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## EXTENDED REPORT

# Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan

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**ABSTRACT**

**Background** Although the reactivation of hepatitis B virus (HBV) is recognised as a serious complication in patients with rheumatic disease (RD) receiving immunosuppressive drugs (ISDs), the incidence and risk factors for reactivation remain controversial.

**Objectives** To investigate the incidence and risk factors for HBV reactivation in patients with RD.

**Methods** We performed a multicentre, observational, prospective study over 2 years in patients with resolved HBV infection. Patients with RD treated with a dose of  $\geq 5$  mg/day prednisolone and/or synthetic or biological ISDs with negative HB virus surface antigen and positive anti-HB virus surface antibody (HBsAb) and/or anti-HB virus core antibody (HBcAb) were enrolled. Quantitative HBV DNA results and related data were regularly recorded.

**Results** Among 1042 patients, including 959 with rheumatoid arthritis, HBV DNA was detected in 35 (1.93/100 person-years), with  $>2.1$  log copies/mL observed in 10 patients (0.55/100 person-years). None of the reactivated patients, including seven treated with a nucleic acid analogue, showed overt hepatitis. Low HBsAb titres and advanced age seemed to be risk factors for HBV reactivation; however, reactivation was observed in three patients with positive HBsAb and negative HBcAb test results. The risk of reactivation was lower with methotrexate but higher with prednisolone among the different types of ISDs. The intervals from the start of ISD to reactivation were relatively long (3–182 months; median, 66 months).

**Conclusions** The incidence of HBV reactivation with ISD use was 1.93/100 person-years in patients with RD with resolved HBV infection. No overt hepatitis was observed in the reactivated patients.

**INTRODUCTION**

It is estimated that approximately 350 million people are infected with the hepatitis B virus (HBV) worldwide and that one-third of the world's population is presently infected or has a history of past HBV infection. End-stage liver disease related to HBV is responsible for over 0.5–1 million deaths per year.<sup>1</sup>

HBV infection is responsible for 40.2%, and HBV reactivation due to immunosuppressive drugs (ISDs) has been observed in 6.8%, of fulminant hepatitis cases in Japan.<sup>2</sup> Because HBV reactivation could be caused by biological or non-biological disease-modifying antirheumatic drugs (DMARDs),<sup>3</sup> HBV infection is a serious problem for rheumatologists. HBV reactivation occurs in two forms: one involves the harmful proliferation of virus seen in HB virus surface antigen (HBsAg)-positive people, healthy carriers or patients with chronic HBV hepatitis and the other is seen in people with occult HBV infection who are HBsAg-negative and anti-HB virus core antibody (HBcAb)-positive and/or anti-HB virus surface antibody (HBsAb)-positive. Even though the latter is less frequently seen than the former, strict monitoring and preventive treatment are recommended by guidelines in the USA,<sup>4</sup> Europe,<sup>1</sup> Asia-Pacific<sup>5</sup> and Japan.<sup>6–8</sup>

Because the prevalence of resolved HBV infection in Japan (23.2%) is much higher than that in Western countries,<sup>9</sup> all patients with rheumatoid arthritis (RA) and other rheumatic diseases (RDs) in Japan who receive immunosuppressive DMARDs, including methotrexate (MTX), leflunomide (LEF), tacrolimus (TAC), mizoribine (MZB), corticosteroids and biological DMARDs, are recommended to be screened and managed according to the guideline developed by the Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology.<sup>7</sup> Patients with negative HBsAg results should be screened for HBsAb and HBcAb. If the result for either of these antibodies is positive, the patient needs to be monitored for HBV DNA (using reverse transcription (RT)-PCR) every 1–3 months.

Because the guideline has been strictly followed in Japan, the costs for HBV DNA monitoring and preventive treatment with nucleic acid analogues (NAAs) have been increasing. However, there is insufficient clinical evidence to support the concepts of the guideline currently, and its effectiveness for preventing fatal hepatic damage is unknown.

Our objective was to elucidate the frequency and risk factors for HBV reactivation in patients with resolved HBV infection and RD.



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## METHODS

This multicentre, observational, prospective study was conducted by a study group consisting of rheumatologists in Japanese Red Cross hospitals beginning in 2013 and spanning 2 years.

## Subjects

Patients eligible for enrolment were those with RA or other RDs, over 18 years of age and attending a clinic for RDs in one of the 16 Japanese Red Cross hospitals in Japan. Patients being treated with corticosteroids ( $\geq 5$  mg of prednisolone or its equivalent dose); immunosuppressive synthetic DMARDs, namely MTX, LEF, TAC, MZB or its equivalent and/or biological DMARDs, namely infliximab, etanercept, adalimumab, tocilizumab, abatacept, golimumab and certolizumab pegol were tested for HBsAg, HBsAb and HBcAb using chemiluminescent immunoassays. Patients with negative HBsAg ( $< 0.05$  IU/mL) and positive HBsAb ( $\geq 10.0$  mIU/mL) and/or positive HBcAb ( $\geq 1.0$  S/CO (sample/cut-off)) results were tested for HBV DNA with RT-PCR, and those with negative results were enrolled. Patients positive for HBsAb alone need HBV DNA monitoring except those with a history of HBV vaccination according to the Japanese Society of Hepatology guideline for the management of HBV infection,<sup>7</sup> as HBV reactivation is reported in such patients.<sup>10 11</sup> We excluded patients with positive HBsAb and negative HBcAb with a history of vaccination from this study.

## Registration

All data of the enrolled patients were recorded anonymously and sent to the Japanese Red Cross Kyoto Daiichi Hospital Centre for Rheumatic Disease as password-protected digital information. The initial data collection was conducted from February 2013 to October 2014 and included the following information: basic patient characteristics, such as age, sex and disease duration; data related to hepatitis, such as HBsAg, HBsAb and HBcAb titres and aspartate transaminase and alanine transaminase levels within the last 3 months; immunological data, such as blood lymphocyte count and serum IgG levels; parameters related to disease activity, such as tender and swollen joints, Global Visual Analogue Scale score, Disease Activity Score 28, C reactive protein level and erythrocyte sedimentation rate and information about medications, such as dose of steroids and MTX and use or no use of a biologic or other ISDs. After the second year, serial results of quantitation of HBV DNA measured by RT-PCR, immunological data, parameters related to disease activity and medication information were recorded.

## Primary and secondary end-points

We defined HBV reactivation as a positive conversion of HBV DNA measured using RT-PCR and included unquantifiable cases with positivity  $< 2.1$  log copies/mL. We consulted a hepatologist regarding the guidelines<sup>6-8</sup> for cases with positivity  $\geq 2.1$  log copies/mL and administered NAA if necessary without stopping ISDs. The primary end-point of this study was the frequency of HBV reactivation in HBsAg-negative and HBsAb-positive and/or HBcAb-positive patients with RD. We also examined risk factors for HBV reactivation and analysed the clinical and serological course after the reactivation as secondary end-points.

## Statistical analysis

We analysed the primary end-point, which is the frequency of HBV reactivation in person/years. We used univariate Poisson

regression analysis to evaluate risk factors for HBV reactivation and calculate risk ratios and its 95% CIs. We did not use multivariate analysis because the number of events was too small for analysis in a multivariate fashion.

## Ethics

In this study, we evaluated only information that is collected in usual medical practice, and we substituted the agreement acquisition in the document with posting based on 'Ethical Guidelines for Epidemiological Research'.<sup>12</sup>

## RESULTS

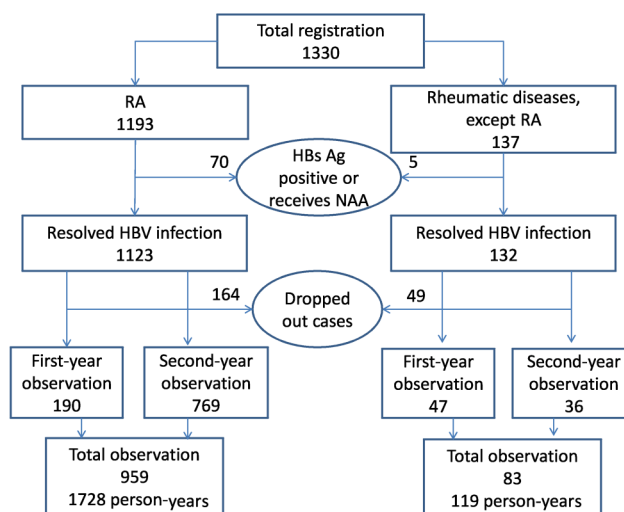
## Characteristics of enrolled patients

Of 1330 patients, 1193 patients with RA and 137 other patients with RD, initially enrolled, 75 patients who were HBsAg-positive or who received NAA were excluded. We then excluded 213 other patients who dropped out for various reasons, including non-attendance, unrelated death or inadequate HBV DNA monitoring. Finally, we analysed 805 cases observed for 24 months and 237 patients observed for 12 months (figure 1). The characteristics of the enrolled patients at the initial registration are shown in table 1. The average dose of prednisolone in other patients with RD was more than twice the dose in patients with RA. In the RA group, the majority of patients were treated with MTX, and almost one-third used biologics, most (73.7%) of which were tumour necrosis factor (TNF) inhibitors. Other than MTX, TAC and MZB were used as ISDs in patients with RA.

The results regarding the presence of HBsAb and HBcAb are shown in table 2. The majority of patients were positive for both antibodies.

## Incidence of HBV reactivation

HBV reactivation, as defined by positivity of HBV DNA, was found in 32 patients with RA and 3 with other RDs (in 1815 person-years) (table 3), and positivity  $\geq 2.1$  log copies/mL was seen in 8 patients with RA and 2 with other RDs (in 1831 person-years). Therefore, the frequency of HBV reactivation was calculated to be 1.93/100 person-years, and the frequency of quantitative positivity ( $\geq 2.1$  log copies/mL) was 0.55/100 person-years. Seven of these patients were started on NAA



**Figure 1** Flow diagram of patient selection. HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; NAA, nucleic acid analogue; RA, rheumatoid arthritis.

**Table 1** Demographic features of enrolled patients at registration

	RA	Other RDs	Total
Patients (n)	959	83	1042
Age, years (median, IQR)	24–93 (69, 13)	40–92 (70, 16)	10–93 (69, 13.25)
Sex, female/male	257/702 (73.2)	27/57 (67.9)	284/759 (72.8)
Disease duration, months (median, IQR)	1–697 (98, 130)	3–350 (43, 76)	1–697 (93.5, 128)
<b>Prednisolone</b>			
Patients (n) (%)	373 (38.9)	81 (97.6)	454 (43.6)
Average dose, mg/day	4.02	9.03	5.10
≥5 mg, number (%)	186 (19.4)	71 (85.5)	257 (24.7)
<b>Biologic DMARDs, number (%)</b>			
Etanercept	103		
Infliximab	34		
Adalimumab	33		
Tocilizumab	48		
Abatacept	24		
Golimumab	29		
Others	3		
<b>Methotrexate</b>			
Patients (n) (%)	751 (79.1)	17 (18.9)	
Average dose, mg/week	7.52		
Other ISDs (%)	154 (16.2)	32 (35.6)	
Tacrolimus	122	10	
Mizoribine	28	8	
Leflunomide	6		
Azathiopurine		10	
Others		3	

Patients with other RDs, including 24 patients with polymyalgia rheumatica, 15 with systemic lupus erythematosus, 15 with vasculitis syndrome, 7 with myositis and 22 with others. DMARDs, disease-modifying antirheumatic drugs; ISDs, immunosuppressive drugs; RA, rheumatoid arthritis; RD, rheumatic disease.

**Table 2** HBV-related antibodies in enrolled patients

Group	HBcAb-negative, number (%)	HBsAb-positive, number (%)	Total
<b>HBsAb-negative number (%)</b>			
RA	0	177	177
Other RDs	0	13	13
Total*	0	190 (18.2)	190 (18.2)
<b>HBsAb-positive number (%)</b>			
RA	109	673	782
Other RDs	18	52	70
Total*	127 (12.2)	725 (69.6)	852 (81.8)
Total	127 (12.2)	915 (87.8)	1042

In the table, 'Total\*' indicates the total number of patients in the upper two columns, RA and other RDs. HBcAb, hepatitis B virus core antibody; HBsAb, hepatitis B virus surface antibody; HBV, hepatitis B virus; RA, rheumatoid arthritis; RD, rheumatic disease.

medication, and none of the patients with HBV reactivation showed hepatic dysfunction during our observation. The incidence of reactivation in patients with negative HBsAb, 4.32/100 person-years, was higher than the patients with negative HBcAb or positive both antibodies, 1.36/100 person-years and 1.42/100 person-years, respectively (see online supplementary table S1).

### Analysis of risk factors for HBV reactivation

According to the Poisson regression analysis for investigation of risk factors for HBV reactivation, the risk ratio of a low HBsAb

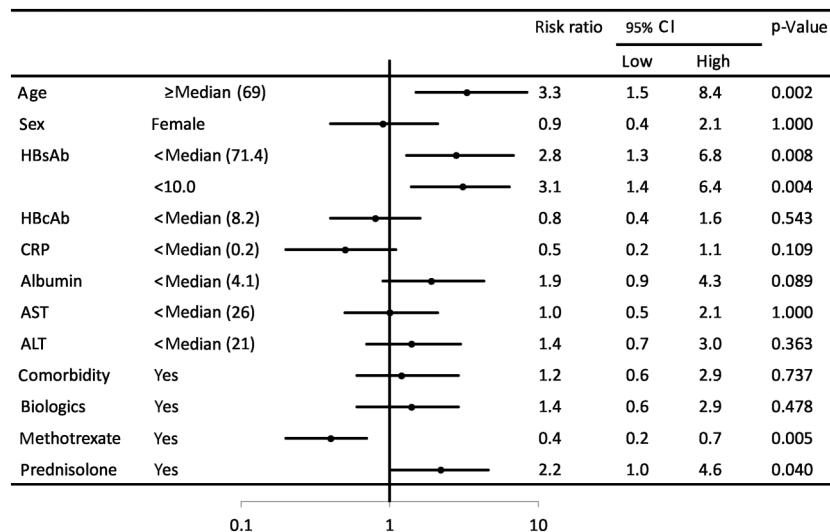
**Table 3** Incidence of HBV reactivation in the first year and second year in patients with RA and other RDs

Group	Year of observation	Cases (n)	Sample size (person-years)	Incidence (/100 person-years)	Use of NAA
<b>Reactivated cases</b>					
RA	First	22	959	2.29	3
	Second	10	740	1.35	3
Other RDs	First	3	83	3.61	0
	Second	0	33	0	1
Total		35	1815	1.93	7
<b>Cases with HBV DNA ≥2.1 log copies/mL</b>					
RA	First	4	959	0.42	2
	Second	4	755	0.5	3
Other RDs	First	2	83	2.41	0
	Second	0	34	0	1
Total		10	1831	0.55	6

HBV, hepatitis B virus; NAA, nucleic acid analogue; RA, rheumatoid arthritis; RDs, rheumatic diseases.

titre below the median (71.4) was 2.8 (95% CI 1.3 to 6.8) and below the cut-off (titre <10.0) was 3.1 (95% CI 1.4 to 6.4). Advanced age over the median (69 years old) increased the risk to 3.3 (95% CI 1.5 to 8.4). Patients treated with MTX showed low risk ratios but those treated with prednisolone showed high risk ratios of 0.4 (95% CI 0.2 to 0.7) and 2.2 (95% CI 1.0 to 4.6), respectively (figure 2).

**Figure 2** Risk ratios of clinical indicators for hepatitis B virus reactivation. The forest plot shows the risk ratios and 95% CIs of clinical parameters calculated by univariate Poisson regression analysis for HBV reactivation. ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; HBcAb, hepatitis B virus core antibody; HBsAb, hepatitis B virus surface antibody.



### Clinical course of HBV reactivation

The interval between the beginning of ISDs and HBV reactivation ranged from 3 to 182 months (average, 66.2 months; median, 66 months; IQR, 60) in 35 reactivated cases (table 4). In 21 cases of HBV reactivation that we were able to observe 1 year later, NAA was started in seven cases, cases 2, 3, 4, 6, 7, 22 and 34, and has not yet been started in cases 5 and 33 with the increasing of HBV DNA in 1-year observation. HBV DNA spontaneously turned negative in six patients, cases 13–18, who were not administered NAA, and no deterioration was observed in the other six cases. HBV DNA negative conversion occurred immediately in all cases in which NAA was administered after the reactivation.

### DISCUSSION

Some small-sized clinical studies of HBV reactivation in patients with RD with resolved infection were reported (see online supplementary table S2).<sup>13–26</sup> The incidence of reactivation in Japan (2–5.3%) is higher than that found in other south-eastern Asian countries (1.4–2.1%). In the reports from Europe, mainly in the cases for which TNF blockers were used, HBV reactivation was not found. In two systematic reviews, the incidence of HBV reactivation was reported as 5.4% and 1.7%, respectively. Differences in the prevalence of HBV infection and in the viral genotype or interval of HBV DNA monitoring could account for the differences in the incidence of reactivation among these countries.

In our study, the frequency of reactivation in patients with resolved HBV infection on immunosuppressive therapy for RD was 1.93/100 person-years, and >2.1 log copies/mL was observed in 0.55/100 person-years over 1–2 years of observation. Seven patients were treated with NAA and none developed overt hepatic damage. Although the frequency of HBV reactivation in patients with RD was lower in this study than in previous reports, it cannot be neglected as a complication of immunosuppressive therapy in RA and other RDs. On the other hand, the fact that overt hepatitis was not found in any of the reactivated cases shows that the prognosis of HBV reactivation is not always poor in RDs during a short-term follow-up.

Although a low HBsAb titre has been considered a candidate risk factor for HBV reactivation,<sup>1 3</sup> we had no direct evidence to support this idea. However, our results show that low HBsAb titres at baseline were significant risk factors for HBV

reactivation. On the other hand, HBV reactivation was seen in eight cases with HBsAb titres higher than 100 mIU/mL and in three cases negative for HBcAb (see table 4 and online supplementary table S1). We should realise that although HBsAb is a neutralising antibody against HBsAg, it cannot completely prevent HBV reactivation in patients with RD. Although screening for resolved HBV infection only in those with positive HBcAb is recommended in some guidelines,<sup>1 4</sup> revision may be necessary considering the risk of reactivation in cases negative for HBcAb.

ISDs, that is, biologics, steroids, MTX and other synthetic DMARDs used for RD, can cause HBV reactivation. To evaluate the risk for reactivation for each drug is very important in order to stratify the patients to prevent HBV reactivation. According to a case-control study based on US Food and Drug Administration registration of patients with RA<sup>27</sup> the OR for HBV reactivation for steroids was 2.3, and the OR for TNF blockers was significantly lower than that for steroids or MTX. In our study, we showed the risk ratio of MTX was low and that of prednisolone was high among these groups of drugs. The discrepancy about the risk of MTX between these studies may be caused by the doses of MTX, which tend to be lower in Japan than in the USA or the combinations of drugs are variable in daily clinical practice. Since the results at this time are not enough to precisely evaluate the risk of each drug, we will continue this study to obtain more data for risk factor analysis.

HBV reactivation in patients with ISDs frequently evokes fulminant hepatitis, and its prognosis is very poor,<sup>28</sup> which is why careful follow-up and early preventive treatment are necessary for these patients. From the results of our study, the clinical course after reactivation in patients with RD was not very aggressive in either group of patients with and without NAA treatment, and a non-progressive course or spontaneous improvement was frequently seen, especially in cases with HBV DNA of <2.1 log copies/mL. These results support the effectiveness of preventive treatment with NAA in reactivated patients and the possibility that the cut-off value of HBV DNA for preventive therapy could be set at higher level.

HBV reactivation is supposed to have occurred in short term after the start of ISDs. Our study shows the interval between the start of ISD and reactivation ranged from 3 to 182 months (median, 66 months), which is longer than that reported in a previous study. Mochida *et al*<sup>22</sup> reported that the cumulative reactivation rate was 3.2% at 6 months, and the increase of the

**Table 4** Characteristics of 35 HBV reactivated cases

No.	Diagnosis	Sex	Age (years)	Disease duration (months)	HBV DNA titre (log copies/mL)	NAA	Clinical course	HBsAb (mIU/ml)	HbCAb (S/CO)	Interval (months)	Medication
1	RA	F	81	16	2.6	–	–	222.6	0.5	10	MTX
2	RA	M	76	95	2.3	+	Worse	2.16	12	36	PSL
3	RA	M	86	303	7.1	+	Stable	25.5	10.3	30	ABC
4	RA	F	80	133	2.5	+	Stable	73.8	0.5	131	MTX
5	RA	F	60	85	2.3	–	Worse	124.7	1.16	5	TAC
6	RA	F	81	63	9.1	+	Worse	3.1	10.2	74	PSL
7	RA	F	70	6	3.5	+	Worse	28.6	9.01	138	PSL, MTX
8	RA	M	51	135	<2.1	–	Stable	0.5	8.54	86	TCZ, MTX
9	RA	F	71	220	<2.1	–	Stable	4.1	37.7	101	IFX, MTX
10	RA	F	80	64	<2.1	–	Stable	1000	95.6	52	MTX
11	RA	M	79	73	<2.1	–	Stable	11.8	19.1	73	MTX
12	RA	M	70	10	<2.1	–	Stable	113.5	19.3	14	PSL, TAC
13	RA	F	70	59	<2.1	–	Better	851	2.2	38	ADA, MTX
14	RA	F	73	409	<2.1	–	Better	13.5	7.12	27	ABC, MTX
15	RA	F	77	64	<2.1	–	Better	9.5	5	50	GLM, MTX
16	RA	F	76	141	<2.1	–	Better		12.63	157	MTX
17	RA	M	65	205	<2.1	–	Better	50.2	27.9	148	ETA, PSL
18	RA	F	72	201	<2.1	–	Better	147	0.5	3	GLM, PSL, MTX
19	RA	F	83	6	<2.1	–	–	45	10.15	14	ETA
20	RA	F	76	11	<2.1	–	–	10.8	1.23	19	MZB
21	RA	F	85	23	<2.1	–	–	47.1	6.04	32	PSL, MTX
22	RA	F	65	112	<2.1	+	Stable	5.7	8.96	90	MTX
23	RA	F	75	505	2.3	–	–	0.4	98.5	83	MZB
24	RA	F	72	39	<2.1	–	–	24.9	29.9	73	IFX, MTX
25	RA	F	67	193	<2.1	–	–	0	5.13	38	ABC, MTX
26	RA	M	75	35	<2.1	–	–	0	9.14	66	MTX
27	RA	F	81	434	<2.1	–	–	1.9	8.62	56	MZB
28	RA	M	76	65	<2.1	–	–	54.2	8.79	100	PSL
29	RA	F	84	157	<2.1	–	–	32.8	7.36	182	PSL
30	RA	F	82	614	<2.1	–	–	155.3	2.25	39	PSL
31	RA	F	66	171	<2.1	–	–	1000	5.71	87	MTX
32	RA	F	76	97	<2.1	–	–	1.4	88	12	GLM, PSL
33	PM	F	68	235	2.7	–	Stable	3.5	8.09	87	PSL
34	SLE	F	63	84	2.3	+	Worse	8.78	6.54	96	PSL
35	PMR	M	82	54	<2.1	–	Stable	0.4	12.1	70	PSL

Titres of HBsAb and HbCAb were collected at registration. 'Age', 'Disease duration', 'Medication' and 'Interval' between the beginning of immunosuppressive drugs and reactivation were at the point of reactivation. Administration of 'NAA' and 'Clinical course' was checked at the last observation. HBV DNA titre was the highest value during the observation period. In the column of 'clinical course', 'worse' means increase of HBV DNA and/or start of NAA, 'stable' and 'better' reveal 'unchanged' and 'decreased' HBV DNA levels without using NAA, respectively. The negative ranges of HBsAb and HbCAb are <10.0 mIU/mL and <1.0 S/CO, respectively.

ABC, abatacept; ADA, adalimumab; ETA, etanercept; F, female; GLM, golimumab; HbCAb, hepatitis B virus core antibody; HBsAb, hepatitis B virus surface antibody; HBV, hepatitis B virus; IFX, infliximab; M, male; MTX, methotrexate; MZB, mizoribine; NAA, nucleic acid analogue; PM, polymyositis; PMR, polymyalgia rheumatica; PSL, prednisolone; RA, rheumatoid arthritis; S/CO, sample/cut-off; SLE, systemic lupus erythematosus; TAC, tacrolimus; TCZ, tocilizumab.

rate at 48 months compared with that at 6 months was +1.5%. We must consider that, compared with cancer chemotherapy, treatment with ISDs in RDs usually results in patients being in a lower-grade and longer-term immunosuppressive state. The difference between intensity and duration of immunosuppression may be the basis of the differences in the pathophysiology of HBV reactivation.

As a limitation of this study, the risk and latency of immunosuppression caused by ISDs to HBV reactivation could not be accurately estimated for two reasons. First, we enrolled patients who were just starting ISDs and who were also already given ISDs. Second, the dosage and combination of ISDs were changed in many enrolled cases after the start of medication. Although it has been suggested that the clinical course of HBV reactivation in RD is different from that in cancer

chemotherapy, we could not clarify the frequency or pathophysiology of de novo hepatitis due to viral replication in RD. As this may be a limitation of our study design (observational cohort study), we should consider a randomised control study to clarify the clinical question.

## CONCLUSIONS

The incidence of HBV reactivation in patients with RD with resolved HBV infection was 1.93/100 person-years, and the incidence of quantitative HBV DNA positivity was 0.55/100 person-years. None evoked clinical hepatitis in reactivated patients.

Low titres or negative HBsAb and advanced age were risk factors in HBV reactivation in patients with RD, but in patients with high HBsAb titres and negative HbCAb, the possibility of

HBV reactivation could not be excluded. The risk ratio of MTX for HBV reactivation was lower than that of steroid and biologics.

The intervals from the start of ISD to HBV reactivation were variable, and the clinical course after reactivation was not always aggressive.

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