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Review

Pretreatment Screening for Hepatitis B Virus Infection in Patients with Systemic Lupus Erythematosus

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Hepatitis B virus (HBV) infection is one of the most common diseases, and approximately two billion people are infected with HBV in the world. Until recently, hepatitis B surface antigen (HBsAg)-negative patients, carrying hepatitis B surface antibody (anti-HBs) and/or hepatitis B core antibody (anti-HBc), have been considered to have achieved the resolution of HBV infection; however, among those patients, the reactivation of HBV has been increasingly reported after chemotherapy, hematopoietic stem cell transplantation, or immunosuppressive therapy. The reactivation of HBV can cause lethal hepatitis called *de novo* hepatitis B. Therefore, serological examination for HBV infection before starting immunosuppressive therapy is now recommended for all patients with rheumatic diseases. Systemic lupus erythematosus (SLE) is one of the autoimmune diseases characterized by the production of autoantibodies and usually requires immunosuppressive therapy. However, to date, a few reports are available regarding the prevalence and time course of HBV infection in patients with SLE under immunosuppressive therapy. In this review, we update the prevalence and time course of HBV infection in lupus patients using our data and previous papers available, with a special emphasis on occult HBV infection and a decrease of HBV-related antibodies (anti-HBs and anti-HBc) under immunosuppressive therapy. This review also highlights the screening and management of HBV infection currently recommended and the potential role of HBV infection in the pathogenesis of SLE. Throughout the present review, we recommend the pretreatment screening for HBV infection in patients with SLE as well as patients with other rheumatic diseases.

Keywords: hepatitis B virus; immunosuppressive therapy; reactivation; resolved HBV infection; systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the loss of tolerance to self-antigens and the production of pathogenic autoantibodies, which damages multiple organs, such as the brain, the kidney, the skin, the joints, and others (Tsokos 2011). Generally, the liver is not considered to be a major target in SLE; however, 25-50% of lupus patients have abnormal liver function at some point during the disease course (Youssef and Tavill 2002; Chowdhary et al. 2008; Takahashi et al. 2010, 2013; Her et al. 2011; Huang et al. 2012; Bessone et al. 2014). Liver dysfunction can be caused by a wide range of factors, such as drugs, steatosis, SLE itself, viral hepatitis, and comorbid autoimmune hepatitis or primary biliary cirrhosis. It is important to differentiate among these causes because prompt and appropriate management may be required.

Hepatitis B virus (HBV) infection is one of the most common infectious diseases in the world (Lee 1997). About two billion people have been infected and more than 350 million are chronic carriers of the virus (Trepo et al. 2014). Seventy-five percent of these infected people live in Southeast Asia and the Western Pacific countries (Lee 1997). Until recently, hepatitis B surface antigen (HBsAg)-negative patients, carrying hepatitis B surface antibody (anti-HBs) and/or hepatitis B core antibody (anti-HBc), have been considered to have achieved the resolution of HBV infection; however, the reactivation of HBV, which can cause lethal hepatitis called *de novo* hepatitis B, after chemotherapy, hematopoietic stem cell transplantation, or immunosuppressive therapy in patients with resolved HBV infection has been increasingly recognized (Umemura et al. 2008; Urata et al. 2011; Oketani et al. 2012; Vassilopoulos

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and Calabrese 2012; Boyman et al. 2014). Although previous reports indicated that the prevalence of hepatitis B was lower than that of hepatitis C in lupus patients (Chowdhary et al. 2008; Takahashi et al. 2010, 2013; Huang et al. 2012), *de novo* hepatitis B may increase in the future because new biological agents for treating lupus patients are being introduced.

In this review, we address the prevalence and time course of HBV infection in lupus patients under immunosuppressive therapy using our data (Watanabe et al. 2013) and previous reports available. We also discuss the screening and management of HBV infection in lupus patients, with a focus on the possible role of HBV infection in the pathogenesis of SLE.

Prevalence of HBV infection in lupus patients

To clarify the prevalence of HBV infection in patients with SLE, we performed a cross-sectional study from January 2008 to April 2010 at our department in Japan (Watanabe et al. 2013). All lupus patients enrolled fulfilled at least four of the 1997 American College of Rheumatology (ACR) criteria (Hochberg 1997) and were tested for HBV markers, including HBsAg, anti-HBs, and anti-HBc, with a chemiluminescent immunoassay (CLIA).

Of the 248 lupus patients enrolled, only two patients (0.8%) were positive for HBsAg (Fig. 1). Of the remaining 246 HBsAg-negative patients, 41 (16.5%) patients showed the patterns of resolved HBV infection (anti-HBs-positive and/or anti-HBc-positive). Thus, the prevalence of HBV infection in lupus patients was 17.3% (43/248). In Japan, the prevalence of HBsAg is estimated to be 0.6-0.8%, and approximately 20% of individuals are infected with HBV (Yuki et al. 2003). Therefore, the prevalence of HBV infection in lupus patients was comparable to that in healthy individuals. In the case of rheumatoid arthritis (RA), the prevalence of resolved HBV infection was reported to be 31.5% (135/428), 25.1% (60/239), and 25.2% (177/703) in Japan (Mori 2011; Urata et al. 2011; Watanabe et al. 2014). These reports suggested that the rate of HBV infection in lupus patients was lower than in RA patients. This may be related to the difference in ages of RA and SLE onset.

Previous reports regarding the prevalence of HBV infection in lupus patients from various countries are summarized in Table 1 (Permin et al. 1982; Bonafede et al. 1986; Chng et al. 1993; Abu-Shakra et al. 1997; Lu et al. 1997; Ram et al. 2008; Watanabe et al. 2013). In previous studies by other groups, anti-HBs and anti-HBc were measured with a radioimmunoassay that was less sensitive than CLIA used in our study (Watanabe et al. 2013). About 20% of lupus patients, including those from Denmark and South Africa, showed a pattern of resolved HBV infection (Permin et al. 1982; Bonafede et al. 1986), indicating that serological examination for HBV should be performed not only in Asia and the Pacific countries but also worldwide.

Clinical features of lupus patients with resolved HBV infection

There are no reports describing clinical characteristics of lupus patients who have achieved the resolution of HBV infection except for our study (Watanabe et al. 2013). We compared the baseline characteristics (age, sex, and current liver function) of patients with resolved HBV infection and

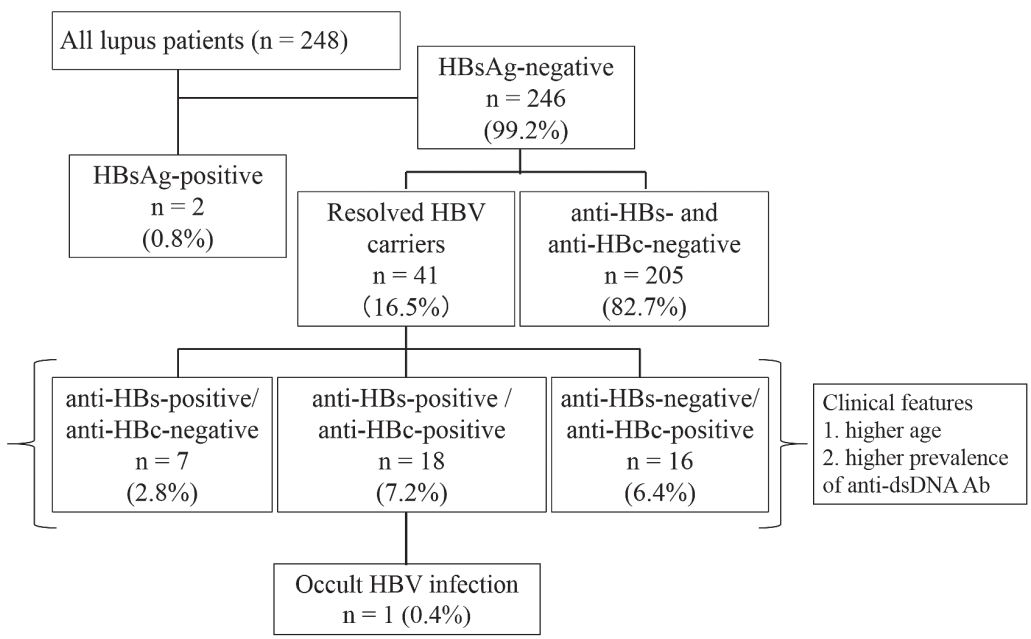

Fig. 1. Summary of our cross-sectional study.
Among 248 lupus patients, 41 patients showed the pattern of resolved HBV infection (Watanabe et al. 2013). Those patients had higher age and higher prevalence of anti-dsDNA antibody compared with anti-HBs- and anti-HBc-negative patients. Among resolved carriers, one patient had occult HBV infection.

Table 1. Summary of previous reports regarding the prevalence of HBV infection in lupus patients.

		Denmark	South Africa	Singapore	Israel	Taiwan	Israel	Japan
Reported year		1982	1986	1993	1997	1997	2008	2013
First author		Permin	Bonafede	Chng	Abu-Shakra	Lu	Ram	Watanabe
Healthy donors	Number tested (n)	ND	ND	19%* (19/100) unspecified	ND	692	140	ND
	HBsAg-positive				2%	14.7% (102/692)	ND	
	anti-HBs-positive				ND	ND	ND	
	anti-HBc-positive				ND	ND	10.7% (25/140)	
Lupus patients	Number tested (n)	32	100	76	95	173	117	248
	HBsAg-positive	0% (0/32)	1% (1/100)	19.7%* (15/76) unspecified	0% (0/95)	3.5% (6/173)	ND	0.8% (2/248)
	anti-HBs-positive	25% (8/32)	25% (25/100)		ND	ND	ND	10.1% (25/248)
	anti-HBc-positive	ND	ND		ND	ND	2.5% (3/117)	13.7% (34/248)

*19% of healthy donors and 19.7% of lupus patients had one or more of serological markers for HBV.
ND, no data.

those of anti-HBs- and anti-HBc-negative patients. Although there were few statistically significant differences in baseline characteristics between the two groups, the mean age of the former was significantly higher than that of the latter (50.3 ± 15.0 vs. 43.2 ± 14.7 years, p = 0.006), suggesting that older patients had higher incidence of resolved HBV infection (Fig. 1).

Clinical characteristics, autoantibodies listed in the ACR criteria, and SLE disease activity index (SLEDAI) were then compared between the two groups (Hochberg 1997; Petri et al. 2005). No statistically significant differences in clinical characteristics, autoantibodies, and SLEDAI were observed between the two groups, with the exception of the frequency of anti-double stranded (ds) DNA antibodies (92.7% vs. 76.6%, p = 0.02, Fig. 1). The reason behind patients with resolved HBV infection having a significantly higher incidence of anti-dsDNA antibodies compared with anti-HBs- and anti-HBc-negative patients remains unknown. We will discuss this issue again in the last section.

Occult HBV infection in lupus patients

In our study, serum HBV DNA levels were measured in 41 patients who showed the patterns of resolved HBV infection (Watanabe et al. 2013). HBV DNA quantification was performed using real-time polymerase chain reaction (RT-PCR) assay and the detection threshold was 2.1 log copies/mL. Among 41 lupus patients with resolved HBV infection, approximately half had previously been administered prednisolone (PSL) at doses higher than 40 mg/day and any immunosuppressive agents; however, no patients had experienced an acute exacerbation of hepatitis B, although it is widely known that corticosteroids can directly stimulate HBV DNA replication, and any kind of agents which have immunosuppressive potential may cause the reactivation of HBV (Tur-Kaspa and Laub 1990; Harigai et al. 2014).

Of these 41 patients, positive results for HBV DNA were obtained in one (2.4%) patient, a 61-year-old woman requiring a low dose of PSL (5 mg/day) and hemodialysis due to lupus nephritis (Fig. 1). Both anti-HBs and anti-HBc were positive. Although serum HBV DNA was detected (2.4 log copies/mL), the results of her liver function tests were within normal limits. Her condition was diagnosed as occult HBV infection (OBI) and was treated with entecavir (Watanabe et al. 2013).

OBI refers to the presence of HBV DNA in the absence of detectable HBsAg (Kwak and Kim 2014). The precise mechanisms underlying OBI are not well understood; however, both host and viral factors, such as defective host immune system and mutations in HBV DNA sequence, seem to have crucial roles in the pathogenesis of OBI (Kwak and Kim 2014). OBI has important clinical significance in patients with rheumatic disease because it can cause acute hepatitis after chemotherapy or immunosuppressive therapy (Onozawa et al. 2005; Yeo and Johnson 2006; Kusumoto et al. 2009). In our patient with OBI (Watanabe et al. 2013), its onset and duration and the involvement of immunosuppressive therapy remained unclear. However, to the best of our knowledge, this was the first report demonstrating that OBI is a possible complication in lupus patients (Watanabe et al. 2013).

Time course of HBV infection under immunosuppressive therapy

In addition to serum HBV DNA, positive markers of HBV infection (anti-HBs or anti-HBc) in patients with resolved HBV infection were repeatedly examined in our

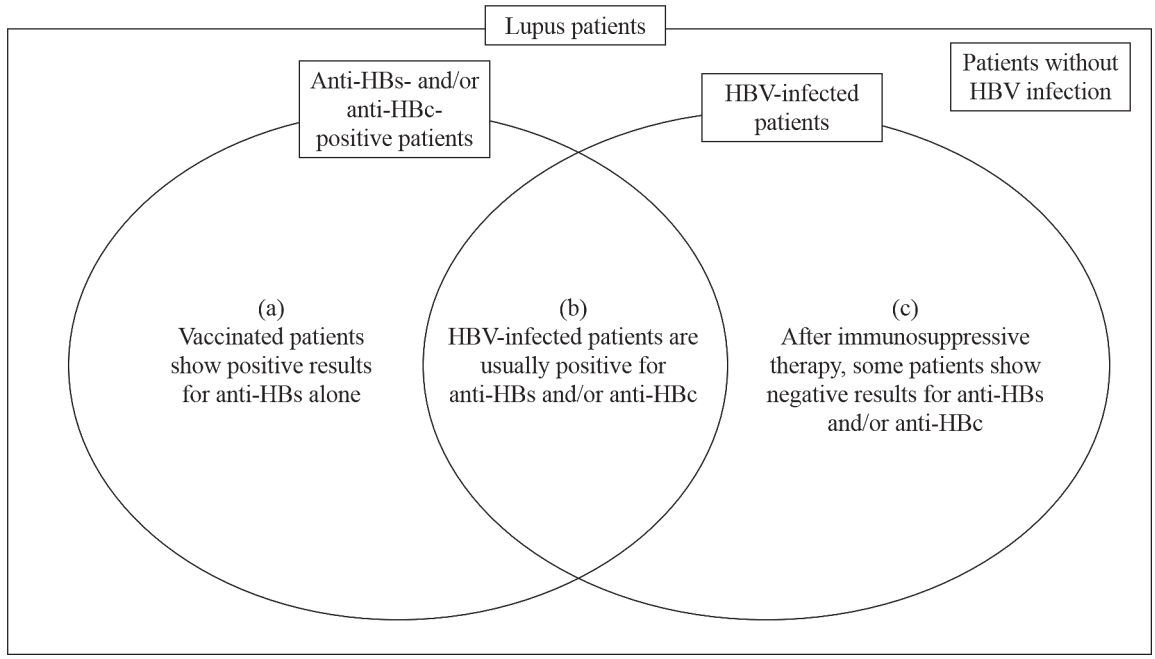

Fig. 2. Relationship between past HBV infection and HBV-related antibodies.
Most of the patients with past HBV infection show positive results for HBV-related antibodies (anti-HBs and anti-HBc). However, vaccinated patients without HBV infection are positive for anti-HBs alone. In addition, some patients who had already received immunosuppressive therapy show negative results for HBV-related antibodies. These patients still have the risk of the reactivation of HBV.

study (Watanabe et al. 2013). After a mean interval of six months between the first and the second test, the average anti-HBc titer (n = 12) did not significantly change; however, the anti-HBc titer decreased below the cut-off point in two patients (2/12, 16.7%). Similar to the anti-HBc titer, anti-HBs titer decreased below the threshold in two patients (2/10, 20%). Of the four patients whose anti-HBs or anti-HBc disappeared, immunosuppressive therapy was intensified in two patients because of disease onset or flare of lupus nephritis, whereas the treatment regimen of the others was not changed.

Decreases in anti-HBs or anti-HBc titer have been reported in patients receiving hematopoietic stem cell transplantation, chemotherapy, or anti-tumor necrosis factor inhibitor (Wands et al. 1975; Onozawa et al. 2005; Charpin et al. 2009). In addition, a decrease in anti-HBs has been shown to precede the reactivation of HBV in hematological disorders (Wands et al. 1975; Onozawa et al. 2005). Collectively, these findings suggest two important things. First, because even low-dose PSL therapy induced the disappearance of these HBV-related serum markers in patients with SLE, measurements of anti-HBs and anti-HBc titers should be performed before immunosuppressive drug administration. Second, if the patients have already received immunosuppressive therapy, we must recognize the risk of HBV reactivation even if all HBV-related markers are negative (Fig. 2).

Screening and management of HBV infection in lupus patients

Based on the reports regarding the reactivation of HBV and *de novo* hepatitis B, the Centers for Disease Control, the ACR, the European League Against Rheumatism (EULAR), and the Japanese College of Rheumatology (JCR) now recommend HBV serological screening before administering immunosuppressive therapy to patients with rheumatic diseases (Weinbaum et al. 2008; Mosca et al. 2010; Singh et al. 2012; Harigai et al. 2014). According to the algorithm proposed by JCR (Harigai et al. 2014), all patients should be screened for HBsAg before immunosuppressive therapy. In addition, those who are negative for HBsAg should be tested for anti-HBs and anti-HBc. HBV DNA quantification using RT-PCR should be performed in patients with resolved HBV infection. If the patients show positive results for HBsAg or HBV DNA, prophylactic nucleoside analogs, such as entecavir, should be administered (Harigai et al. 2014). However, the evidence to support the validity of this algorithm to prevent severe hepatitis may not be sufficient. In addition, monthly monitoring of HBV DNA is recommended in this algorithm on the basis of the previous report describing *de novo* hepatitis B in patients who received cytotoxic agents including rituximab (Hui et al. 2006); however, no data is available regarding whether monthly monitoring of HBV DNA is required in lupus patients. Considering that our patient who had positive result for HBV DNA still had normal liver function, a time interval between the positive conversion of HBV DNA

and the acute exacerbation of liver function abnormalities may exist in lupus patients.

Hepatitis B vaccination in lupus patients

In the case of RA, ACR recommends that all killed (pneumococcal, influenza, and hepatitis B), recombinant (human papillomavirus), and live attenuated (herpes zoster) vaccines should be administered before the start of immunosuppressive therapy (Singh et al. 2012). Moreover, ACR recommends that killed hepatitis B vaccine should be administered even in RA patients under treatment if vaccination was not previously done (Singh et al. 2012). Although the EULAR recommendation includes a description regarding hepatitis B vaccination in lupus patients, the level of evidence to recommend hepatitis B vaccination is low (Mosca et al. 2010). In addition, hepatitis B vaccination has been implicated as a potential trigger for the occurrence or exacerbation of lupus (Aron-Maor and Shoenfeld 2001; Geier and Geier 2004; Millet et al. 2009). Moreover, in a murine model, immunization with hepatitis B vaccine induced the acceleration of kidney disease with the elevation of anti-dsDNA antibodies in lupus-prone mice (Agmon-Levin et al. 2014). On the other hand, small-sized prospective studies demonstrated that hepatitis B vaccination was safe in inactive juvenile and adult patients with SLE and that the antibody response was not affected by immunosuppressive therapy (Kuruma et al. 2007; Aytac et al. 2011). Taken together, lupus patients should provide an informed consent regarding whether or not they should be vaccinated with the help of their physician.

A role of HBV infection in the pathogenesis of SLE

Several studies from HBV-endemic countries, such as Taiwan, Israel, and China, suggest that patients with SLE have lower prevalence of serum HBsAg or anti-HBc compared with healthy individuals (Lu et al. 1997; Ram et al. 2008; Zhao et al. 2010). For example, in China, the prevalence of serum HBsAg is 2.33% in lupus patients and 9.56% in healthy individuals (Zhao et al. 2010). In addition, anti-HBc was detected in 2.5% (3/117) of lupus patients and 10.7% (15/140) of normal controls in Taiwan (Lu et al. 1997). Those authors suggested that the hypersecretion of interferon alpha found in the sera of lupus patients could protect these patients from HBV infection (Lu et al. 1997; Ram et al. 2008; Zhao et al. 2010). On the contrary, other studies showed that the prevalence of HBV infection was comparable between lupus patients and healthy individuals (Chng et al. 1993; Watanabe et al. 2013). This issue remains controversial; however, these differences may result from various factors, such as selection bias or small group sizes, and remain a matter of speculation.

As described above, Agmon-Levin et al. (2014) showed the acceleration of lupus-like kidney disease following immunization with HBV vaccine in NZBWF1 mice, which are genetically prone to develop SLE-like disease. As an additional line of evidence relating HBV antigens and lupus kidney disease, Looi and Prathap (1982) reported that HBV-associated antigen deposition was found in the renal tissue of 63.8% (30/47) of lupus patients. Consistent with their report, Wang et al. (2012) demonstrated that HBV-associated antigen deposition was present in 50.6% (84/166) of renal biopsies from lupus patients. However, they also showed the HBV-associated antigen deposition in patients who had negative results of serological HBV screening tests, suggesting the cross-reactivity between the deposited immunoglobulins and the anti-HBsAg antibody used to stain HBsAg in the renal tissues (Wang et al. 2012). In our study (Watanabe et al. 2013), the patients with resolved HBV infection had a significantly higher prevalence of anti-dsDNA antibodies compared with anti-HBs- and anti-HBc-negative patients. However, it remains to be clarified whether these differences may be a result of selection bias, small group sizes, or cross-reactivity between anti-dsDNA antibodies and HBV-related antibodies.

Conclusion

Although the prevalence of HBV infection in lupus patients was comparable to that in healthy individuals and the reactivation of HBV was not observed, OBI and a decrease in anti-HBs and anti-HBc titers in patients with resolved HBV infection were found in our study. These results indicate that serological screening for HBV infection should be performed before starting immunosuppressive therapy in lupus patients. The role of the HBV infection in the pathogenesis of SLE remains a matter of speculation, and further research is warranted.

Conflict of Interest

The authors declare no conflict of interest.

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