates (online supplemental table S9).

DISCUSSION

Among patients with resolved HBV infection on corticosteroid therapy, we found an inverted V-shaped relationship rather than a positive correlation between cumulative prednisone dose and risk of HBV reactivation or hepatitis flare. Instead, time-weighted average prednisone dose independently showed a positive association with the event risk, which appeared to have reasonably

Table 2 Baseline demographic and clinical characteristics according to time-weighted average prednisone dose categories

Characteristics	Time-weighted average prednisone dose*			
	Q1	Q2	Q3	Q4
No. of participants	328	346	494	135
Age, median (IQR), years	47.5 (37–56)	48 (40–58.3)	47.5 (36–56)	47 (36–53)
Female, no. (%)	157 (47.9)	188 (54.3)	234 (47.4)	50 (37.0)
BMI, median (IQR), kg/m^2	23.2 (21.4–24.5)	23.2 (22.2–24.5)	23.2 (21.6–24.9)	23.2 (23.2–23.9)
Rural residents, no. (%)	102 (31.1)	123 (35.5)	215 (43.5)	65 (48.1)
Education level, no. (%)				
Primary school and less	71 (21.6)	81 (23.4)	141 (28.5)	47 (34.8)
Middle school	88 (26.8)	111 (32.1)	153 (31.0)	42 (31.1)
High school	68 (20.7)	72 (20.8)	101 (20.4)	31 (23.0)
College and higher	101 (30.8)	82 (23.7)	99 (20.0)	15 (11.1)
Smoking status, no. (%)				
None	229 (69.8)	229 (66.2)	313 (63.4)	68 (50.4)
Past	46 (14.0)	45 (13.0)	66 (13.4)	46 (34.1)
Current	53 (0.3)	72 (20.8)	115 (23.3)	21 (15.6)
Drinking alcohol, no. (%)				
None	192 (58.5)	215 (62.1)	326 (66.0)	63 (46.7)
Past	67 (20.4)	55 (15.9)	90 (18.2)	54 (40.0)
Current	69 (21.0)	76 (22.0)	78 (15.8)	18 (13.3)
Hypertension, no. (%)	30 (9.1)	44 (12.7)	45 (9.1)	13 (9.6)
Diabetes, no. (%)	18 (5.5)	15 (4.3)	16 (3.2)	8 (5.9)
Coronary heart disease, no. (%)	5 (1.5)	9 (2.6)	6 (1.2)	1 (0.7)
Malignancy, no. (%)	4 (1.2)	3 (0.9)	4 (0.8)	0 (0.0)
Dose of cyclosporine used, median (IQR), mg/day	0 (0–0)	100 (0–100)	100 (50–125)	100 (75–125)
Uveitis affected eye, no. (%)				
One eye	233 (71.0)	224 (64.7)	248 (50.2)	70 (51.9)
Both eyes	95 (29.0)	122 (35.3)	246 (49.8)	65 (48.1)
BCVA in the worse-seeing eye, median (IQR), LogMAR	0.10 (0–0.40)	0.15 (0–0.52)	0.30 (0.10–1)	0.30 (0–1.30)
Anti-HBs (+), no. (%)	207 (63.1)	217 (62.7)	347 (70.2)	71 (52.5)
ALT level, median (IQR), U/L	18 (13–23)	18 (13–23)	18 (14–24)	19 (14–26)
AST level, median (IQR), U/L	18 (15–21)	18 (15–22)	18 (15–22)	18 (14–21)
Total bilirubin level, median (IQR), µmol/L	9.9 (7.5–12.5)	9.9 (7.5–12.3)	9.9 (7.4–12.7)	9.8 (7.2–14.4)
Creatinine level, median (IQR), µmol/L	70 (61–78)	70 (61.7–77.3)	70 (60–78.3)	71 (66–79)

*Values are reported according to the quartile (Q) of time-weighted average prednisone dose. The time-weighted average prednisone dose was categorised as: Q1 ≤10 mg/day; Q2 >10 mg/day but ≤15 mg/day; Q3 >15 mg/day but ≤20 mg/day; Q4 >20 mg/day.
ALT, alanine aminotransferase; Anti-HBs, antibody against hepatitis B surface antigen; AST, aspartate aminotransferase; BCVA, best corrected visual acuity; BMI, body mass index; LogMAR, logarithm of the minimum angle of resolution (higher logMAR scores indicate a worse visual acuity).

explained the dose–response relationship between the extent of corticosteroid exposures and risk for HBV reactivation or hepatitis flare. Use of prednisone with a time-weighted average dose greater than 20 mg/day resulted in an incidence of HBV reactivation or hepatitis flare more than 10 per 100 person-years in patients with resolved HBV infection.

There has been controversy about key determinants of HBV reactivation or hepatitis flare during corticosteroid therapy. Earlier studies found that even a short episode of high-dose corticosteroids increased the risk of hepatitis flare.[23 24] The peak daily dose of corticosteroids was, therefore, assigned more importance as a predictor of hepatitis flares than drug duration.[23 25] However, a peak dose does not usually reflect the continuous exposure extent of corticosteroids. One observation showed that the risk of hepatitis flare correlated with the corticosteroid dose during long-term maintenance but not with the peak dose of pulse therapy.[26] Another study showed that chronic and high-dose treatment with corticosteroids each contributed significantly to HBV reactivation.[27] These findings indicate that both dose and duration would predict the outcome of HBV reactivation, but each only explains a limited proportion of variance in the risk.

Cumulative prednisone dose synthetically incorporates the effects of treatment dose and duration, reflecting the accumulation of corticosteroid exposure over a certain period of time. Nevertheless, with the increase of cumulative dose, the event risk exhibited a trend from ascent to descent. The V-shaped relationship was in line with previous observations on long-term and low-dose use of corticosteroids.[25 28] A low daily dose of corticosteroids, even if resulting in a relatively high cumulative dose over a long course of treatment, would not be expected to pose a substantial risk of HBV reactivation or hepatitis flare. Thus, the cumulative dose might not be a driving factor related to the negative consequences of HBV reactivation or hepatitis flare during corticosteroid use.

Our study further implied that time-weighted average dose would be a more reasonable indicator to characterise the positive association between corticosteroid use and risk for HBV reactivation or hepatitis flare. This dose–response relationship seemed to be independent of Anti-HBs status, use of cyclosporine and baseline serum ALT levels. Thus,

Table 3 Incidence of the primary composite outcome

Categories*	Cumulative prednisone dose	Time-weighted average prednisone dose
No. with event/total no.		
Q1	11/383	1/328
Q2	33/269	15/346
Q3	6/328	22/494
Q4	1/323	13/135
Crude incidence, 100py		
Q1	4.35	0.35
Q2	46.53	5.06
Q3	2.16	6.16
Q4	0.23	12.67
Inverse probability weighted incidence†, 100py		
Q1	9.68	0.75
Q2	48.00	4.89
Q3	3.33	5.64
Q4	0.17	16.67

*Values are reported according to the quartile (Q) of cumulative prednisone dose and time-weighted average prednisone dose. The cumulative prednisone dose was categorised as: Q1 ≤300 mg; Q2 >300 mg but ≤3000 mg; Q3 >3000 mg but ≤6750 mg; Q4 >6750 mg. The time-weighted average prednisone dose was categorised as: Q1 ≤10 mg/day; Q2 >10 mg/day but ≤15 mg/day; Q3 >15 mg/day but ≤20 mg/day; Q4 >20 mg/day.
†Each observation was weighted by the inverse of the probability of a patient being in each quartile. The probability was generated using the multinomial logistic regression with cyclosporine daily dose, age, sex, BMI, HBs antibody status, serum ALT level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, BCVA in the worse-seeing eye, AST level, total bilirubin level and creatinine level as independent variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCVA, best corrected visual acuity; BMI, body mass index; HBs, hepatitis B surface; 100py, per 100 person-years.

assessment of time-weighted average prednisone dose would allow for the exploration of risk stratification with implications for HBV reactivation prevention strategies in

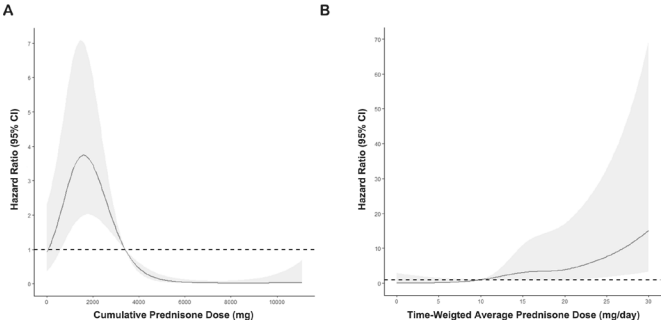

Figure 1 Relationship between the cumulative dose and time-weighted average dose of prednisone use and the primary composite outcome. HRs of the cumulative prednisone dose (A) and time-weighted average prednisone dose (B) for the primary composite outcome were estimated with a multivariable Cox regression analysis adjusted for cyclosporine daily dose, age, sex, BMI, HBs antibody status, serum ALT level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, BCVA in the worse-seeing eye, AST level, total bilirubin level and creatinine level. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCVA, best corrected visual acuity; BMI, body mass index; HBs, Hepatitis B surface.

HBsAg-negative Anti-HBc-positive individuals. Our findings suggested that a time-weighted average dose of 20 mg/day would be a clinically meaningful cut-off value for risk stratification in this population, because greater doses were linked to an incidence of HBV reactivation or hepatitis flare in excess of 10 per 100 person-years, which could be classified into the high-risk group according to the previous guideline[7] and because greater doses were robustly associated with an increased event risk (where the 95% CI for the HR no longer included 1 when the dose was 21 mg/day or greater). Prophylactic Anti-HBV therapy may, therefore, be

Table 4 Risk for the primary composite outcome

Primary outcome	HR (95% CI)* Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	Per quartile increase†	P value for trend†
Cumulative prednisone dose					
Univariate model‡	6.20 (2.98 to 12.92)	0.45 (0.17 to 1.23)	0.07 (0.01 to 0.51)	0.58 (0.45 to 0.75)	3.3×10^{-5}
Minimally adjusted model§	6.42 (2.81 to 14.65)	0.48 (0.17 to 1.41)	0.07 (0.01 to 0.53)	0.45 (0.32 to 0.63)	4.0×10^{-6}
Further adjusted model¶	5.95 (2.61 to 13.57)	0.48 (0.16 to 1.39)	0.06 (0.01 to 0.51)	0.46 (0.32 to 0.64)	5.0×10^{-6}
Fully adjusted model**	6.03 (2.60 to 14.01)	0.51 (0.17 to 1.52)	0.06 (0.01 to 0.49)	0.46 (0.33 to 0.65)	9.0×10^{-6}
Time-weighted average prednisone dose					
Univariate model‡	14.05 (1.86 to 106.35)	15.70 (2.12 to 116.52)	30.66 (4.01 to 234.39)	1.96 (1.43 to 2.67)	2.0×10^{-5}
Minimally adjusted model§	22.64 (2.96 to 173.36)	27.20 (3.58 to 206.72)	50.30 (6.40 to 395.63)	2.16 (1.59 to 2.95)	1.0×10^{-6}
Further adjusted model¶	21.50 (2.81 to 164.59)	26.30 (3.46 to 199.82)	48.87 (6.17 to 386.83)	2.17 (1.58 to 2.98)	2.0×10^{-6}
Fully adjusted model**	23.90 (3.09 to 184.65)	24.82 (3.23 to 190.54)	49.48 (6.24 to 392.48)	2.15 (1.56 to 2.98)	4.0×10^{-6}

*Values are reported according to the quartile (Q) of cumulative prednisone dose and time-weighted average prednisone dose. The cumulative prednisone dose was categorised as: Q1 ≤300 mg; Q2 >300 mg but ≤3000 mg; Q3 >3000 mg but ≤6750 mg; Q4 >6750 mg. The time-weighted average prednisone dose was categorised as: Q1 ≤10 mg/day; Q2 >10 mg/day but ≤15 mg/day; Q3 >15 mg/day but ≤20 mg/day; Q4 >20 mg/day.
†HRs per quartile increase and p values for linear trend were computed by modelling the factor as a continuous variable.
‡Crude HRs were estimated by using the univariate Cox regression analysis.
§HRs were adjusted for cyclosporine daily dose, age, sex and BMI.
¶HRs were adjusted for the minimally adjusted model, HBs antibody status and serum ALT level.
**Hazard ratios were adjusted for the further adjusted model, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, BCVA in the worse-seeing eye, AST level, total bilirubin level and creatinine level.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCVA, best corrected visual acuity; BMI, body mass index; HBs, hepatitis B surface.

needed for these high-risk patients according to the previous recommendation.[7]

A major advantage of our study design is that we have appropriately chosen patients with uveitis as the study population. This ocular disease is considered to be independent of HBV status and hepatic outcomes, and has a wide association with a variety of autoimmune and autoinflammatory diseases, including ankylosing spondylitis, juvenile idiopathic arthritis, Behçet's disease, inflammatory bowel disease, psoriasis and sarcoidosis.[13 14] Some uveitis subtypes, such as Fuchs uveitis syndrome and Posner-Schlossman syndrome, are usually treated with topical eye drops or even observation (accounting for roughly 25% in this cohort); other subtypes such as acute anterior uveitis associated with or without ankylosing spondylitis can be treated with topical therapies or shortly tapered systemic corticosteroids (accounting for roughly 30% in this cohort); while, some refractory subtypes, such as uveitis in Behçet's disease, juvenile idiopathic arthritis, Vogt-Koyanagi-Harada disease, inflammatory bowel disease, psoriasis and sarcoidosis, often require a long-term systemic corticosteroid therapy (accounting for roughly 45% in this cohort).[15] Therefore, the study population of uveitis has allowed us to naturally compare the effect of corticosteroids on HBV reactivation and also to explore the generalisability of time-weighted average dose in the analysis of different corticosteroid medication patterns. Therefore, findings on the relationship between time-weighted average dose and risk of HBV reactivation or hepatitis flare would be expected to be extrapolated to all those patients with resolved HBV infection who require corticosteroid therapies for various acute or chronic rheumatic diseases and connective tissue disorders. Prospectively and continuously documented dose and duration of prescription drugs have prevented misclassification of drug exposures due to dynamic changes in medication.

Our study has certain limitations. First, owing to the ethical considerations, the corticosteroid therapy was not randomly assigned, and unmeasured treatments may have residual confounding effects in this observational study. Several measures have been taken to minimise the confounding bias, including prespecified prohibition of other immunosuppressive drugs than cyclosporine, maintaining the cyclosporine dose throughout the study if used, adjustment for a detailed list of covariates, including cyclosporine dose, censoring data from those who subsequently initiated other immunosuppressive agents if any. Second, due to the fact that data on drug dose and duration were recorded in line with prescriptions and we applied an intention-to-treat design in data analysis, we could not correct for minor patient self-non-compliance. Third, our study was conducted in China, a hepatitis B high prevalence area, and thus, the results described here need to be further confirmed in countries with a lower incidence rate of HBV infection. Fourth, we noted an extremely high HR with a wide CI for the top quartile of time-weighted average prednisone dose (Q4: >20 mg/day) as compared with the bottom one (Q1: ≤10 mg/day). Such a condition may be due to the fact that the primary endpoint event of the bottom quartile was rare (only one event) and that there was a certain degree of deviation from linearity of the associations for quartile-related time-weighted average dose data. Therefore, the quartile-related HR may be misleading, and we further used the restricted cubic splines to characterise the non-linear relationship. Nevertheless, the association of the time-weighted average dose of 21 mg/day or greater with a high event risk remained essentially unchanged in cubic spline analyses. Finally, interpretation of composite endpoints used in this study remains difficult. We have observed the association between time-weighted average dose and risk for primary composite endpoints, but we could not precisely estimate the HR for each of the components. It has been shown that the course of HBV reactivation can be depicted as several phases according to the severity of the disease.[29 30] The Anti-HBV treatment initiated at the first sign of HBV reactivation would prevent the evolution of disease toward more severe phases. We, therefore, recognised that there was a competing risk among each component whose occurrence precluded the occurrence of the other primary event of interest, and that the HR for each component could not be precisely estimated. Moreover, this study might not be powered for detecting the each component, especially severe hepatitis, which is individually rare in corticosteroid users with resolved HBV infection. Nevertheless, the use of composite endpoints had several advantages. We noted that not all patients may follow the reactivation phases in a sequence and some severe events may rapidly occur within a few weeks (or days in some cases) in the progression of HBV reactivation.[1] The use of composite endpoints may avoid missing observation of events and result in an increase in event rates as well as statistical power compared with the use of a single endpoint. Moreover, all the components of the composite endpoints are of the similar nature of importance to patients, of which any occurrence indicates the need for further intervention and may serve as the basis for medical decision-making.

In conclusion, among patients with resolved HBV infection on corticosteroid therapy for acute or chronic immune-related diseases, time-weighted average prednisone dose but not cumulative dose has reasonably represented the extent of corticosteroid exposures and independently predicted a monotonic increase in the risk of HBV reactivation or hepatitis flare. These patients using a time-weighted average prednisone dose greater than 20 mg/day would be classified as the high-risk level for HBV reactivation or hepatitis flare, and prophylactic Anti-HBV therapy may, therefore, be needed for these high-risk patients.

Contributors ZZ designed the study. PY supervised the study. WL, LD, XF, GS, YG and QW collected clinical data. ZZ and WL analysed and interpreted the data. ZZ wrote the first draft of the paper. PY, ZZ and WL reviewed and edited the manuscript. PY served as the overall content guarantor. All authors provided a final review and approved the manuscript before submission.

Funding The work was supported by National Natural Science Foundation Key Program (81930023), Natural Science Foundation Major International (Regional) Joint Research Project (81720108009), Chongqing Key Laboratory of Ophthalmology (2008CA5003), Chongqing Outstanding Scientists Project (2019), Chongqing Chief Medical Scientist Project (2018) and Chongqing Science and Technology Platform and Base Construction Program (cstc2014pt-sy10002).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the First affiliated Hospital of Chongqing Medical University (approval number: 20195001). Participants gave informed consent to participate in the study before enrolment. Study procedures were conducted in compliance with the provisions of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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REFERENCES

1 Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology* 2017;152:1297–309.
2 Tan J, Zhou J, Zhao P, *et al*. Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. *Clin Rheumatol* 2012;31:1169–75.
3 Reddy KR, Beavers KL, Hammond SP, *et al*. American gastroenterological association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:215–9.
4 Yim HJ, Kim JH, Park JY, *et al*. Comparison of clinical practice guidelines for the management of chronic hepatitis B: when to start, when to change, and when to stop. *Clin Mol Hepatol* 2020;26:411–29.
5 Cholongitas E, Haidich A-B, Apostolidou-Kiouti F, *et al*. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. *Ann Gastroenterol* 2018;31:480–90.
6 Chen M-H, Lee I-C, Chen M-H, *et al*. Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease. *Ann Rheum Dis* 2021;80:1393–9.
7 Perrillo RP, Gish R, Falck-Ytter YT. American gastroenterological association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:221–44.
8 Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. *Clin Mol Hepatol* 2019;25:93–159.
9 Pawłowska M, Flisiak R, Gil L, *et al*. Prophylaxis of hepatitis B virus (HBV) infection reactivation – recommendations of the Working group for prevention of HBV reactivation. *Ceh* 2019;5:195–202.
10 Fukuda W, Hanyu T, Katayama M, *et al*. Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. *Ann Rheum Dis* 2017;76:1051–6.
11 Lin T-C, Yoshida K, Tedeschi SK, *et al*. Risk of hepatitis B virus reactivation in patients with inflammatory arthritis receiving disease-modifying antirheumatic drugs: a systematic review and meta-analysis. *Arthritis Care Res* 2018;70:724–31.
12 Lin WT, Chen YM, Chen DY, *et al*. Increased risk of hepatitis B virus reactivation in systemic lupus erythematosus patients receiving immunosuppressants: a retrospective cohort study. *Lupus* 2018;27:66–75.
13 Yang P, Zhong Z, Du L, *et al*. Prevalence and clinical features of systemic diseases in Chinese patients with uveitis. *Br J Ophthalmol* 2021;105:75–82.
14 Zhong Z, Su G, Kijlstra A, *et al*. Activation of the interleukin-23/interleukin-17 signalling pathway in autoinflammatory and autoimmune uveitis. *Prog Retin Eye Res* 2021;80:100866.
15 Jabs DA, Rosenbaum JT, Foster CS, *et al*. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000;130:492–513.
16 Tang W, Chen L, Zheng R, *et al*. Prophylactic effect of lamivudine for chemotherapy-induced hepatitis B reactivation in breast cancer: a meta-analysis. *PLoS One* 2015;10:e0128673.
17 Seto W-K, Chan TSY, Hwang Y-Y, *et al*. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014;32:3736–43.
18 Dick AD, Rosenbaum JT, Al-Dhibi HA, *et al*. Guidance on Noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: fundamentals of care for uveitis (focus) initiative. *Ophthalmology* 2018;125:757–73.
19 Terrault NA, Lok ASF, McMahon BJ, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560–99.
20 Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med* 2010;29:2137–48.
21 Knüppel S, Stang A. Dag program: identifying minimal sufficient adjustment sets. *Epidemiology* 2010;21:159.
22 Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 2011;22:745.
23 Wong GL-H, Yuen BW-Y, Chan HL-Y, *et al*. Impact of dose and duration of corticosteroid on the risk of hepatitis flare in patients with chronic hepatitis B. *Liver Int* 2019;39:271–9.
24 Hoofnagle JH, Davis GL, Pappas SC, *et al*. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1986;104:12–17.
25 Wong GL-H, Wong VW-S, Yuen BW-Y, *et al*. Risk of hepatitis B surface antigen seroreversion after corticosteroid treatment in patients with previous hepatitis B virus exposure. *J Hepatol* 2020;72:57–66.
26 Lin Y-C, Lee S-W, Yeh H-Z, *et al*. The prevalence and risk factors of hepatitis B flares in chronic hepatitis B patients receiving glucocorticoid pulse therapy. *Int J Clin Pharm* 2018;40:169–74.
27 Kim TW, Kim MN, Kwon JW, *et al*. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. *Respirology* 2010;15:1092–7.
28 Yang S-S, Hung C-T, Li S-F, *et al*. Hepatitis B virus-related mortality in rheumatoid arthritis patients undergoing long-term low-dose glucocorticoid treatment: a population-based study. *J Formos Med Assoc* 2018;117:566–71.
29 Hwang JP, Lok AS-F. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014;11:209–19.
30 Gentile G, Antonelli G. Hbv reactivation in patients undergoing hematopoietic stem cell transplantation: a narrative review. *Viruses* 2019;11:1049.