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Prevalence of Reactivation of Hepatitis B Virus DNA Replication in Rheumatoid Arthritis Patients

Yukitomo Urata[1], Ryoko Uesato[2] and Dai Tanaka[2]
[1]*Department of Rheumatology Seihoku Chuo Hospital, Gosyogawara,*
[2]*Department of Orthopaedic Surgery, Seihoku Chuo Hospital, Gosyogawara,*
Japan

1. Introduction

Hepatitis B virus and rheumatoid arthritis

More than one-third of the worldwide population is infected with hepatitis B virus (HBV), and 350 million individuals have chronic HBV infection [1], with 75% of those living in the Southeast Asia and Western Pacific regions. HBV infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) [2] and is estimated to be responsible for 500,000–700,000 deaths annually. Reactivation of hepatitis B in patients undergoing immunosuppressive therapy is a clinically important complication [3-5]. Hepatitis B reactivation can be transient and clinically silent but is often severe and results in acute hepatic failure.

Two clinical scenarios contribute to the reactivation of hepatitis B. The first occurs in patients with chronic hepatitis B. Fulminant HBV has been reported in hepatitis B surface antigen (HBsAg)-positive patients with rheumatoid arthritis (RA) taking tumor necrosis factor agents (TNFA) [6, 7].

Second, reactivation of hepatitis B occurs in patients with resolved hepatitis B. In these patients, low levels of HBV replication have been shown to persist in the liver and in peripheral blood mononuclear cells for decades [8-10], and reactivation occurs after transplantation, immunosuppressive therapy, and allogeneic and autologous hematopoietic stem-cell transplantation, with the reappearance of HBsAg [11-15]. Reactivation of hepatitis B can occur in RA patients with resolved hepatitis B who are on immunosuppressive therapy, including corticosteroids (CS), methotrexate (MTX) [16], and TNFA [17,18], and can result in fulminant or lethal hepatitis [4]. Optimal management practices for this group of patients are unclear [9].

We performed this study to determine the rate of reactivation of HBV DNA replication in RA patients with resolved hepatitis B.

2. Materials and methods

2.1 Patients and methods

In our departments, 516 patients who were treated for RA between January 2008 and August 2009 fulfilled the American College of Rheumatology 1987 revised criteria for RA.

All patients were evaluated for HBV markers, including HBsAg, anti-hepatitis B surface antibody (anti-HBs), and anti-hepatitis B core antibody (anti-HBc). HBV markers were detected using commercial enzyme immunoassays (HBsAg: ARCHITECT HBsAg QT, anti-HBs: ARCHITECT Anti-HBs, and anti-HBc: ARCHITECT Anti-HBc; Abbott Laboratories, Wiesbaden, Germany). If patients were HBsAg-positive or HBsAg-negative and anti-HBs- and/or anti-HBc-positive, HBV DNA levels were assessed. Sensitivity was 2 log copies/mL. When negative HBV DNA results were obtained, measurements were repeated every 3 months, and if HBV DNA became positive, measurements were repeated every month. Medications, including biologic agents, were generally not discontinued, irrespective of HBV DNA levels. All study protocols were approved by the ethics committees of the participating centers, and all patients provided written informed consent before enrolment.

2.2 Quantification of HBV DNA in blood by real-time PCR

HBV DNA levels were quantified using the automated COBAS TaqMan HBV Test version 2·0 (Roche, Basel, Switzerland). Samples were pretreated using the COBAS AmpliPrep System for amplification and quantification by real-time PCR and were analyzed using the COBAS TaqMan gene analyzer [19].

2.3 Statistical analysis

The Fisher's exact test, Student's *t*-test, and Mann–Whitney *U* test were used to compare baseline patient characteristics between subgroups. Two-tailed values of $p \leq 0.05$ were regarded as significant. Cox regression hazard analyses were used to separately investigate the influence of biologic agents, MTX, CS, and disease-modifying antirheumatic drugs (DMARDs) on reactivation of HBV DNA replication. To identify the relative important of these factors, we performed a stepwise forward elimination multiple logistic regression model. All analyses were performed using JMP version 8.0 software (JMP Japan, Tokyo, Japan).

3. Results

Background characteristics of the 516 patients are listed in Table 1. Seven patients were HBsAg-positive, while 157 were HBsAg-negative and anti-HBs- and/or anti-HBc-positive (30.4%). No resolved hepatitis B patients were positive for HBV DNA at baseline.

Subjects were followed for 18 months, and HBV DNA became positive (3.44 log copies/mL) in 13 of 157 patients (8.3%), whereas hepatic function remained normal in all cases (Table 1). Details of patients developing reactivation of HBV DNA replication are listed in Table 2; 1 patient developed reactivation of HBV DNA replication twice, 10 patients showed HBV DNA replication during biologic agent therapy [etanercept (ETN), n = 8; abatacept, n = 2; adalimumab, n = 1; infliximab, n = 1; tocilizumab, n = 1; and rituximab, n = 1], whereas 3 patient showed replication without biologic agent therapy. Types of DMARDs and immunosuppressants used for RA treatment during the study and numbers of patients being administered each pharmacotherapy are shown in Table 3. In 2 of the 13 patients, HBV DNA became negative without therapy. In 10 of the 13 patients, HBV DNA became negative with entecavir therapy (mean, 3.3 months). In the remaining 1 patient, after HBV DNA became positive, she suddenly died due to unknown causes.

Exploratory analysis was conducted on factors that were potentially associated with HBV replication development (Table 3). Among resolved hepatitis B patients who did and did not

Baseline demographic, clinical, and laboratory characteristics	HBV replication (+)	HBV replication (-)	*P* value
n	13	144	
Age, years (mean)	66.6 ± 10.7 (67.6)	64.9 ± 11.8 (66.2)	0.670
Female, n	8 (61.5%)	114 (77.9%)	0.505
RA duration, years	8.0 ± 7.7 (4.7)	7.6 ± 9.0 (4.0)	0.241
CRP, mg/dL	0.92 ± 2.46 (0.09)	1.04 ± 2.11 (0.20)	0.218
ESR, mm/h	26.0 ± 30.0 (13.0)	26.1 ± 26.8 (15.0)	0.476
IgM RF, IU/mL	46.2 ± 34.0 (49.3)	88.0 ± 151.2 (24.5)	0.791
AST, U/L	25.5 ± 6.5 (27.0)	27.9 ± 16.4 (23.0)	0.688
ALT, U/L	19.9 ± 6.8 (20.5)	26.0 ± 19.2 (19.0)	0.959
IgG, mg/dL	1454 ± 573 (1382)	1432 ± 450 (1358)	0.604
Neutrophil count	3326 ± 1567 (2722)	4462 ± 2302 (3868)	0.063
Lymphocyte count	1503 ± 425 (1431)	1732 ± 813 (1562)	0.323

Values are given as mean ± standard deviation (median)
RA, rheumatoid arthritis; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *Ig,* immunoglobulin; *RF,* rheumatoid factor; *AST,* aspartate aminotransferase; *ALT,* alanine aminotransferase

Table 1. Comparison of hepatitis B virus (HBV) replication-positive and HBV replication-negative patients for baseline demographic, clinical, and laboratory characteristics

develop reactivation of HBV DNA replication, a significant difference was noted between the use of biologic agents (76.9% vs. 36.1%, respectively; p = 0.006), ETN (61.5% vs. 22.2%, respectively; p = 0.005), MTX (76.9% vs. 46.5%, respectively; p = 0.044), high-dose CS (15.4% vs. 1.4%; p = 0.035), and tacrolimus hydrate (30.8% vs. 5.6%; p = 0.010). Cox regression hazard analysis also revealed that biologic agent and ETN use can be as predictors for reactivation of HBV DNA replication. The hazard ratio (HR) for use of a biologic agent and etanercept was 10.9 (p = 0.008) and 6.9 (p = 0.001), respectively. Age at presentation, duration of RA, male gender, use of MTX and CS, dose of MTX and CS, levels of alanine aminotransferase and aspartate aminotransferase, immunoglobulin G level, neutrophil counts, and lymphoid cell counts were not associated with the reactivation of HBV DNA replication. The four variables extracted from the stepwise analysis were then entered as predictors of HBV DNA replication in a multivariate logistic regression model to determine their independent importance. The results of this model are shown in table 4. Predictive capacity was recognized for the use of tacrolimus hydrate only.

A recent study investigated 244 HBsAg-negative lymphoma patients receiving cytotoxic chemotherapy [13]. Reactivation of hepatitis B developed following therapy in 8 of these 244 patients (3.3%). Patients appeared to have a greater tendency to develop fulminant hepatic failure (3 of 8 patients, 37.5%). Direct DNA sequencing results confirmed that all 8 patients showed reactivation of hepatitis B from resolved hepatitis B. These patients were initially HBsAg-negative, and HBsAb- and/or HBcAb-positive, and serum liver enzyme levels were not elevated. At the time of hepatitis B reactivation, these patients became HBsAg positive. This change was associated with a more than 100-fold increase in serum HBV DNA levels, which occurred before the elevation of serum transaminases [13].

CD4+ T-helper cells may contribute to the control of HBV infection primarily by facilitating the induction and maintenance of HBV-specific cytotoxic T lymphocytes (CTL). MTX and

Case	Age (years)	RA disease duration (months)	Biologic agent	MTX (mg/week)	DMARDs	Prednisolone (mg/day)	HBV (log copies/ml)	Entecavir	Final status of HBV DNA	Time between emergence of HBV DNA and its disappearance (months)	ALT (U/L)
1	77	35	tocilizumab[a]	6	none	none	2.0	none	DNA negative	1	27
2	65	53	etanercept	none	none	2	5.0	yes	DNA negative	5	20
3	46	120	etanercept	8	tacrolimus 1 mg/day bucillamine 200 mg/day leflunomide 10 mg/day	none	3.7	yes	DNA negative	1	30
4	49	60	etanercept	none		none	7.4	yes	DNA negative	18	20
5[b]	60	36	etanercept	none		3mg	2.0	none	DNA negative	1	25
	61	48	adalimumab	2	tacrolimus 1mg/day bucillamine 200 mg/day	3mg	2.1	yes	DNA negative	1	25
6	75	18	etanercept	8	none	6	2.4	yes	DNA negative	2	26
7	74	19	none	7.5	none	5	3.0	yes	DNA negative	2	14
8	84	162	rituximab	7.5	tacrolimus 1mg/day bucillamine 200 mg/day	30	2.2	none			22
9	74	73	none	8		4	2.1	yes	DNA negative	1	11
10	69	180	abatacept	8		2.5	7.8	yes	DNA positive		21
11	60	224	abatacept[c]	7.5			4.1	yes	DNA negative	1	13
12	66	317	etanercept		bucillamine 200 mg/day		2.2	yes	DNA negative	1	6
13	72	2		7.5		25	2.1	yes	DNA negative	1	18

RA, rheumatoid arthritis; *MTX*, methotrexate; *DMARDs*, disease-modifying antirheumatic drugs; *ALT*, alanine aminotransferase

[a]This patient sequentially received 3 biologic agents: infliximab, etanercept, and tocilizumab.

[b]This patient had HBV-DNA reactivation twice.

[c]This patient sequentially received 2 biologic agents: etanercept, and abatacept.

Table 2. Demographic, clinical, and laboratory characteristics of patients with HBV replication

Variables	Number of patients[a]		*P* value	HR (95% CI)
	HBV replication (+)	HBV replication (-)		
Total	13	144		
Biologic agent	10 (76.9%)	52 (36.1%)	0.006	2.1 (1.5–3.1)
Adalimumab	1 (7.7%)	8 (5.6%)	0.550	1.4 (0.2–10.2)
Etanercept	8 (61.5%)	32 (22.2%)	0.005	2.8 (1.6–4.7)
Infliximab	1 (7.7%)	17 (11.8%)	1.000	0.7 (0.1–4.5)
Tocilizumab	1 (7.7%)	7 (4.9%)	0.507	1.6 (0.2–11.9)
Abatacept	2 (15.4%)	3 (20.8%)	0.055	7.4 (1.4–40.3)
Rituximab	1 (7.7%)	0	0.08	
Methotrexate	10 (76.9%)	67 (46.5%)	0.044	1.7 (1.2–2.3)
mean dose	7.1 ± 1.9 mg/week	6.8 ± 1.9 mg/week	0.707	
Corticosteroids	6 (46.2%)	57 (39.6%)	0.770	1.2 (0.6–2.2)
mean dose	12.7 ± 15.6 mg/day	5.7 ± 5.0 mg/day	0.533	
High dose of corticosteroids (≥0.5mg·kg^{-1}·day^{-1})	2 (15.4%)	2 (1.4%)	0.035	11.1 (1.7–72.3)
Sulfasalazine	1 (7.7%)	36 (25.0%)	0.303	0.3 (0.0–2.1)
Bucillamine	3 (23.1%)	29 (20.1%)	0.729	1.1 (0.4–3.3)
Tacrolimus hydrate	4 (30.8%)	8 (5.6%)	0.010	5.5 (1.9–15.9)
Sodium aurothiomalate	1 (7.7%)	5 (3.5%)	0.410	2.2 (0.3–17.6)
Leflunomide	1 (7.7%)	2 (1.4%)	0.230	5.5 (0.5–57.1)
D-penicillamine	0	2 (1.4%)	1.000	
Actarit	0	1 (0.7%)	1.000	
Auranofin	0	7 (4.9%)	1.000	
Cyclosporine	0	1 (0.7%)	1.000	
Minocycline hydrochloride	0	2 (1.4%)	1.000	
Cyclophosphamide	0	1 (0.7%)	1.000	

[a]Values are given as the number of patients taking a drug; patients can take more than one drug and can switch to another biologic agent
HR, hazard ratio; *95% CI,* 95% confidence interval

Table 3. Number of patients using concomitant drugs related to rheumatoid arthritis during the study [comparing hepatitis B virus (HBV) replication-positive patients with HBV replication-negative patients]

	Odds Ratio (95% CI)	*p* value
Tacrolimus hydrate	11.1 (2.0-50.6)	0.0015
Sulfasalazine	0.3 (0.0-1.7)	0.2604
Abatacept	1.5 (0.1-17.4)	0.7726
immunoglobulin G	1.9 (0.0-160.3)	0.7572

95% CI, 95% confidence interval

Table 4. Logistic regression model predicting hepatitis B virus replication in rheumatoid arthritis patients

tacrolimus hydrate may inhibit the function of CTL that controls HBV proliferation, and trigger reactivation of HBV-DNA replication [20, 21]. CS has shown to have direct stimulatory effects on HBV replication, in addition to indirect effects mediated via generalized immune system suppression [4].

TNF is a proinflammatory cytokine that plays a key role in host responses to several types of infection and other stimuli [22]. Various observations have strongly implicated TNF in the pathogenesis of RA and ankylosing spondylitis (AS), and increased TNF production propagates rheumatoid synovitis, promotes osteoclast formation, and results in characteristic bone and joint destruction [23]. TNFA significantly affects the current treatment of RA and AS [24] but is associated with adverse reactions such as reactivation of tuberculosis [25]. Studies regarding the safety of TNFA with chronic viral infection are limited. Several theories exist regarding how TNF inhibitors reactivate hepatitis B. Elevated TNF levels are seen in both the serum and hepatocytes of patients with chronic hepatitis B [26], and are secreted by HBV-specific CTL [27]. TNF has biological activity and an amino acid sequence similar to lymphotoxin, which inhibits HBV replication [28]. Infected cells are also reported to be selectively killed by TNF [33]. TNF acts to suppress HBV DNA replication by reducing intracellular HBV transcription [29]. Animal studies have shown that TNF-knockout mice have defects in the proliferative capacity of HBV-specific CTL [30], suggesting that TNF plays a role in clearing or controlling HBV [30, 31]. Moreover, HBV-specific CTL inhibits HBV gene expression by secreting antiviral cytokines, such as interferon γ and TNF, and inducing apoptosis in HBV-infected hepatocytes [32, 33].

With increasing use of biologic agents such as TNFA, anti-IL-6 receptor, anti-CD20 [34], and anti-CD28, reactivation of HBV DNA replication in patients with resolved HBV will likely increase, particularly in endemic areas. Among patients who are scheduled to receive MTX, CS, tacrolimus hydrate, and biologic agents, patients who are HBsAg negative should be further screened for anti-HBc and anti-HBs.

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Conflict of interest statement

None

5. References

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The study of DNA advanced human knowledge in a way comparable to the major theories in physics, surpassed only by discoveries such as fire or the number zero. However, it also created conceptual shortcuts, beliefs and misunderstandings that obscure the natural phenomena, hindering its better understanding. The deep conviction that no human knowledge is perfect, but only perfectible, should function as a fair safeguard against scientific dogmatism and enable open discussion. With this aim, this book will offer to its readers 30 chapters on current trends in the field of DNA replication. As several contributions in this book show, the study of DNA will continue for a while to be a leading front of scientific activities.

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