Incidence and clinical characteristics of hepatitis B virus reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for rheumatoid arthritis

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Abstract

Objective

To analyse the incidence, clinical characteristics, and prognosis of patients with rheumatoid arthritis (RA) and hepatitis B virus (HBV) surface antigen negative/core antibody positive serostatus (HBsAg-/HBcAb+), who underwent rituximab therapy and developed HBV reactivation.

Methods

Medical records of RA patients with different HBV serostatus who received rituximab from January 2000 through January 2015 were reviewed. Case notes of four HBsAg-/HBcAb+ patients with RA who had HBV reactivation during treatment with rituximab were excerpted and summarised. We also searched the Medline (PubMed) database to identify published reports of other HBsAg-/HBcAb+ RA patients who likewise developed HBV reactivation during rituximab treatment.

Results

The study cohort comprised 54 RA patients who received rituximab, of whom 44 (81.5%) were HBsAg-/HBcAb+ whilst receiving rituximab. Four HBsAg-/HBcAb+ patients had HBV reactivations during rituximab therapy; thus, the incidence of HBV reactivation in the HBsAg-/HBcAb+ group was 9.1%. The literature search discovered another three cases, making a total of at least seven known rituximab-treated HBsAg-/HBcAb+ RA patients who have developed HBV reactivation. The mean duration from the first rituximab infusion to HBV reactivation was 25.4±4.6 months; no fatalities occurred.

Conclusion

Approximately 9% of Taiwanese RA patients with HBsAg-/HBcAb+ serostatus had HBV reactivation around 2 years after starting regular rituximab therapy; they all had a relatively good prognosis.

Key words

rheumatoid arthritis, hepatitis B virus, virus activation, rituximab

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Introduction

Hepatitis B virus (HBV) infection is common and currently affects more than one-third of the world's population. Hepatitis B is endemic in Taiwan, where 15–20% of the population test HBV surface antigen positive (HBsAg+) and HBV core antibody positive (HBcAb+) seroprevalence was 80–90% before universal newborn immunisation was initiated in 1986 (1).

Rituximab is a monoclonal antibody that acts against CD20 B-cells; it is approved for treating B-cell lymphoma and certain autoimmune diseases, including rheumatoid arthritis (RA) (2, 3), and it is increasingly used for other chronic inflammatory diseases (4). It is well known that HBsAg+ patients with hematological malignancies, such as lymphoma and autoimmune diseases, who receive rituximab therapy are at high risk of HBV reactivation; therefore, antiviral prophylaxis for HBsAg+ patients undergoing immunosuppressant therapy is becoming standard practice (5, 6). Moreover, cases of HBV reactivation have even been reported in HBsAg-negative (HBsAg-) patients after rituximab-based chemotherapy for lymphoma, most of whom were HBcAb+ (7, 8). Higher incidence of HBV reactivation in HBsAg-/HBcAb+ patients with lymphoma has been reported in those receiving rituximab-containing chemotherapy (23.8–41.5%) (7, 9) compared to rates with conventional chemotherapy (1.0–2.7%) (8). However, there are limited data on HBV reactivation in patients with autoimmune diseases such as RA who are HBsAg-/HBcAb+ and being treated with rituximab (10-12). There are significant disparities between patients with RA and lymphoma in terms of the dose and infusion regimen of rituximab, the prescription of concomitant medications, and the underlying disease itself. Therefore, data are lacking on the characteristics of patients with HBV reactivation and its incidence among RA patients receiving rituximab.

We conducted this retrospective study to investigate the incidence and prognosis of HBV reactivation, and their relationship with rituximab therapy, in RA patients with different HBV serostatus. We also reviewed the literature and our cohort for cases of RA patients who were HBsAg-/HBcAb+ and who had HBV reactivation during rituximab therapy.

Materials and methods

Study population and definitions

Medical charts of 54 patients who received rituximab treatment for RA from January 2000 through January 2015 were reviewed. In accordance with Taiwan National Health Insurance Administration policy, rituximab was prescribed as second-line therapy for RA patients who had failed treatment with another biological agent; therefore, most of these 54 patients had already received at least one other biologic. All were HBsAg- when they received the first dose of rituximab therapy. They were grouped according to HBV serostatus: HBsAg-/HBcAb+; HBsAg-/HBcAb-negative (HBcAb-)/HBV surface antibody positive (HBsAb+); and HBsAg-/HBcAb-/HBsAb-negative (HBsAb-). We defined HBV reactivation as a change from HBsAg- to HBsAg+ serostatus, a ≥10-fold increase in HBV DNA level above baseline, or an absolute increase of more than 10^5 copies/mL in the HBV DNA level. Hepatitis was defined as a three-fold or more increase in alanine aminotransferase (ALT) above the upper limit of the normal range, which is 40 international units (IU) per litre (1). The Institutional Review Board of Changhua Christian Hospital reviewed and approved this protocol, and each patient included in the study provided written informed consent.

Serology

The presence of HBsAg, HBcAb, and HBsAb were ascertained using chemiluminescent microparticle immunoassays (Architect i2000sr System, Abbott Laboratories, Abbott Park, Illinois, USA). Serum HBV DNA was quantified using an Abbott RealTimeTM HBV system (Abbott m2000rt RealTime system, Abbott Laboratories, Abbott Park, Illinois, USA).

Literature search strategy

We searched the Medline database

(PubMed, National Library of Medicine, Bethesda, MD, USA) using the search terms: "rheumatoid arthritis" AND "hepatitis" AND "rituximab", to recover articles that included HBsAg- patients with RA being treated with rituximab who developed HBV reactivation; the search cut-off date was 31 December 2015.

Results

Characteristics of study population

Figure 1 and Table I show the HBV status and background characteristics of 54 RA patients who received rituximab therapy during the retrospective observation period. All four patients who developed HBV reactivation during rituximab therapy were HBsAg-/HBcAb+, giving an incidence of 9.1%. No HBV reactivation was evident in groups with other HBV serology profiles.

There were no significant differences between HBsAg-/HBcAb+ patients with *versus* without HBV reactivation in terms of age, sex, disease duration, concomitant use and cumulative dose of methotrexate and prednisolone during rituximab therapy, prior use of biologics, or the infused dose of rituximab (data not shown).

Cases of HBV reactivation during rituximab therapy

Our literature search identified only three additional cases of HBV reactivation in RA patients with HBsAg- serostatus following rituximab treatment, all of whom were HBcAb+ before initiating rituximab therapy (10-12). Table II shows the detailed characteristics of these three cases from the literature and the four identified in this study cohort. Four (57.1%) were female, and the mean age at HBV reactivation was 67.7±10.2 years (range 57–80 years). Concomitant medications used to treat RA at the time of HBV reactivation included: prednisolone (five patients, mean dose 9.0±4.2 mg/day); methotrexate (four patients, mean dose 11.9±3.8 mg/week); and leflunomide (one patient, 20 mg/day). All of the patients received rituximab therapy in cycles comprising two 1000 mg doses given intravenously 2 weeks apart, and repeated at least every 6–12 months, as necessary. Most developed HBV reactivation approximately 2 years after initiating rituximab therapy, with a mean duration from the first rituximab infusion to HBV reactivation of 25.4±4.6 months (range 17–32 months). Discontinuing rituximab treatment and the prescription of antiviral agents resulted in good outcomes with no cases of mortality.

Case 1

A 57-year-old woman, diagnosed with RA in 2007, was treated with etanercept from November 2009 to May 2010; due to a poor response, she started rituximab in June 2010, before which she was HBsAg-. She received three cycles, each comprising two doses of rituximab 1000 mg given 2 weeks apart, at regular 6-month intervals. In June 2012, 10 months after completing the last cycle in August 2011, routine blood tests showed an elevated ALT level (1069 IU/mL), and serology results showed HBsAg+ with a high HBV load (24037343 IU/mL; 7.38 log IU/

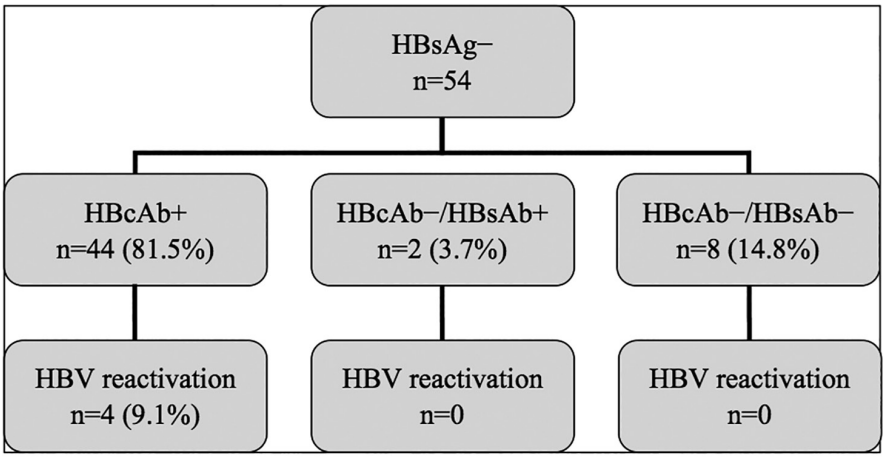

Fig. 1. Hepatitis outcomes of HBsAg-negative patients receiving rituximab for RA.
Flowchart shows the hepatitis B virus (HBV) infection serostatus distribution at baseline and the development of HBV reactivation in 54 rheumatoid arthritis (RA) patients who were treated with rituximab. HBsAg, HBV surface antigen; HBcAb, antibody against HBV core antigen; HBsAb, antibody against HBV surface antigen.

Table I. Characteristics of 54 HBsAg-negative patients receiving rituximab for RA.

Data values show: mean±SD [n][a]; or number (%)	HBsAg-/HBcAb+ (n=44)	HBsAg-/HBcAb-/HBsAb+ (n=2)	HBsAg-/HBcAb-/HBsAb- (n=8)
Age (years)	58.9 ± 9.8	67.6 ± 14.3	42.5 ± 15.3
Female	38 (86.4)	0 (0)	8 (100)
Disease duration (years)	7.9 ± 5.5 [36]	1.5 [1]	4.3 ± 3.0 [7]
Follow-up from first RTX (years)	3.4 ± 1.7	6.1 ± 0.8	3.5 ± 1.8
Prednisolone dose (mg/day)[b]	6.0 ± 2.4 [43]	4.5 ± 0.4	6.1 ± 3.6
Cumulative prednisolone dose (mg)[b]	7733.5 ± 4019.6 [43]	94747.5 ± 540.9	6250.0 ± 3700.9
MTX dose (mg/week)[b]	12.2 ± 4.2 [37]	3.6 [1]	12.8 ± 7.9 [7]
Cumulative MTX dose (mg)[b]	2107.0 ± 1206.3 [37]	1232.5 [1]	2578.6 ± 1992.9 [7]
Number who previously used:			
Etanercept	31	1	6
Adalimumab	11	0	1
Golimumab	3	0	1
Abatacept	2	0	1
RTX cycles	4.4 ± 2.5	5.5 ± 4.9	5.0 ± 3.3
Cumulative RTX dose (mg)	8215.9 ± 4743.9	9250.0 ± 7424.6	11812.5 ± 9281.1

[a]Number of patients, where data from fewer than all were available for analysis.
[b]During rituximab therapy.
HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBcAb: antibody against HBV core antigen; HBsAb: antibody against HBV surface antigen; RA: rheumatoid arthritis; RTX: rituximab; MTX: methotrexate.

Table II. Clinical features of HBsAg-/HBcAb+ patients with RA who developed HBV reactivation during rituximab therapy.

Patient (data source)	Age[a] (years)	Sex	Co-morbidity	Prior biologic therapy	Concomitant immuno-suppressants	Time to HBV reactivation (months)		RTX cycle	Cumul-ative RTX dose (mg)	Clinical findings at at time of HBV reactivation			Treatment for HBV reactivation	Outcome
						From first RTX	From last RTX			HBV DNA (log U/ml)	Peak ALT (IU/mL)	Bil-T (mg/dL)		
1 (Ghrénassia 2012)[10]	80	M	Low-grade mantle B-cell lymphoma	IFX	Pd 10 mg/day	27	3	5	10000	>7	421	NR	Entecavir	Alive & well
2 (Salman-Monte 2014)[11]	77	M	NR	IFX, ETA	Pd 15 mg/day	17	9	2	4000	>8	349	0.7	Entecavir	Alive & well
3 (Gigi 2013)[12]	64	F	NR	NR	MTX 10 mg/week	24	NR	4	9000	>8	605	NR	Entecavir	Alive & well
4 (Case 1)	57	F	Osteoporosis	ETA	Pd 5 mg/day, MTX 7.5 mg/week	24	10	3	6000	>7	1069	17.45	Entecavir	Alive & well
5 (Case 2)	59	F	Hypertension	ETA	Pd 5mg/day, MTX 15 mg/week	27	2	4	8000	5	1105	1.62	Tenofovir	Alive & well
6 (Case 3)	78	F	Latent tuberculosis	ADA	LEF 20 mg/day	27	0.5	5	9000	>8	218	0.48	Entecavir	Alive & well
7 (Case 4)	59	M	No	ETA	MTX 15 mg/week	32	8	4	8000	>8	25	0.4	Entecavir	Alive & well

[a]At time of HBV reactivation.
HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBcAb: antibody against HBV core antigen; RA: rheumatoid arthritis; ALT: alanine aminotransferase; IU: international units; Bil-T: total-bilirubin; M: male; F: female; IFX: Infliximab; ETA: etanercept; ADA: adalimumab; Pd: prednisolone; MTX: methotrexate; LEF: leflunomide; RTX: rituximab; NR: not reported.

mL). As these findings were consistent with HBV reactivation, entecavir was initiated and rituximab discontinued thereafter. Eight months later, the HBV viral load was undetectable (<1 log IU/mL) and the ALT level had normalised.

Case 2

A 59-year-old woman, diagnosed with RA in 2004, received etanercept from May 2005 to August 2009. She started rituximab infusion for RA in December 2009, before which she was HBsAg-; each cycle comprised two doses of rituximab 1000 mg given 2 weeks apart, with 6–12-month intervals between cycles, the last of which was administered in December 2011 (total four cycles). Two months after the last rituximab infusion, an elevated ALT level was found (1105 IU/mL) during a routine examination. At this time, her HBV serostatus became HBsAg+, with a high viral load (368806 IU/mL; 5.57 log IU/mL). Tenofovir was initiated and rituximab was no longer used. Seven months later, the HBV load was undetectable and ALT was normal.

Case 3

A 78-year-old woman was diagnosed with RA in 2003 and started on rituximab in June 2011, due to a lack of response to adalimumab; before receiving rituximab, she was HBsAg-. She received rituximab infusions at regular 6-month intervals, with each cycle consisting of two doses of rituximab 1000 mg given 2 weeks apart. Two weeks after the first dose of the fifth cycle, a mildly elevated ALT level was found (218 IU/mL) during a routine examination. Her serum HBsAg was found to be positive, with an HBV load of 272011239 IU/mL (8.43 log IU/mL). The second dose of the fifth cycle was not given, and entecavir was initiated. Two months later, her ALT level returned to normal, and 5 months after entecavir was initiated, the HBV load had decreased to 471 IU/mL (2.67 log IU/ml).

Case 4

A 59-year-old man, diagnosed with RA in 2005, was treated with etanercept from June 2010 to December 2010. She was HBsAg- before rituximab therapy, which was initiated in March 2011; each cycle comprised two 1000 mg doses that were given 2 weeks apart, with 6–12-month intervals per cycle, for a total of four cycles, the last being given in January 2012. Eight months after the last rituximab infusion, a routine evaluation showed normal transaminase level but HBsAg+ serostatus, with a high HBV load (105850020; 8.02 log IU/mL). Due to apparent HBV reactivation, entecavir was initiated and rituximab was not used thereafter. Six months later, the HBV load had decreased to 897 IU/mL (2.95 log IU/mL) and her transaminase remained normal.

Discussion

This is the first study to evaluate the incidence of HBV reactivation according to different HBV serostatus in patients receiving rituximab to treat RA, with a rate of 9.1% in 44 HBsAg-/HBcAb+ patients in Taiwan, most of whom developed HBV reactivation approximately 2 years after rituximab was initiated.

Previous studies that investigated patients who received rituximab-containing chemotherapy for lymphoma, reported HBV reactivation incidence rates of up to 23.8–41.5% in HBsAg-/HBcAb+ patients (7, 9), compared to zero HBV reactivation in HBcAb- patients. Most cases of HBV reactivation have been reported at the end or after completing rituximab-containing chemotherapy (8), with a mean time to HBV reactivation of 10.4±9.2 months

(range 1–45 months) from the first dose of rituximab (9, 13-17). Contrastingly, the incidence of HBV reactivation in our patients with RA was lower, with a much longer lag since the first dose of rituximab. These differences may be explained by differences in the rituximab infusion regimen and the underlying disease, despite using the same drug (rituximab): First, patients with lymphoma and RA have distinct rituximab infusion regimens; specifically, the dose for RA is much lower with less intensive infusion frequency compared to the regimen used for lymphoma. The typical regimen for lymphoma is 375 mg/m^2 on day 1 every 3 weeks for a total of 6–7 cycles, plus high-dose steroids and other anti-cancer agents (18). By comparison, our patients received the rituximab regimen recommended for RA, which comprises cycles of two 1000 mg doses given intravenously 2 weeks apart, and repeated after 6 months or later if necessary (3). Second, concomitant medications in our RA patients had lesser immunosuppressive and cytotoxic effects. It has been reported that regimens containing rituximab plus steroids carry a higher risk of HBV reactivation compared to conventional chemotherapy in patients with lymphoma (8). Patients with RA in our study received only prednisolone 0–15 mg, with or without a low dose of methotrexate or leflunomide, which is less cytotoxic than the concomitant high-dose steroids and other anti-cancer agents given to patients with lymphoma. Furthermore, patients with lymphoma also have different immune status than those with RA. In patients with lymphoma, the ability of cancer cells to evade destruction by the host immune system involves several immune evasion strategies to maintain an immunosuppressive microenvironment (19). In contrast, breakdown of immune tolerance and aberrant activation of innate and adaptive immune responses in patients with RA, leads to autoimmunity and ongoing systemic inflammation (20). We suggest that differences in basic immune responses between patients with lymphoma and RA may also interfere with the process of HBV reactivation. Therefore, many factors may affect the process of HBV reactivation in patients undergoing rituximab therapy, and further studies are warranted to elucidate the mechanism.

Many cases of fulminant hepatitis or liver failure (defined as an elevated ALT level with encephalopathy or coagulopathy) have been reported in patients with lymphoma who were HBsAg-/HBcAb+ and receiving rituximab (8, 17). The mortality rate due to liver failure after HBV reactivation in patients with lymphoma who are HBsAg-/HBcAb+ and receiving rituximab has been reported to be up to 50%, despite antiviral treatment (8). However, none of the seven cases described here had severe hepatic consequences, including encephalopathy or coagulopathy, and none died after HBV reactivation. Thus, unlike patients with lymphoma receiving rituximab-containing chemotherapy, outcomes following HBV reactivation in patients with RA while undergoing rituximab treatment appear to be better.

It is important to note that HBV reactivation rates may differ between populations: the incidence of HBV reactivation in HBcAb+ patients, is high in Asian countries where HBV is endemic but is relatively low in Europeans (21, 22). Incidences of HBV reactivation may vary for several reasons, including different patient or virologic characteristics, and geographic differences in HBV.

This study had several limitations. First, due to the retrospective design, lack of data on serial changes in serum HBsAb meant that we could not evaluate the possible protective role of HBsAb in patients with RA undergoing rituximab therapy. Second, there is currently no standard definition of HBV reactivation in patients who are HBsAg-/HBcAb+; we used the most common definition according to the literature review. However, without a standardised definition, direct comparisons of the incidence of HBV reactivation between studies should be interpreted with caution. Third, the small number of patients limited the statistical analysis, and we could not investigate the clinical factors associated with HBV reactivation in RA patients treated with rituximab who were HBsAg-/HBcAb+. Fourth, due to including only Asian patients, it is uncertain whether our findings apply to Europid patients. Validation studies in different patient populations are warranted.

Conclusions

The incidence of HBV reactivation in Taiwan among patients with RA who were HBsAg-/HBcAb+ and undergoing rituximab therapy, was 9.1%. Most developed HBV reactivation 2 years after initiating rituximab therapy. In such cases, discontinuing rituximab and prescribing antiviral agents generally had a good prognosis.

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