

ORIGINAL ARTICLE

Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids

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ABSTRACT

Background and objective: Reactivation of hepatitis B virus (HBV) is thought to be associated with immunosuppressive treatments, but insufficient information is available on the effect of corticosteroids. The aim of this study was to evaluate the risk of HBV reactivation in hepatitis B surface antigen-seropositive patients with asthma or COPD, who were treated with systemic corticosteroids (SCS) in addition to inhaled corticosteroids (ICS).

Methods: Patients with asthma or COPD ($n = 198$), who were hepatitis B surface antigen-seropositive and had been treated with ICS, were identified retrospectively. To evaluate the additional effects of SCS, the SCS group was divided into those who received intermittent or continuous SCS (≥ 3 months of continuous SCS treatment), and into those who received low-dose (≤ 20 mg/day of prednisolone) or medium-to-high-dose SCS. The study outcome was HBV reactivation.

Results: HBV reactivation occurred in 11.1% of patients in the SCS group, which was significantly higher than the reactivation rate in the ICS group. HBV reactivation was more frequent in the SCS group compared with the ICS group (OR 3.813, 95% CI: 1.106–13.145, $P = 0.032$), and in the continuous and medium-to-high-dose SCS subgroups compared with the ICS group (OR 5.719, 95% CI: 1.172–27.905, $P = 0.048$ and OR 4.884, 95% CI: 1.362–17.511, $P = 0.014$, respectively).

Conclusions: These results suggest that addition of SCS to ICS increases the risk of HBV reactivation, especially when SCS are administered chronically or at high doses.

SUMMARY AT A GLANCE

The risk of HBV reactivation was investigated in HBsAg-seropositive patients with asthma or COPD, who were treated with systemic (SCS) in addition to inhaled corticosteroids (ICS). Addition of SCS to ICS treatment increased the risk of HBV reactivation, especially when SCS were administered chronically or at high doses.

Key words: asthma, chronic obstructive pulmonary disease, hepatitis B virus reactivation, inhaled corticosteroid, systemic corticosteroid.

INTRODUCTION

Hepatitis B virus (HBV) infection is by far the most common chronic hepatic viral infection in the world, and is endemic in Asia, Africa and parts of the Pacific Rim. In South Korea, the prevalence of hepatitis B surface antigen (HBsAg) is as high as 5.1% in men and 4.1% in women, with a lower prevalence in those under 20 years of age.¹ As in other areas where it is endemic, HBV infection is the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma.²

Hepatitis B virus reactivation has been reported to occur spontaneously when individuals are in the inactive HBsAg carrier state, and numerous studies have shown that spontaneous reactivation of HBV occurs in approximately 10–20% of inactive HBsAg carriers who are followed up.³ Moreover, HBV reactivation is a well-recognized complication of solid organ or haematopoietic stem cell transplantation, immunosuppressive treatment, cancer chemotherapy, transarterial chemoembolization, liver irradiation and other immunomodulatory drugs, such as anti-tumour necrosis factor agents (infliximab), methotrexate, azathioprine and others^{4–9}; in theory,

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any form of immune suppression may lead to HBV reactivation.¹⁰ Occasionally, such exacerbations may lead to life-threatening liver failure, but such fatal events can now be successfully prevented by screening for HBV and by the use of lamivudine prophylaxis in susceptible patients.^{4,10}

Corticosteroids are frequently used as chemotherapeutic and immunomodulatory agents in many diseases, including asthma and COPD, and it has been suggested that this may be an important predisposing factor for HBV reactivation. Two mechanisms have been proposed for exacerbations associated with use of corticosteroids. *In vitro* studies have demonstrated that corticosteroids have a direct stimulatory effect on HBV replication by interacting with the corticosteroid responsive element in HBV and inducing its replication and transcription.^{11,12} This mechanism may be responsible for HBV reactivation related to the chronic use or dose-dependent effects of corticosteroids. The second mechanism involves an indirect immunosuppressive effect on the host immune response, which facilitates HBV replication.¹¹ This mechanism possibly explains HBV reactivation after withdrawal or reduction of corticosteroid treatment, during which an intense rebound of cytotoxic T-cell function may play an important role.¹³

Several studies have reported a correlation between HBV reactivation and corticosteroid treatment in HBsAg-seropositive patients. However, the majority of these have been *in vitro* studies,¹¹ or were performed in subjects with rheumatic diseases,^{8,14} or malignancies,¹⁵ organ transplant recipients,^{16–18} and others.¹⁹ Although some studies have addressed the effects of corticosteroids on HBV reactivation during chemotherapy,²⁰ little information is available on the effects of corticosteroid administration over longer periods of time at lower doses, in patients with asthma, COPD, rheumatic diseases or inflammatory bowel disease. In particular, to our knowledge, there has been only one such report on a patient with

asthma or COPD, which was a case report of HBV reactivation after high-dose corticosteroid therapy for asthma exacerbations.²¹

The present study was conducted to evaluate the risk of HBV reactivation in patients with asthma or COPD, who were HBsAg-seropositive and had been treated with corticosteroids. In particular, we sought to determine whether the risk of HBV reactivation is increased when systemic corticosteroids (SCS) are added to inhaled corticosteroid (ICS) treatment.

METHODS

Subjects

Data for asthma or COPD patients who visited Seoul National University Hospital and Seoul National University Bundang Hospital from January 1997 to May 2007 were analysed retrospectively. Initially, patients who were HBsAg-seropositive and who had received ICS treatment at some time were identified. In total, 269 patients met these criteria, but 71 patients were excluded because (i) they were not diagnosed as having asthma or COPD; (ii) they were receiving systemic chemotherapy due to a malignancy; (iii) they had undergone haematopoietic stem cell transplantation or solid organ transplantation; (iv) they were receiving immunomodulatory treatment other than corticosteroids, that is, infliximab, methotrexate or azathioprine for Crohn's disease or rheumatic diseases; (v) they had undergone transarterial chemoembolization or liver irradiation; or (vi) they were being treated with antiviral drugs, such as lamivudine, before corticosteroid treatment, because of spontaneous HBV reactivation, or for prophylaxis of HBV reactivation due to immunomodulatory treatment. Therefore, data for 198 patients were included in the analysis (Fig. 1). The study protocol was approved by the institutional review board.

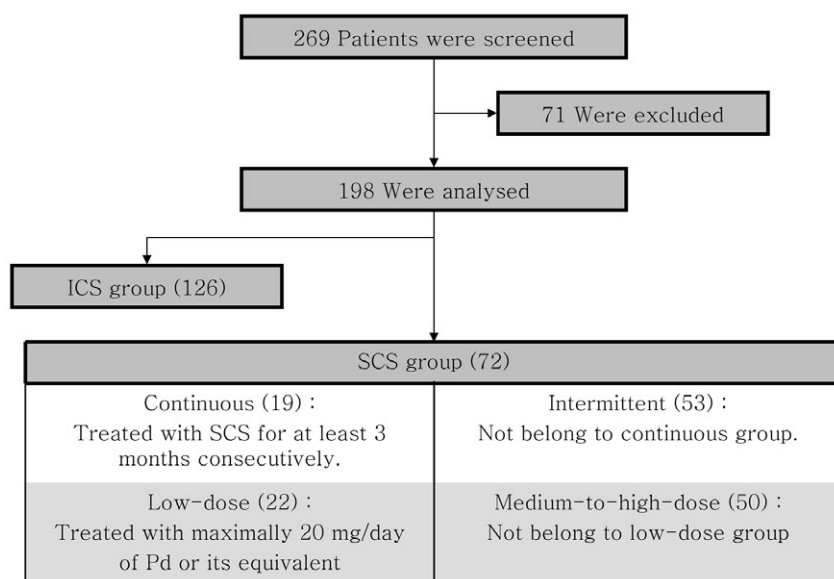


Figure 1 Diagram showing the classification of patients into the inhaled corticosteroid (ICS) and systemic corticosteroid (SCS) groups, and into the intermittent, continuous, low-dose and medium-to-high-dose SCS subgroups. Pd, prednisolone.

Review of data

Initially, serum alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg), anti-HBe and HBV DNA levels, as well as the time of initiation of antiviral therapy for HBV reactivation, were reviewed.

All patients included in the study were treated with ICS, and therefore, types of ICS, doses and durations of treatment were checked. To evaluate the additional effects of SCS on HBV reactivation, data for all patients who had ever been treated with SCS were analysed, and the types of SCS, doses and durations of treatment were determined.

Grouping of patients

Acute exacerbations of asthma or COPD may be triggered by various events, and require short-term treatment with high-dose SCS. Long-term administration of SCS is required for treatment of severe asthma or COPD, and fluctuating doses of SCS are administered to patients experiencing intermittent exacerbations.^{22,23} To evaluate the risk of HBV reactivation, given these variable dosing schedules, especially when SCS were added to ICS, the patients were divided into groups, and the rates of HBV reactivation were compared between these groups (Fig. 1).

The 198 study subjects were first grouped into those who had received ICS or SCS; the SCS group comprised patients with any history of SCS added to ICS treatment. Second, in order to evaluate the additional effects of SCS, the SCS group was divided into four subgroups as follows: (i) to evaluate the long-term effect of SCS, the SCS group was divided into continuous and intermittent subgroups, where the continuous subgroup comprised patients who were treated with SCS for a continuous period of at least 3 months; and (ii) to evaluate whether low doses of SCS play a role in HBV reactivation, the SCS group was divided into low-dose and medium-to-high-dose subgroups. A low dose of SCS is usually regarded as ≤ 10 mg/day of prednisolone (Pd) or equivalent;⁸ however, the present data showed that relatively few patients in the SCS group had been treated with conventional low doses of SCS. Therefore, the low-dose subgroup was defined as patients treated with ≤ 20 mg/day of Pd or equivalent (Fig. 1).

Study outcomes

The outcome variable was HBV reactivation. The definition of HBV reactivation was based on that used in other studies.^{24,25} HBV reactivation was defined as an absolute increase in ALT to more than 100 U/L, when compared with baseline values or a threefold or greater increase in serum ALT levels that exceeded the upper limit of normal (<58 IU/L), with an absolute increase in HBV DNA level that exceeded 2×10^4 IU/mL. Confirmation of HBV reactivation by a hepatologist was also reviewed.

Table 1 Baseline characteristics of the patients who were treated with ICS or SCS

	ICS group (<i>n</i> = 126)	SCS group (<i>n</i> = 72)	<i>P</i> -value
Age, mean $\pm$ SD	55.2 $\pm$ 14.6	57.6 $\pm$ 14.6	0.27
Gender			
Male, <i>n</i> (%)	65 (51.6)	34 (47.2)	0.56
Female, <i>n</i> (%)	61 (48.4)	38 (52.8)	
HBeAg			
Positive, <i>n</i> (%)	40 (87)	26 (74.3)	0.146
Negative, <i>n</i> (%)	6 (13)	9 (25.7)	

HBeAg, hepatitis B e antigen; ICS, inhaled corticosteroid; SCS, systemic corticosteroid.

Statistical analysis

Data were analysed by Pearson's chi-square test, Fisher's exact test or Student's *t*-test, using SPSS ver 12.0 software. *P*-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

Among the 198 patients, 126 were assigned to the ICS group and 72 to the SCS group. The 72 patients in the SCS group were assigned to the subgroups as follows: (i) 53 to the continuous subgroup and 19 to the intermittent subgroup; and (ii) 22 to the low-dose subgroup and 50 to the medium-to-high-dose subgroup.

Table 1 summarizes the characteristics of the 198 patients at enrolment and provides details on the ICS and SCS groups. There were no significant differences between the ICS and SCS groups in terms of age, gender or HBeAg positivity. There were also no significant differences between the pairs of subgroups of the SCS group (Table S1 in the online supplementary information). To evaluate the effects of duration of corticosteroid treatment and cumulative dose of SCS on HBV reactivation, these variables were compared between the pairs of subgroups of the SCS group. As shown in Table S2 in the online supplementary information, there were no significant differences between the pairs of subgroups except for duration of SCS treatment and cumulative dose of SCS for the continuous compared with the intermittent subgroup.

Hepatitis B virus reactivation

Among the 198 patients, a total of 12 cases (6.1%) met the definition of HBV reactivation and were confirmed as such by a hepatologist (Table 2). As to the response to antiviral treatment, all patients diagnosed with HBV reactivation were successfully treated with lamivudine. Of these 12 patients, four were in the ICS group (4 of 126, 3.2%) and eight were in the SCS group

Table 2 Demographic and clinical details of the 12 patients who were diagnosed with HBV reactivation

Gender/age	HBeAg	HBV DNA titre (IU/mL)			ALT (IU/L)			Note
		Pre-reactivation	During reactivation	Post-treatment	Pre-reactivation	During reactivation	Post-treatment	
M/51	+	NC	7 700 000	Negative	78	376	85	LC
F/57	–	NC	812 000	NC	30	277	28	
M/61	+	Negative	1 758 464	Negative	53	399	65	LC
F/51	–	NC	200 000	NC	35	371	21	
F/63	+	NC	110 000 000	109	85	440	78	LC
F/58	+	NC	200 000	Negative	67	522	79	LC
M/59	–	NC	200 000	NC	33	336	36	
F/74	–	NC	2 400 000	NC	25	235	30	
M/58	–	NC	7 710 460	NC	36	244	31	
M/55	+	NC	10 000 000	Negative	55	658	65	LC
M/74	+	Negative	100 000 000	210	68	351	72	LC
F/69	+	Negative	237 872 000	125	75	390	80	LC

ALT, alanine aminotransferase; F, female; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LC, liver cirrhosis; M, male; NC, not checked.

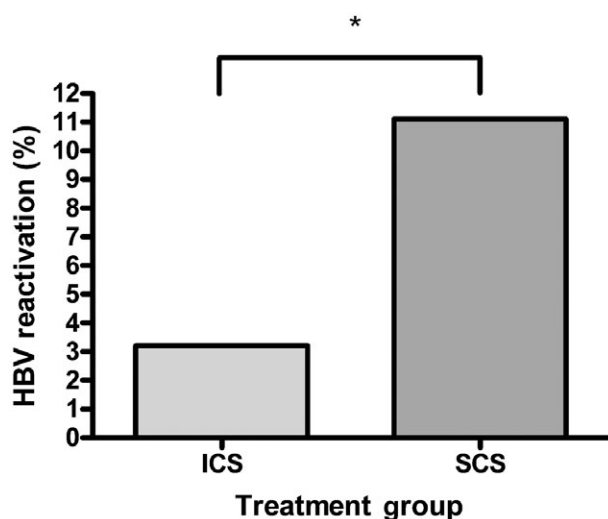


Figure 2 Percentages of patients in the inhaled corticosteroid (ICS) and systemic corticosteroid (SCS) groups who were diagnosed with hepatitis B virus (HBV) reactivation. * $P < 0.05$.

(8 of 72, 11.1%), and this difference was significant (OR 3.813, 95% CI: 1.106–13.145, $P = 0.032$), as shown in Figure 2.

As mentioned previously, the SCS group was divided into four subgroups to further analyse the rates of HBV reactivation. The rate of HBV reactivation was 9.4% (5 of 53 patients) in the intermittent subgroup compared with 15.8% (3 of 19 patients) in the continuous subgroup. Figure 3a shows the rates of HBV reactivation in the ICS group, and in the intermittent and continuous SCS subgroups. The rate of HBV reactivation was significantly higher in the continuous subgroup than in the ICS group (OR 5.719, 95% CI: 1.172–27.905, $P = 0.048$), but there was no significant difference between the ICS group and the

intermittent subgroup ($P = 0.127$), or between the intermittent and continuous subgroups ($P = 0.427$).

Only one patient (4.5%) in the low-dose SCS subgroup experienced HBV reactivation, whereas there were seven such patients (14.0%) in the medium-to-high-dose SCS subgroup. There was a significant difference in HBV reactivation between the ICS group and the medium-to-high-dose SCS subgroup (OR 4.884, 95% CI: 1.362–17.511, $P = 0.014$), but there were no significant differences between the other groups (Fig. 3b).

As mentioned previously, four patients in the ICS group developed HBV reactivation, and all these patients had been treated with low doses of ICS (100–250 µg of fluticasone).

DISCUSSION

Hepatitis B virus reactivation related to corticosteroid treatment is a well-recognized complication of immunomodulatory treatment for various diseases. In the past, corticosteroids were used to treat chronic hepatitis B, but in the 1980s, many studies concluded that such treatments produced no beneficial effects, and that they caused HBV reactivation.²⁶ Subsequently, because of ethical problems, the majority of studies investigating the correlation between corticosteroid treatment and HBV reactivation were performed *in vitro* or were case series, which is why few reports are available, especially on patients with asthma or COPD.

In the present study, the risk of HBV reactivation was found to be greater when SCS was added to ICS treatment. In particular, the risk of HBV reactivation was greater when SCS were used for more than 3 months, or were administered at doses >20 mg/day of Pd or equivalent, suggesting that chronic or high-dose SCS treatment increased the risk of HBV reactivation. This finding has important implications for the treatment of patients with severe asthma or

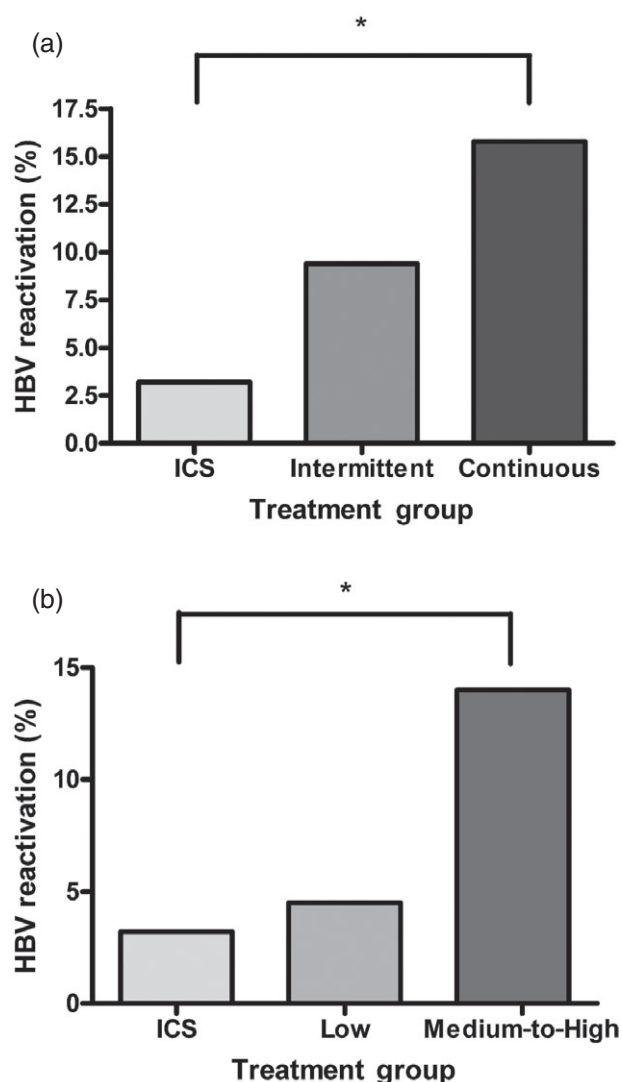


Figure 3 (a) Percentages of patients in the inhaled corticosteroid (ICS) group and the intermittent and continuous systemic corticosteroid (SCS) subgroups who were diagnosed with hepatitis B virus (HBV) reactivation. (b) Percentages of patients in the ICS group and the low-dose and medium-to-high-dose SCS subgroups who were diagnosed with HBV reactivation. * $P < 0.05$.

COPD, who require high-dose or long-term SCS, and suggests that screening for HBV reactivation and prophylactic antiviral treatment may be justified in these patients.

As mentioned previously, the direct stimulatory and indirect immunosuppressive effects of corticosteroids may play a role in HBV reactivation, and in theory, high doses, chronic use, tapering, and sudden withdrawal or initiation of corticosteroids may induce HBV reactivation. However, it is not known whether treatments with lower doses of SCS or ICS are risk factors for HBV reactivation. In this study, the effect of initiation of corticosteroid therapy could not be evaluated, because in all 12 patients who experienced HBV reactivation, this was diagnosed by regular blood

examination, which was performed annually or biannually at a routine check-up. In addition, the effect of SCS tapering could not be evaluated because it was difficult to define SCS tapering due to variable dosage schedules, such as abrupt cessation of high-dose SCS or gradual reduction of SCS dose for variable periods. However, other factors, including dosage and duration of SCS treatment, were evaluated, and the findings suggested that short-term use of low-dose SCS may not represent a greater risk for HBV reactivation than ICS treatment, even though the cut-off dose of Pd for the low-dose group was relatively high.

Inhaled corticosteroids can also have systemic side-effects, including growth retardation, osteoporosis, arterial hypertension, diabetes, suppression of the hypothalamic-pituitary-adrenal axis, obesity, cataracts, glaucoma, thinning of the skin and muscle weakness.^{23,27–30} Because of the nature of the present analysis, the effect of ICS on HBV reactivation could not be determined. The effect of ICS treatment on the risk of HBV reactivation requires further investigation in prospective studies.

The risk factors for HBV reactivation are known to include detectable HBsAg, HBV DNA, HBeAg, antibodies to hepatitis B core antigen (anti-HBc), HBV genotype, younger age and male gender.^{4,10} Data on HBV genotype were not available because this is not routinely assessed in South Korea. However, a previous report on HBV genotype in South Korea suggested that about 98% of Korean HBV carriers have genotype C,³¹ indicating that this would not be a confounding variable. Because in some cases, HBV DNA titres were checked when liver function results were elevated, and older data did not include anti-HBc results, other risk factors, including age, gender and HBeAg status, were compared between the major groups and subgroups of patients. As indicated in Tables 1 and 2, there were no significant differences, which suggests that the present data were reliable and were not biased by risk factors other than corticosteroid treatment.

This study had a number of limitations due to its retrospective nature. First, the data on doses and duration of corticosteroid treatment were obtained from medical records, which meant that poor compliance, for example, may have resulted in different actual exposures to corticosteroids. Second, the actual duration of exposure to corticosteroids, from initiation of treatment to HBV reactivation, may have differed from that recorded in the data, because laboratory findings, including liver function, were checked routinely twice a year, which meant that the time of HBV reactivation in asymptomatic patients could not be accurately estimated. However, despite these limitations, the present findings are consistent with those from previous studies.

In conclusion, the present findings suggest that addition of SCS to ICS treatment increased the risk of HBV reactivation, especially when SCS were administered chronically or at relatively higher doses. However, short-term use of low-dose SCS may not represent a greater risk of HBV reactivation than ICS treatment. Therefore, screening for HBV reactivation should be considered for patients receiving chronic or

high-dose SCS treatment. Furthermore, prophylactic antiviral treatment should be considered for patients with severe asthma or COPD, who require high-dose or long-term SCS treatment, especially during intermittent exacerbations that require higher doses of SCS, and when screening for HBV reactivation is not available.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Baseline characteristics of subgroups of SCS group. (a) Intermittent versus continuous subgroups. (b) Low-dose versus the medium-to-high-dose subgroup.

Table S2 Follow-up duration, duration and accumulated dose of SCS treatment in each subgroup.

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Supplementary table 1. Baseline characteristics of subgroups of SCS group

HBV = Hepatitis B virus, LC = Liver cirrhosis

a. Intermittent vs. Continuous subgroups

	Intermittent subgroup	Continuous subgroup	p-value
	(N = 53)	(N = 19)	
Age	56.3 ± 15.6	61.1 ± 11.0	0.226
Gender			
Male	24 (45.3%)	10 (52.6%)	0.582
Female	29 (54.7%)	9 (47.4%)	
HBeAg			
Positive	6 (20.0%)	3 (60.0%)	0.095
Negative	24 (80.0%)	2 (40.0%)	

b. Low-dose vs. the medium-to-high dose subgroup

	Low-dose subgroup (N = 22)	Medium-to-high dose subgroup (N = 50)	p-value
Age - yr	55.7 ± 13.2	58.4 ± 15.2	0.485
Gender			
Male - no. (%)	10 (45.5%)	24 (48.0%)	0.842
Female - no. (%)	12 (54.5%)	26 (52.0%)	
HBeAg			
Positive - no. (%)	2 (15.4%)	7 (31.8%)	0.431
Negative - no. (%)	11 (84.6%)	15 (68.2%)	

Supplementary table 2. Follow-up duration, duration and accumulated dose of SCS treatment in each subgroup

	f/u duration*	SCS duration	SCS accumulated dose
	(day)	(day)	(mg, Pd equivalent dose)
Intermittent vs	p=0.167	p=0.001	p=0.001
Continuous			
Intermittent	794.55±726.17	18.88±24.34	459.77±694.56
Continuous	1253.95±1331.52	634.37±678.82	4527.63±4234.82
Low-dose vs	p=0.450	p=0.839	p=0.393
Medium-to-high-dose			
Low-dose	788.95±734.05	170.75±325.46	1096.55±1836.48
Medium-to-high-dose	971.58±1014.79	195.14±490.00	1725.38±3202.23

* Follow-up duration is the same concept with duration of ICS treatment.

f/u = follow-up

SCS = systemic corticosteroid

Pd = Prednisolone