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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Hepatitis B virus reactivation associated with antirheumatic therapy: Risk and prophylaxis recommendations

Shunsuke Mori, Shigetoshi Fujiyama

Shunsuke Mori, Department of Rheumatology, Clinical Research Center for Rheumatic Diseases, NHO Kumamoto Saishunsou National Hospital, Kumamoto 861-1196, Japan

Shigetoshi Fujiyama, Department of Hepatology and Gastroenterology, Kumamoto Shinto General Hospital, Kumamoto 862-8655, Japan

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Correspondence to: Shunsuke Mori, MD, PhD, Department of Rheumatology, Clinical Research Center for Rheumatic Diseases, NHO Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan. moris@saisyunsou1.hosp.go.jp
Telephone: +81-96-2421000
Fax: +81-96-2422619

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Abstract

Accompanying the increased use of biological and non-biological antirheumatic drugs, a greater number of cases of hepatitis B virus (HBV) reactivation have been reported in inactive hepatitis B surface antigen (HBsAg) carriers and also in HBsAg-negative patients who have resolved HBV infection. The prevalence of resolved infection varies in rheumatic disease patients, ranging from 7.3% to 66%. Through an electronic search of the PubMed database, we found that among 712 patients with resolved infection in 17 observational cohort studies, 12 experienced HBV reactivation (1.7%) during biological antirheumatic therapy. Reactivation rates were 2.4% for etanercept therapy, 0.6% for adalimumab, 0% for infliximab, 8.6% for tocilizumab, and 3.3% for rituximab. Regarding non-biological antirheumatic drugs, HBV reactivation was observed in 10 out of 327 patients with resolved infection from five cohort studies (3.2%). Most of these patients received steroids concomitantly. Outcomes were favorable in rheumatic disease patients. A number of recommendations have been established, but most of the supporting evidence was derived from the oncology and transplantation fields. Compared with patients in these fields, rheumatic disease patients continue treatment with multiple immunosuppressants for longer periods. Optimal frequency and duration of HBV-DNA monitoring and reliable markers for discontinuation of nucleoside analogues should be clarified for rheumatic disease patients with resolved

HBV infection.

Key words: Hepatitis B virus; Antirheumatic therapy; Resolved hepatitis B virus infection; Occult hepatitis B virus carrier; Reactivation

Core tip: In the literature, the prevalence of resolved hepatitis B virus (HBV) infection varied in rheumatic disease patients, ranging from 7.3% to 66%, which seems to be related directly to the general prevalence of HBV infection in the respective geographic areas. When calculated using data from observational cohort studies, the incidence rate was 1.7% in rheumatic disease patients receiving biological therapy and 3.2% in those treated with non-biological drugs. In antirheumatic therapy, multiple immunosuppressants are administered during long periods. Optimal frequency and duration of HBV-DNA monitoring and reliable markers for discontinuation of nucleoside analogues remain unclear for rheumatic disease patients with resolved HBV infection.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a challenging health problem. According to the World Health Organization, an estimated 240 million individuals (3.7%) suffered from chronic HBV infection worldwide in 2005[1]. In Japan, 1.1-1.4 million (0.9%-1.1%) were estimated to be chronic carriers of hepatitis B surface antigen (HBsAg), as reported by the Ministry of Health, Labor, and Welfare in 2004[2]. A dynamic balance between the host immune response to HBV and the degree of viral replication is a critical factor for the pathogenesis of HBV-related liver disease. Most carriers remain at an inactive state (inactive HBsAg carriers)[3,4]. Reactivation of HBV, defined as an abrupt rise of HBV replication often accompanied by clinical signs of hepatocellular injury, is a well-recognized complication in inactive HBsAg carriers who are receiving immunosuppressive therapy for malignancies, organ transplantation, or autoimmune inflammatory diseases[5,6]. The condition ranges from clinically silent, self-limiting hepatitis to acute, severe hepatitis resulting in fatal hepatic failure.

With the availability of more aggressive, rituximab-based regimens, it has become evident that HBV reactivation following anticancer chemotherapy can occur in HBsAg-negative patients who exhibit evidence of resolved HBV infection [*i.e.*, anti-hepatitis B core antibody (anti-HBc)-positive serology with or without anti-HBs antibody (anti-HBs)][7-12]. Such patients are regarded as potential occult carriers. Occult infection has also been reported in patients without any serological markers[13,14]. With the advent of highly sensitive PCR-based assays, it has come to light that viral replication persists over a long period of time in liver tissues and peripheral blood mononuclear cells at very low levels, despite the apparent serological clearance of HBsAg and the appearance of anti-HBc[15-20]. All of the conditions that induce immunosuppression can provoke reactivation of occult HBV infection with the reappearance of the typical serological profiles of acute hepatitis B[14,21]. Although the incidence of HBV reactivation is lower in HBsAg-negative patients than in inactive HBsAg carriers[22], resultant acute hepatitis, known as *de novo* hepatitis B, often has a severe and sometimes even fulminant clinical course. Mortality is extremely high in such cases[23-25]. Nevertheless, the management of occult HBV infection is still a controversial issue.

Most information on HBV reactivation has come from the fields of oncology and transplantation. Over the years, however, a growing number of cases have been reported in patients with rheumatic conditions receiving biological and/or non-biological antirheumatic drug therapy. In this review, we examine the literature regarding HBV reactivation after exposure to antirheumatic agents, mainly in patients with resolved infection, with the intention of clarifying characteristics and risk of viral reactivation in this patient population. Prophylaxis against HBV reactivation is also addressed. Further, we point out several aspects that most need to be clarified for the effective management of HBV reactivation in rheumatic disease patients.

TERMINOLOGY

In this review, we use several clinical terms regarding HBV infection. The interpretation of serology testing is summarized in Table 1[26,27]. Resolved HBV infection is defined as previous HBV infection without further serological, virological, or biochemical evidence of active viral infection or disease, which represents the HBsAg-negative phase in the natural history of HBV infection. Resolved HBV infection is diagnosed based on HBsAg-negative serology with a previous history of acute or chronic hepatitis B or HBsAg-negative serology with the presence of anti-HBc with or without anti-HBs. Anti-HBc-positive/anti-HBs-positive serology indicates resolved HBV infection with natural immunity, while isolated anti-HBc-positive status indicates resolved infection with undetectable levels of anti-HBs, but it may also indicate possibly persistent HBV infection with undetectable levels of HBsAg in the serum. In either case, low levels of viral replication persist in the liver of patients with resolved infection,

Table 1 Definition of resolved hepatitis B virus infection, inactive carrier state, chronic hepatitis B, and immunization due to vaccination

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	ALT	HBV-DNA in serum (copies/mL)	HBV-DNA in the liver	Liver injury
Resolved infection	-	+/-	-	+/-	+/-	Normal	Negative	+	No
Inactive carriers	+	-	-	+	+	Normal	Negative to 10^4	+	No
Chronic hepatitis B (HBeAg-positive)	+	-	+	-	+	Elevated	$> 10^5$	+	Yes
Chronic hepatitis B (HBeAg-negative)	+	-	-	+	+	Elevated	$> 10^4$	+	Yes
Immunized	-	+	-	-	-	Normal	Negative	-	No

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; anti-HBs: Anti-hepatitis B surface antibody; HBeAg: Hepatitis B e antigen; anti-HBe: Anti-hepatitis B e antibody; anti-HBc: Anti-hepatitis B core antibody; ALT: Alanine aminotransferase.

but viral DNA is generally not detectable in the serum (or very low levels may be detectable using real-time PCR assays).

Occult infection is defined as the presence of HBV-DNA in the liver with detectable or undetectable viral DNA in the serum of individuals testing HBsAg-negative using currently available assays. When detected, the amount of HBV-DNA in the sera is very low (less than 10^3 copies/mL)[28]. All individuals with HBsAg-negative/anti-HBc-positive serology are considered potential occult carriers of HBV (seropositive occult carriers). It is notable that approximately 20% of occult HBV carriers are negative for all serological markers of HBV infection (seronegative occult carriers)[13].

Inactive HBsAg carriers have persistent HBV infection in the liver without significant, ongoing necroinflammatory disease. The inactive HBsAg carrier state is defined as the presence of HBsAg without hepatitis B e antigen (HBeAg), persistently normal aminotransferase levels, and low viral load (less than 10^4 copies/mL).

There is no global consensus on the definition of HBV reactivation. In most studies from the rheumatology field, it was defined as a rise of serum HBV-DNA level by one log or greater compared with the pre-exacerbation baseline period, a reappearance of HBsAg in HBsAg-negative patients, or a new detection of viral DNA in patients with previously undetectable HBV-DNA in the serum. The definition of HBV-DNA positive varied, ranging from more than 2.0 log copies/mL to more than 3.0 log copies/mL. In one study, an at least twofold elevation of alanine aminotransferase (ALT) over the upper limit of normal on two consecutive determinations was used to define HBV reactivation[29].

PREVALENCE OF RESOLVED HBV INFECTION

General populations

HBV infection is one of the most common viral infections in humans, but its prevalence varies greatly from country to country and in different areas and subpopulations. In areas with high prevalence, including much of Asia and the South Pacific Island region, sub-Sahara Africa, and Arctic/sub-Arctic region, the prevalence of HBsAg carriers is 8% or more, while in countries with low endemicity, such as North and Central America, Northern and Western Europe, and Australia, it is less than 2%[1,30,31]. In Japan, the estimated prevalence of HBsAg-positive serology is approximately 0.9%-1.1%, as estimated by HBsAg testing for first-time blood donors from 1995 to 2000[2].

Resolved HBV infection is also found worldwide. Approximately two billion subjects (30%) have serological markers indicating previous exposure to HBV. According to data from several large-scale studies for blood or hematopoietic stem cell donors and the general population, the prevalence of anti-HBc is 1.5% in Germany[32], 0.8% in the United States[33], 4.9% in Italy (Piedmont)[34], 7.3% in France[35], 8.3% in Italy[36], 13.5% in South Korea[37], 16.8% in France (Paris)[38], 19.3% in Greek[39], 20% in Japan (Nagoya)[24], and 41.7% in China (Lianyungang)[40].

Using highly sensitive PCR techniques, Lo *et al*[41] reported a geographical variation in the prevalence of HBV-DNA in the liver tissue of HBsAg-negative patents, in which the prevalence of occult infection was 11% in Italy, 6.9% in Hong Kong, and 0% in the United Kingdom. The prevalence was related to endemic rates of the respective geographical region[41]. HBV-DNA was also detected in the liver tissue of 16 out of 93 (16.3%) liver disease-free individuals in Italy[42]. Studies examining HBsAg-negative subjects showed that HBV-DNA was found in 31 out of 195 (16%) healthy Korean subjects with normal serum ALT levels[43] and in 19 out of 124 (15.3%) hematopoietic stem cell donors in Hong Kong[44]. In studies on blood donors with HBsAg-negative/anti-HBc-positive serology, HBV-DNA was detected in 19 out of 50 subjects (38%) in Japan[45], in 3 out of 189 (1.6%) in Germany[32], and in 4 out of 395 (1.0%) in the United States[33]. It is still controversial whether the anti-HBc status is significantly associated with the presence of occult HBV infection[42,44].

Rheumatic disease patients

Although precise data on the prevalence of resolved

Table 2 Studies evaluating the prevalence of resolved hepatitis B virus infection and hepatitis B surface antigen carriers in patients with rheumatic diseases

Study	Author	Country	Publication (year)	Disease	Total numbers	Resolved infection[1] *n* (%)	HBsAg carriers *n* (%)	Vaccination *n* (%)	Ref.
1	Charpin	France	2009	RA, PsA, AS	504	58 (11.5)	2 (0.4)	ND	[46]
2	Vassilopoulos	Greece	2010	RA, SpA, others	131	19 (14.5)	14 (10.7)	19 (14.5)	[47]
3	Caporali	Italy	2010	RA, AS, PsA	732	67 (9.2)	5 (0.7)	ND	[48]
4	Giardina	Italy	2013	RA, AS, PsA	57	15 (26.3)[2]	3 (5.3)	ND	[55]
5	Biondo	Italy	2014	RA, AS, PsA	169 (HBsAg-negative)	20 (11.8)	-	24 (14.2)	[57]
6	Ballanti	Italy	2014	RA	344	25 (7.3)	1 (0.2)	ND	[58]
7	Barone	Italy	2015	RA, PsA, SpA, AS, others	1138	179 (15.7)	0	ND	[60]
8	Kim	South Korea	2010	RA, AS, PsA, JRA	266	88 (33.1)	8 (3.0)	ND	[29]
9	Urata	Japan	2011	RA	428	135 (31.5)[2]	6 (1.4)	ND	[49]
10	Tamori	Japan	2011	RA	50 (anti-HBc-positive)	45	5 (10)	-	[50]
11	Mori	Japan	2011	RA	239	60 (25.1)	2 (0.8)	ND	[51]
12	Kato	Japan	2011	RA, SLE, Vasculitis, others	414	35 (8.5)	ND	ND	[52]
13	Nakamura	Japan	2014	RA	251	57 (22.7)[2]	1 (0.4)	6 (2.4)	[59]
14	Lan	Taiwan	2011	RA	106	70 (66.0)	18 (17.0)	ND	[53]
15	Tan	China	2012	RA	390	188 (48.2)	27 (6.9)	ND	[54]
16	Ye	China	2014	RA, AS, PsA	98	50 (51.0)	37 (37.8)	ND	[56]

[1]Resolved HBV infection was defined as HBsAg-negative/anti-HBc-positive serology; [2]In these studies, HBsAg-negative/anti-HBs-positive/anti-HBc-negative serology was also considered to indicate resolved infection if patients had no previous HBV vaccination. HBsAg: Hepatitis B surface antigen; anti-HBc: Anti-hepatitis B core antibody; RA: Rheumatoid arthritis; SpA: Spondyloarthropathy; AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; JRA: Juvenile rheumatoid arthritis; SLE: Systemic lupus erythematosus; ND: Not described.

HBV infection in rheumatic disease patients are limited because of a lack of large-scale and nationwide surveys, several studies have reported its prevalence in respective hospitals (Table 2)[29,46-60]. The prevalence of resolved infection varied, ranging from 7.3% to 66%. In Western Europe, resolved HBV infection was observed in 7.3% to 26.3% of cases, which was lower than that found in Asian countries. The prevalence of resolved infection was similar in Japan (8.5% to 31.5%) and South Korea (33.1%), while it was markedly higher in China (48.2% to 51%) and Taiwan (66.0%). The frequency of resolved infection in rheumatic disease patients seems to be directly related to the general prevalence of HBV infection in the respective geographic areas. Real-time or nested PCR testing showed that HBV-DNA is detected in the sera of 1.4% to 2.2% of rheumatic disease patients with resolved infection[50,53,54].

ADVANCES IN PHARMACEUTICAL THERAPY FOR RHEUMATIC DISEASES

Over the past decade, the prognosis of rheumatoid arthritis (RA) patients has improved dramatically with the early use of methotrexate (MTX) as the first-line of disease-modifying antirheumatic drugs (DMARDs). In addition, the emergence of novel biological agents targeted at specific molecules and pathways in the immune system has changed the course of RA and improved patient and social outcomes[61,62]. Biological therapy has also gained popularity in the treatment of other rheumatic diseases, such as ankylosing spondylitis and psoriatic arthritis, because it is a potent therapeutic option for those patients who have experienced failure in the first-line DMARD therapy[63,64]. TNFα inhibitors (infliximab: chimeric anti-TNFα monoclonal antibody; etanercept: soluble TNF receptor; adalimumab: humanized anti-TNFα monoclonal antibody; golimumab: humanized anti-TNFα monoclonal antibody; and certolizumab pegol: antigen-binding fragment of humanized anti-TNFα monoclonal antibody conjugated to polyethylene glycol), humanized anti-interleukin (IL)-6 receptor monoclonal antibody (tocilizumab), a T-cell signaling inhibitor (abatacept), and chimeric anti-CD20 monoclonal antibody (rituximab) are mainly used in biological therapy for rheumatic diseases.

POSSIBLE MECHANISMS OF HBV REACTIVATION IN RHEUMATIC DISEASE PATIENTS

Antirheumatic therapy can disturb the delicate balance between the degree of HBV replication and host immune control in patients with HBV, which may cause viral reactivation. First, HBV replication accelerates. In this phase, HBV-DNA reappears or is raised by at least one log, but patients are usually asymptomatic and ALT levels remain in the normal range or only minimally increase. In the second phase, ALT levels are

elevated with or without symptoms of acute hepatitis. In severe cases, an active necroinflammatory injury progresses, resulting in liver failure and death. This phase is characterized by reconstitution of the host immune response: the suppressed host cellular immune system tries to recover and attacks membranes of HBV-infected hepatocytes expressing viral epitopes, causing hepatocellular injury. Hepatitis seems to occur after a delay of several days or weeks from the rise in or reappearance of serum HBV-DNA. Maximal reduction of viral DNA levels seems to occur before significant hepatic injury[5,6].

Pollicino *et al*[20] showed that HBV isolated from occult carriers are replication-competent *in vitro*, but viral replication and gene expression is strongly suppressed in these individuals. The viral genomic variability did not play a critical role in inducing the occult HBV infection status. The data suggested that the host immune-surveillance system, rather than viral factors, might be responsible for the establishment and/or maintenance of such cryptic HBV infection. Rehermann *et al*[15] showed that HBV persists in the serum and peripheral blood mononuclear cells for decades after a patient's clinical recovery from acute hepatitis B, and that the strength of response by HBV-specific T lymphocytes (CTLs) correlates with the persistence of HBV DNA. The data suggested that host immune control of HBV infection is largely mediated through HBV-specific CTLs. Considering these findings, there is a possibility that rheumatic disease patients may differ in factors that can change the prevalence of occult infection. Recent laboratory data on RA patients showed a contraction of the T cell receptor repertoire and fundamental alterations in T cell dynamics[65,66]. Such perturbation of T lymphocyte homeostasis results in the decreased ability to recognize potential antigens. In this context, rheumatic disease patients may be susceptible to HBV reactivation, even before antirheumatic agents are introduced.

HBV REACTIVATION IN HEPATITIS B SURFACE ANTIGEN CARRIERS DURING ANTIRHEUMATIC THERAPY

MTX

There are several case reports on the development of fulminant hepatitis as a consequence of HBV reactivation after discontinuation of low-dose MTX therapy for RA patients with asymptomatic HBsAg carriage[67-70]. This is attributed to the restoration of immune function following MTX withdrawal, which rapidly causes HBV-specific CTL-mediated destruction of HBV-infected hepatocytes. Reactivation of HBV replication during MTX therapy has also been reported in two prospective cohort studies, in which all patients who suffered from reactivation had received low-dose steroids concomitantly and none had received any antiviral prophylaxis. These patients did not develop clinically apparent hepatitis, and outcomes were satisfactory. No reactivation was observed in patients receiving prophylaxis[50,54].

Steroids

The use of moderate- to high-dose steroids has been clearly associated with HBV reactivation in rheumatic diseases, and steroid pulse therapy is significantly related to HBV reactivation[71-75]. HBV-DNA contains a glucocorticoid-responsive element[76]. Viral reactivation during steroid therapy may occur not only as a result of the suppression of the host immune system but also through the direct stimulation of HBV-gene expression. It is not clear whether treatment with low doses of steroids is associated with the risk of HBV reactivation among rheumatic disease patients because, in most cases, low-dose steroids are used concomitantly with biological and/or non-biological DMARDs.

TNFα inhibitors

TNFα plays a role in promoting HBV eradication by stimulating HBV-specific CTLs, which destroy virus-infected hepatocytes[77]. A recent study showed that TNFα is essential for the proliferation of HBV-specific CTLs[78]. CTLs also inhibit hepatocellular HBV gene expression and replication through a non-cytotoxic mechanism, which is mediated initially by TNFα and interferon α[79,80]. Thus, inhibition of TNFα activity leads to enhanced viral replication. Inactive HBsAg carriers receiving TNFα inhibitors require special attention. In recent years, a growing number of cases of HBV reactivation in patients with chronic hepatitis B (active HBsAg carriers)[47,81-85] and in inactive HBsAg carriers[53,82,84-97] have been described in association with TNFα inhibitors. Unfortunately, the available data are limited to a small number of single case reports and a small series of consecutive patients.

Through a systemic analysis of cases reported, Perez-Alvarez indicated that HBV reactivation was observed in 35 out of 89 (39%) HBsAg carriers receiving TNFα inhibitors; that the rate of reactivation in HBsAg carriers was sevenfold higher than in patients with resolved infection; that the percentage of reactivation was significantly lower in patients who had received antiviral prophylaxis (23% *vs* 62%); and that infliximab was associated with a higher rate of induced liver damage compared with etanercept. Approximately 5% died due to liver failure[98]. Another systemic review also showed that infliximab was associated with the greatest number of reported cases of reactivation[77]. More recently, Cantini *et al*[99] showed that the pooled prevalence of HBV reactivation in HBsAg carriers treated with TNFα inhibitors for rheumatic or dermatologic conditions was 15.4%; that pooled reactivation rates did not differ considerably between etanercept and adalimumab; and that the reactivation risk associated with TNFα inhibitors was

fivefold higher in HBsAg carriers compared with patients with resolved infection. Lee *et al*[100] also performed an electronic search for studies that had examined HBV reactivation in HBsAg carriers who received TNFα inhibitors or DMARDs for rheumatic diseases and found that viral reactivation was observed in 15 out of 122 patients (12.3%).

Other biological DMARDs

IL-6 is a pleiotropic cytokine with a variety of biological activities that induces T-cell proliferation and CTL differentiation. This cytokine also promotes antibody production by B-cells. In chronic HBV infection, serum IL-6 levels significantly correlated with serum aminotransferase levels, which suggested that IL-6 might play a role in viral elimination[101]. Thus blocking of IL-6 activity may influence host immune response to HBV antigens[102]. Nevertheless, no cases of HBV reactivation during tocilizumab therapy have so far been reported in patients with chronic HBV infection. In several case reports, tocilizumab therapy in combination with antiviral prophylaxis produced favorable outcomes in patients with rheumatic disease and chronic hepatitis B[103,104]. In another report, tocilizumab was used, without any prophylaxis, for an RA patient with chronic hepatitis B, but the patient did not experience viral reactivation for more than five years[105].

Abatacept is a soluble fusion protein that comprises the extracellular domain of CTL antigen-4 (CTLA-4) and the Fc region of the IgG molecule. Through interactions with CD80/86 molecules on antigen-presenting cells, abatacept inhibits the co-stimulatory signaling of T-cells[106]. Kim *et al*[107] retrospectively examined eight patients with RA and chronic hepatitis B who had received abatacept with or without antiviral prophylaxis. Four patients started on prophylaxis with the initiation of abatacept and none of them experienced HBV reactivation, while the remaining four patients without antiviral prophylaxis developed viral reactivation.

B-cells are critical for antigen presentation, regulation of T-cells, and antibody production. CD20 molecules are widely expressed on B-cells. Rituximab is thought to destroy CD20-expressing cells through antibody-dependent, cell-mediated cytotoxicity[108]. Although plasma cells do not express the CD20 molecule, a reduction of memory B cells may cause hypogammaglobulinemia. It has been observed that B-cell depletion induces a decrease of anti-HBs titers with an increase in HBV DNA and HBV reactivation[109]. Reactivation of HBV was reported following rituximab therapy for an HBsAg-positive RA patient, despite viral prophylaxis with lamivudine[110]. In other case reports, no reactivation was observed during rituximab therapy for patients with rheumatic diseases and chronic hepatitis B, in which lamivudine was used as the prophylactic agent[111,112].

HBV REACTIVATION IN PATIENTS WITH RESOLVED HBV INFECTION DURING ANTIRHEUMATIC THERAPY

Literature search

We performed an electronic search of the published English literature (as of 31 January 2015), using the PubMed database. The following keywords and subject terms were used in the search: "hepatitis B virus", "HBV reactivation", and "rheumatic diseases". All references listed by studies retrieved from the online database and from previously published systemic reviews were also searched manually to identify additional potential studies that are not indexed by the database. Studies were confined to rheumatic disease. Studies that did not provide detailed information on baseline HBV serology were excluded. In this review, HBV reactivation was defined as a rise in viral load of 1.0 log or more compared with the baseline level, a reappearance of HBsAg in HBsAg-negative patients, or a new detection of viral DNA in patients with previously undetectable HBV-DNA in the serum (with or without associated ALT elevation). The definition of HBV-DNA positivity (a detection threshold) was determined according to that used in each study (range, 2.0 log to 3.0 log copies/mL). Patients with raised hepatic enzymes and/or clinical signs of liver disease in the absence of viral or serological changes were not diagnosed as suffering from HBV reactivation.

Prospective or retrospective cohort studies

Nineteen observational cohort studies evaluating the prevalence of HBV reactivation in rheumatic disease patients with resolved infection were identified: 18 studies included data on patients receiving biological DMARDs[29,46-53,55-60,113-115] and 5 included data regarding patients receiving non-biological DMARDs[49-52,54]. A total of 800 patients with resolved HBV infection who had received biological DMARDs were identified from the 18 studies. In all studies, except for two that did not detail the number of drugs prescribed (studies 2 and 4), the biological DMARDs used were etanercept in 354 patients, adalimumab in 173, infliximab in 207, golimumab in 1, tocilizumab in 35, rituximab in 30, abatacept in 11, and anakinra in 3. A total of 327 patients with resolved HBV infection were treated with non-biological DMARDs alone. No patients, except for two, received antiviral prophylaxis before or during biological or non-biological DMARD therapy. Mean follow-up periods ranged from 6 to 55 mo. Details of the extracted data are summarized in Table 3.

The prevalence of HBV reactivation associated with biological therapy varied, ranging from 0% to 16.7%. Since HBV reactivation was not confirmed by HBV-DNA in one study, the 88 patients in this study were excluded when calculating the following reactivation

Table 3 Studies evaluating reactivation rates in rheumatic disease patients with resolved hepatitis B virus infection[1]

Study[2]	Patient number	Age (yr)	Biological DMARDs (number)	Non-biological DMARDs and PSL (%)	Follow-up (mo)	Prophylaxis (number)	Reactivation number (%)	Ref.
1	21	58 (mean)	ETN (14), ADM (3), IFX (4)	MTX (48)	27 (mean)	No	0	[46]
2	19	52 (mean)[5]	ETN, ADM, IFX	ND	24	No	0	[47]
3	67	57 (mean)	ETN (23), IFX (25), ADM (19)	MTX (76), PSL (64)	43 (mean)	No	0	[48]
4	15[3]	49 (mean)[5]	ETN, IFX	MTX(42)[5], PSL(60)[5]	24	No	0	[55]
5	20	63 (mean)	ETN (10), ADM (7), IFX (2), GOL (1)	MTX (80), others (35), PSL (65)	45 (mean)	No	0	[57]
6	25	63 (mean)[5]	ETN (15), ADM (10)	DMARDs (72)[5]	27 (mean)[5]	2	0	[58]
7	179	57 (mean)	ETN (74), IFX (43), ADM (29), RTX (14), TCZ (7), ABT (9), ANK (3)	DMARDs (75), PSL (46), High-dose PSL (4)	55, 32, 17 (median)	No	0[10]	[60]
8	88	51 (mean)	ETN (60), IFX (12), ADM (16)	ND	25 (mean)	No	14[4]	[29]
9	52[3]	ND	ETN (38), IFX (15), ADM (7), TCZ (4), RTX (1)[8]	MTX (48)[6], others (59)[6], PSL (39)[6]	12	No	6 (11.5)	[49]
9	83[3]	ND	Not used	MTX (48)[6], others (59)[6], PSL (39)[6]	12	No	1 (1.2)	[49]
10	42	59 (mean)[6]	ETN (19), IFX (21), ADM (2)	DMARDs (93)[6], PSL (76)[6]	23 (mean)[6]	No	0	[50]
10	3	59 (mean)[6]	Not used	DMARDs (93)[6], PSL (76)[6]	23 (mean)[6]	No	1 (33)	[50]
11	36	73 (median)[6]	ETN (18), IFX (19), ADM (2), TCZ (5)[8]	MTX (90)[6], others (50)[6], PSL (63)[6]	ND	No	1 (2.8)	[51]
11	24	73 (median)[6]	Not used	MTX (90)[6], others (50)[6], PSL (63)[6]	ND	No	1 (4.2)	[51]
12	6	62 (mean)[6]	ETN (1), IFX (1), TCZ (1), RTX (3)	DMARDs (60)[6], PSL pulse (60)[6]	6	No	1 (16.7)	[52]
12	29	62 (mean)[6]	Not used	DMARDs (60)[6], PSL pulse (60)[6]	6	No	5 (17.2)	[52]
13	57	64 (median)	ETN (22), IFX (20), ADM (22), TCZ (18), ABT (2)[8]	MTX (74), others (18), PSL (74)	18 (median)	No	3 (5.3)	[59]
14	70	51 (mean)	ETN (31), ADM (39)	MTX (91), PSL (100)	ND	No	1 (1.4)	[53]
15	188	ND	Not used	DMARDs (123), PSL (65)	20 (mean)	No	2 (1.1)	[54]
16	50	46 (mean)	ETN (9), IFX (41)	MTX (780), others (16)	12 (mean)	No	0	[56]
17[7]	7	51 (mean)	ADM (7)	ND	ND	No	0	[114]
18[7]	34	54 (mean)[9]	ETN (20), ADM (10), IFX (4)	ND	19, 28, 29 (mean)	No	0	[113]
19	12	60 (mean)[5]	RTX (12)	DMARDs (80)[5], MTX (41)[5], PSL (85)[5]	19 (mean)[5]	No	0	[115]

[1]Resolved HBV infection was defined as HBsAg-negative/anti-HBc-positive serology; [2]Study numbers 1-16 correspond to those used in Table 2; [3]In these studies, HBsAg-negative/anti-HBs-positive/anti-HBc-negative serology was also considered to indicate resolved infection if patients had no history of HBV vaccination; [4]In this study, 14 patients showed an abnormality in a liver function test (a twofold or greater increase of aminotransferases on two consecutive tests), but HBV reactivation could not be confirmed (no data on viral load); [5]Data reported for all patients included in this study, not just for those with resolved infection; [6]Data reported for all patients included in this study, not separately reported according to the use or nonuse of biological DMARDs; [7]This study was performed on psoriatic arthritis patients in Italy; [8]Some patients in these studies received two or three different biological DMARDs; [9]Data reported for all psoriasis patients included in this study, not just for those with psoriatic arthritis; [10]In this study, seven patients showed an abnormality in a liver function test (among those, three had a twofold or greater increase of aminotransferases), but no HBV DNA was detected. DMARDs: Disease-modifying antirheumatic drugs; PSL: Prednisolone; MTX: Methotrexate; RTX: Rituximab; TCZ: Tocilizumab; ANK: Anakinra; ABT: Abatacept; ADM: Adalimumab; IFX: Infliximab; ETN: Etanercept; GOL: Golimumab; ND: Not described.

rate (study 8). Among 712 patients receiving biological DMARDs, 12 experienced HBV reactivation (1.7%) during treatment with these drugs (cases 2, 4-13, and 15 in Table 4). HBV reactivation occurred in seven patients during treatment with etanercept, three with tocilizumab, one with adalimumab, and one with rituximab. No patients experienced HBV reactivation during infliximab therapy. When calculated using data from all studies (except for studies 2, 4, and 8), the reactivation rates were 2.4% for etanercept therapy, 8.6% for tocilizumab, 0.6% for adalimumab, and 3.3% for rituximab. There were no fatal cases.

HBV reactivation was observed in 10 out of 327 patients who were treated with non-biological DMARD alone (3.2%: cases 2, 3, 7, and 9-15 in Table 5). Four patients were treated with MTX, four with cyclophosphamide, three with tacrolimus, two with sulfasalazine, and one with leflunomide at the time of reactivation. Thirty-percent of cases received two non-biological DMARDs. Most patients received steroids concomitantly with DMARDs, and in half of such cases, reactivation occurred after steroid pulse therapy. Three patients died of causes not directly related to liver disease.

Recently Lee *et al*[116] showed in a systemic review that HBV reactivation associated with anti-TNFα therapy was observed in 8 out of 468 rheumatic disease patients with resolved infection (1.7%). In

Table 4 Characteristics and outcomes of rheumatic disease patients with resolved hepatitis B virus infection who experienced viral reactivation during treatment with biological disease-modifying antirheumatic drugs

Case	Age/sex	Disease	Anti-HBs/ anti-HBe	DMARDs	Duration	HBV-DNA[1] (copies/mL)	ALT[2] (IU/L)	Antiviral therapy	Outcomes	Ref
1	71/F	RA	Pos./Pos.	IFX, MTX, PSL	16 mo	ND	NR	-	-	[119]
				ADM, MTX, PSL	11 mo	1×10^9	674	Yes	Died[5]	
2	80/F	RA	ND	IFX, MTX, PSL	48 mo	Neg.	NR	-	-	[51]
				ETN, MTX, PSL	4 mo	Neg.	NR	-	-	
				ADM, MTX, PSL	15 mo	Pos.[3]	NR	No	Recovered	
3	73/M	AS	Pos./Pos.	ETN, PSL	14 mo	8.8×10^3	65	Yes	Recovered	[118]
4	54/F	RA	Neg./Pos.[4]	ETN, MTX, PSL	5 mo	1.6×10^6	199	Yes	Recovered	[53]
5	75/ND	RA	ND	ETN, MTX, PSL	ND	2.5×10^2	NR	Yes	Recovered	[49]
6	60/ND	RA	ND	ETN, LEF	ND	1.0×10^2	NR	No	Recovered	[49]
7	49/ND	RA	ND	ETN, BUC, PSL	ND	2.5×10^7	NR	Yes	Recovered	[49]
8	46/ND	RA	ND	ETN, MTX, TAC	ND	5.0×10^3	NR	Yes	Recovered	[49]
9	65/ND	RA	ND	ETN, PSL	ND	1.0×10^5	NR	Yes	Recovered	[49]
10	77/ND	RA	ND	TCZ, MTX	ND	1.0×10^2	NR	No	Recovered	[49]
11	75/M	RA	ND	TCZ, PSL[6]	2 mo	Pos.[3]	NR	No	Recovered	[59]
12	55/F	RA	ND	IFX	25 mo	Neg.	NR	-	-	[59]
				ETN	35 mo	Neg.	NR	-	-	
				TCZ, MTX PSL[6]	2 mo	Pos.[3]	NR	No	Recovered	
13	60/F	RA	ND	ETN, MTX, PSL[6]	65 mo	Pos.[3]	NR	No	Recovered	[59]
14	64/F	RA	Pos./ND	RTX, MTX	24 mo	$> 1.0 \times 10^8$	72	Yes	Recovered	[123]
15	71/F	RA	Neg./ND	RTX, PSL	4 wk	Pos.	NR	No	Recovered	[52]
16	64/F	RA	Pos./Neg.	RTX, MTX	2 yr	1.1×10^8	605	Yes	Recovered	[124]
17	78/M	RA	Pos./ND	IFX, MTX, PSL	ND	ND	NR	-	-	[122]
				RTX, PSL	27 mo	10^7	421	Yes	Recovered	
18	68/F	RA	Neg./Pos.	ABT, MTX	10 mo	1.1×10^8	NR	Yes	Recovered	[125]
19	72/F	RA	Pos./Pos.	ADA, PSL	2 yr	Neg.	NR	-	-	[120]
			Pos./Pos.	ABT, LEF, PSL	13 mo	7.0×10^4	2 × ULN	Yes	Recovered	

No patients had received preemptive therapy against HBV infection. Underlined entries represent biological agents. [1]HBV-DNA levels were determined at diagnosis of HBV reactivation; [2]ALT values were determined at diagnosis of HBV reactivation or were the highest values measured after HBV reactivation; [3]HBV-DNA tested positive on real-time PCR, but DNA levels were below 2.1 log copies/mL; [4]An HBV-DNA level was 3.5 log copies/mL; [5]The patient died of hepatic failure; [6]The patient continued biological therapy after HBV reactivation. RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; DMARDs: Disease-modifying antirheumatic drugs; PSL: Prednisolone; MTX: Methotrexate; BUC: Bucillamine; LEF: Leflunomide; TAC: Tacrolimus; RTX: Rituximab; ADM: Adalimumab; IFX: Infliximab; ETN: Etanercept; TCZ: Tocilizumab; ABT: Abatacept; HBV: Hepatitis B virus; anti-HBs: Anti-hepatitis B surface antibody; anti-HBe: Anti-hepatitis B e antibody; ALT: Alanine aminotransferase; Neg.: Negative; Pos.: Positive; ULN: Upper limits of normal; NR: Normal range; ND: Not determined or not described.

another systemic review, Cantini *et al*[99] reported that the pooled prevalence of HBV reactivation during anti-TNFα therapy was 3.0% for patients with rheumatic or dermatologic conditions who were diagnosed as having resolved infection. Pérez-Alvarez *et al*[98] reported that in patients with resolved infection receiving TNFα inhibitors, the reactivation rate was 5% (9 out of 168 patients).

Cases of HBV reactivation in the literature

Through the literature search, we identified 34 cases of HBV reactivation occurring in patients with resolved infection who were receiving biological and/or non-biological DMARDs for rheumatic diseases (Tables 4 and 5)[49-54,59,75,117-125]. Among these cases, 22 were identified in the cohort studies mentioned above (studies 9-15 in Table 3) and the others were published as case reports. No patients received antiviral prophylaxis, 19 received biological DMARDs, and 15 were treated with non-biological DMARDs alone.

Concerning the case of HBV reactivation associated with biological DMARDs, all except one (an ankylosing spondylitis case) were RA. The biological DMARDs used at the reactivation were etanercept in eight patients, adalimumab in two, tocilizumab in three, rituximab in four, and abatacept in two. One patient was HBV-DNA positive at baseline (case 4), and six patients were anti-HBs-positive. A mean interval from the start of biological DMARDs to the time of reactivation was 16.4 mo in 13 patients for whom data were available. Among 19 patients experiencing HBV reactivation, seven (37%) had an increase in serum ALT following HBV reactivation, suggesting the development of *de novo* hepatitis (cases 1, 3, 4, 14, 16, 17, and 19). One patient developed fulminant hepatitis and died of hepatic failure (case 1). Seven patients recovered without antiviral treatment (cases 2, 6, 10-13, and 15), and their HBV-DNA was positive but below 2.1 log copies/mL at the time of reactivation.

In cases involving HBV reactivation associated with non-biological DMARD therapy alone, half were RA patients. All patients except for one received steroids in combination with non-biological DMARDs at the time of reactivation. One third of patients underwent steroid pulse therapy. HBV-DNA was detected in one patient at baseline (case 3), and three was anti-HBs-positive. A mean interval between the start of non-biological DMARD therapy and reactivation was 14.1 mo in all

Table 5 Characteristics and outcomes of rheumatic disease patients with resolved infection who experienced viral reactivation during treatment with non-biological disease-modifying antirheumatic drugs

Case	Age/sex	Disease	Anti-HBs/anti-HBe	DMARDs	Duration	HBV-DNA[1] (copies/mL)	ALT[2] (IU/L)	Antiviral therapy	Outcomes	Ref
1	74/F	DM	ND /Pos.	AZA, PSL	12 mo	1.7×10^7	146	Yes	Died[7]	[75]
2	43/F	RA	ND/Pos.	LEF, SSZ, PSL	1 mo	3.5×10^3	79	Yes	Recovered	[54]
3	73/F	RA	Pos./Pos.[3]	MTX	10 mo	5.0×10^4	480	Yes	Recovered	[50]
4	72/M	TA	Neg./ND	MTX, PSL	6 mo	$> 1.0 \times 10^8$	308	Yes	Recovered	[123]
5	57/F	RA	ND[4]	MTX, PSL	5 mo[5]	$> 1.0 \times 10^9$	2012	Yes	Recovered	[121]
6	59/F	RA	ND	MTX, PSL	7 yr	1.6×10^7	378	Yes	Died[7]	[117]
7	47/F	RA	ND/Pos.	MTX, SSZ, PSL	15 mo	6.5×10^3	31	No	Recovered	[54]
8	75/M	DM	Neg./ND	MTX, AZA, CYA, PSL	15 mo	7.4×10^5	657	Yes	Recovered	[123]
9	67/F	RA, MCD	ND	MTX	37 mo	Neg.	NR	-	-	[51]
				MTX, TAC, PSL[6]	5 mo	Pos.[3]	NR	Yes	Recovered	
10	74/ND	RA	ND	MTX, PSL	ND	1.0×10^3	NR	Yes	Recovered	[49]
11	77/F	RA, IP	Pos./ND	TAC, PSL[6]	4 wk	4.2 log	NR	Yes	Recovered	[52]
12	78/F	MPA	Neg./ND	CPA, PSL	8 wk	1.8 log	NR	No	Recovered	[52]
13	58/F	SLE	Neg./ND	CPA, TAC, PSL[6]	4 wk	7.5 log	NR	Yes	Died[7]	[52]
14	30/F	SLE	Neg./ND	CPA, PSL[6]	8 wk	Pos.	Elevated	ND	Died[7]	[52]
15	59/F	SLE	Pos./ND	CPA, PSL[6]	4 wk	Pos.	NR	ND	Died[7]	[52]

No case had received preemptive therapy against HBV infection. [1]HBV-DNA levels were determined at diagnosis of HBV reactivation; [2]ALT values were determined at diagnosis of HBV reactivation or were the highest values measured after HBV reactivation; [3]HBV-DNA level was below 2.1 log copies/mL but HBV-DNA tested positive on real-time PCR; [4]Anti-HBc was also not searched; [5]The patient had received PSL and MTX (10 mg/wk) for 15 and 5 years prior to viral reactivation, respectively. Five months previously, the MTX dose had been increased to 12 mg/wk; [6]The patient received steroid pulse therapy; [7]The patients died of cerebral infarction (case 1), liver failure (case 6), sepsis (cases 13 and 14), and hemolytic anemia (case 15). DM: Dermatomyositis; RA: Rheumatoid arthritis; MCD: Minimal change disease; IP: Interstitial pneumonia; MPA: Microscopic polyangiitis; SLE: Systemic lupus erythematosus; DMARDs: Disease-modifying antirheumatic drugs; PSL: Prednisolone; MTX: Methotrexate; AZA: Azathioprine; CYA: Cyclosporine A; LEF: Leflunomide; SSZ: Sulfasalazine; TAC: Tacrolimus; CPA: Cyclophosphamide; HBV: Hepatitis B virus; anti-HBs: Anti-hepatitis B surface antibody; anti-HBe: Anti-hepatitis B e antibody; ALT: Alanine aminotransferase; Neg.: Negative; Pos.: Positive; ULN: Upper limits of normal; NR: Normal range; ND: Not determined or not described.

studies, except for one that lacked data on the interval period. Half of the patients had normal ALT levels at the time of reactivation. One patient died of hepatic failure (case 6) and four others of diseases not directly related to hepatitis (cases 1 and 13-15).

MANAGEMENT OF HBV REACTIVATION IN RHEUMATIC DISEASE PATIENTS

In 2014, the Japan Society of Hepatology updated the guidelines for the management of HBV infection[126]. Based on these updates, we recommend the following measures to prevent HBV reactivation in patients who are scheduled to receive biological and/or non-biological DMARDs.

Screening

Considering the risk of HBV reactivation during antirheumatic therapy and the effectiveness of antiviral prophylaxis with oral nucleoside analogue (NA), all rheumatic disease patients who are scheduled to start treatment with biological and/or non-biological DMARDs should receive screening for HBV infection. HBV serology (HBsAg, anti-HBc, and anti-HBs) should be screened first since it provides information regarding the status of HBV infection, as shown in Table 1. Chemiluminescent immunoassay/chemiluninescent enzyme immunoassay (CLIA/CLEIA) is recommended for determining HBV serology. HBV-DNA should be determined using a highly sensitive PCR technique such as a real-time PCR method.

One study pointed out that low baseline anti-HBs titers might be a risk factor for HBV reactivation in rheumatic disease patients with HBsAg-negative serology[52]. Several studies, however, reported a significant decrease in anti-HBs titers of rheumatic disease patients with resolved HBV infection or vaccinated patients during treatment with TNFα inhibitors and/or MTX. Yet no reactivation was observed in these patients, except in one who was HBV-DNA-positive at baseline[46,50,53,127]. In addition, as shown in Tables 4 and 5, viral reactivation occurred even in anti-HBs-positive rheumatic disease patients. In vaccinated subjects, immune memory appears to remain intact for more than 20 years following immunization, which allows for an anamnestic anti-HBs response upon exposure to HBsAg, even in subjects who have lost this antibody[128]. Thus, a decrease in anti-HBs or even their disappearance does not necessarily indicate loss of protection. This might be true for rheumatic disease patients with resolved HBV infection, although it should be kept in mind that antigen-specific memory B cell responses may decrease during anti-TNFα therapy[129,130].

Prophylaxis and treatment of HBV reactivation

For HBsAg-positive patients, HBV-DNA should be determined. If HBV-DNA levels are higher than 10^4 copies/mL with or without increased ALT levels, NA therapy should be started as soon as possible, whether antirheumatic therapy is required or not. When HBV-DNA levels range from negative to 10^4 copies/mL and normal ALT levels are present, patients are categorized as inactive HBsAg carriers and considered to be at increased risk of HBV reactivation during antirheumatic therapy. These patients should receive universal antiviral prophylaxis before starting therapy.

Although patients with resolved HBV infection seem to be less likely to develop viral reactivation compared with HBsAg carriers, HBV-DNA levels should also be measured. If the level is equal to or higher than 2.1 log copies/mL, prophylactic NA therapy should be started before the beginning of antirheumatic therapy. If HBV-DNA is lower than 2.1 log copies/mL, careful and periodical monitoring of serum levels of HBV-DNA, ALT, and HBsAg during antirheumatic therapy is recommended. Theoretically, the implementation of antiviral prophylaxis for all patients with resolved infection might be the most effective in preventing HBV reactivation. Considering the prevalence of the HBsAg-negative/anti-HBc-positive serology in endemic areas and the high cost of entecavir, however, universal prophylaxis is not recommended. The administration of antiviral NA can be deferred until the detection of serum HBV-DNA or HBsAg seroconversion[25].

For patients with completely negative serology, a conventional follow-up is generally performed, but the measuring of HBV-DNA is desirable prior to the start of antirheumatic therapy because of the presence of occult infection in patients negative for all serological markers for HBV[13].

For all patients who need the use of NAs, the type, length, and appropriate monitoring measures should always be decided upon through consultation with a hepatologist experienced in the management of HBV infection. Prophylaxis should be started as early as possible prior to commencing DMARD therapy. There are several NAs approved for the prophylactic treatment of HBV infection, including lamivudine, adefovir, and entecavir. When considering potent antiviral activity, extremely low rates of resistance development, and long-term use of antirheumatic drugs, entecavir is preferable as the first-line antiviral prophylaxis for rheumatic disease patients[131,132].

If HBV reactivation occurs during antirheumatic therapy, the medical advice of a hepatologist should be sought. Ongoing antirheumatic therapy should be continued, because immune restoration following withdrawal of DMARDs can cause rapid, immune-mediated destruction of HBV-infected hepatocytes and resultant hepatitis[25].

IMPORTANT, UNANSWERED QUESTIONS REGARDING PROPHYLAXIS OF HBV REACTIVATION DURING ANTIRHEUMATIC THERAPY, ESPECIALLY FOR PATIENTS WITH RESOLVED INFECTION

A number of recommendations/consensus statements have been established, but most of the supporting evidence was derived from the oncology and transplantation fields. Compared with patients in these fields, rheumatic disease patients generally undergo immunosuppressive therapy for longer periods. In addition, these patients are subject to a more tailored treatment for better control of disease activity. As a result, multiple immunosuppressants are administered throughout the patient's life.

How frequently should HBV-DNA monitoring be performed during antirheumatic therapy?

Two study groups in Japan jointly developed guidelines for the prevention of HBV reactivation in patients receiving chemotherapy or immunosuppressive therapy[25]. Based on these guidelines, the Japan College of Rheumatology (JCR) has recommended that monitoring of viral load and ALT levels be performed at monthly intervals during antirheumatic therapy and that this monitoring be continued for at least 12 mo after the cessation of therapy[133]. For rituximab-treated lymphoma patients, periodic monitoring of HBV-DNA allowed early commencement of antiviral therapy, which prevented the development of hepatitis and produced favorable outcomes[10,12]. But clinical evidence has not provided enough information to determine the optimal frequency and duration of HBV-DNA monitoring in such patients[24]. Hepatitis seems to occur after a delay that lasts for several days or weeks from the rise in or reappearance of serum HBV-DNA[5,6]. Hui *et al*[8] showed that a 100-fold increase in serum HBV-DNA preceded *de novo* HBV-related hepatitis by a median of 18.5 wk (range, 12-28 wk) in lymphoma patients who were receiving chemotherapy. There is no such data for rheumatic disease patients.

What is the optional duration of antiviral prophylaxis?

The optimal time point for the initiation of antiviral prophylaxis has not entirely been established. How early should antiviral prophylaxis be started to avoid viral reactivation? Several studies recommended that NAs should be administered 1-2 wk before immunosuppressive therapy for HBsAg carriers[102,134,135]. When can antiviral prophylaxis be discontinued? Most guidelines and consensus statements recommend that

antiviral prophylaxis be continued at least 6-12 mo after the cessation of immunosuppressive therapy. However, rheumatic disease patients often change DMARDs according to disease activity scores, and, in most cases, antirheumatic therapy continues throughout the patient's life. Expensive entecavir prophylaxis, in addition to biological therapy, is an economic burden to patients and societies. Reliable markers for making a decision regarding the discontinuation of antiviral prophylaxis are required for rheumatic disease patients.

CONCLUSION

With the increased use of biological and/or non-biological DMARDs, it has become evident that HBV reactivation occurs in rheumatic disease patients with HBsAg-negative/anti-HBc-positive serology. This is a critical issue requiring special attention, especially in endemic regions. The incidence of HBV reactivation is lower in HBsAg-negative patients than in inactive HBsAg carriers. While the mortality of *de novo* hepatitis is reportedly high in patients receiving anticancer chemotherapy, the outcome in rheumatic disease patients is favorable, which may be explained by an increased awareness of the risk for HBV reactivation in this patient population, the close monitoring of serum HBV-DNA, and the use of NAs at an early stage of HBV reactivation. At present, regular monitoring of serum viral DNA seems to be the most rational approach to preventing the devastating outcomes of HBV reactivation during antirheumatic therapy. Prophylactic strategies with NAs should be determined through a consultation with a liver specialist. Considering the lifelong use of multiple antirheumatic drugs, we need more specific guidelines for the management of rheumatic disease patients who are scheduled to receive biological and/or non-biological DMARDs.

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