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Review Article

Risk-stratified management strategies for HBV reactivation in RA patients receiving biological and targeted therapy: A narrative review

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Abstract It is estimated that more than two billion people around the world have been infected by Hepatitis B virus (HBV). Reactivation of HBV (rHBV) is a potentially fatal complication after biological therapy. With the increasing use of biologics and targeted therapy in rheumatoid arthritis (RA) patients who are refractory to conventional synthetic disease-modifying anti-rheumatic drugs, rHBV in those with past infection has become increasingly problematic, especially in HBV-endemic regions. Among those receiving biological therapy, the risk of rHBV varies according to the status of HBV infection and the degree of biologic-related immunosuppression. As rHBV is largely preventable, it is imperative that the risk status of rHBV in RA patients receiving biological and targeted therapy be stratified. Therefore, the aim of this review was to summarize the reported data on rHBV, and propose management strategies for RA patients with different risks of rHBV based on evidence presented in the current literature.
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Introduction

It is estimated that more than two billion people around the world have been infected by HBV.[1] Hepatitis B virus (HBV) is highly endemic in Southeast Asia, Africa, South America, and other parts of the world outside North America and Western Europe.[2,3] Although the prevalence of chronic HBV infection has fallen due to mass HBV vaccination programs for children, the estimated population of HBV carriers continued to grow from 223 million in 1990 to 240 million in 2005.[4] Moreover, a substantial number of rheumatoid arthritis (RA) patients have coexisting HBV infection, and RA is a risk factor for developing HBV reactivation (rHBV) due to the use of immunosuppressive agents including biological agents.[5–8]

With the advancement of pharmaceutical technology, biological and targeted therapy is increasingly used in RA patients who are refractory to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).[9] The available biological and targeted therapy to date are as follows: a) tumor necrosis factor (TNF)-α inhibitors including infliximab, etanercept, adalimumab, golimumab, and certolizumab; b) antibodies targeting CD20 of B-cell (rituximab); c) interleukin (IL)-6 receptor inhibitor (tocilizumab); d) T-cell costimulatory molecule inhibitor (abatacept) and e) janus kinase inhibitor (tofacitinib). However, cytokines, B-cell, costimulatory molecules and janus kinase play important roles in controlling HBV infection, rHBV is a critical challenge in RA patients receiving biological or targeted therapy.[7,8,10–13] Because rHBV is largely preventable, guidelines have been proposed for HBV screening at baseline and antiviral prophylaxis is initiated before therapy with immunosuppressants including biologics in RA patients with chronic HBV infection.[6,14,15]

rHBV is a potentially fatal complication after biological or targeted therapy. Thus, stratification of the risk status of rHBV in RA patients receiving biological or targeted therapy is crucial. Therefore, the aim of this review was to summarize the reported data on rHBV, and to propose management strategies for RA patients with different risks of rHBV based on the current literature.

Natural history and pathophysiology of rHBV

After acute HBV infection, persistent existence of HBsAg for more than six months is considered chronic HBV infection.[16] For unclear mechanisms, immune responses to HBV are not effective for years or decades.[17] Despite enhanced viral replication, vigorous immune responses to HBV and liver injuries are absent, suggesting T-cell exhaustion in chronic HBV infection.[1,17] rHBV can occur either spontaneous or after immunosuppressants or cancer chemotherapy. It can be divided into three phases.[1,16] Phase one usually occurs after initiation of therapy with immunosuppressive therapy. Host immunity against HBV is impaired and therefore, HBV replication accelerates, while serum alanine transaminase (ALT) levels may be within the normal range. In this phase, patients can be asymptomatic. Phase two occurs after a certain period following dose reduction or cessation of immunosuppressives. As cellular immune function restoration attempts to clear HBV-infected hepatocytes, HBV DNA levels decrease but serum ALT typically rises. Patients in phase two may have fatigue, malaise or jaundice. Finally, rHBV may result in either clearance of HBV, persistent hepatocellular injury and cirrhosis or fulminant hepatic failure in phase three.

Definition of HBV infection and rHBV

Chronic HBV infection can be divided into 4 phases.[14] Phase 1: HBeAg-positive chronic HBV infection, previously termed "immune tolerant" phase. It is characterized by the presence of very high levels of HBV DNA but normal ALT. There is minimal or no liver necroinflammation or fibrosis. Phase 2: HBeAg-positive chronic hepatitis B. There is high levels of HBV DNA and elevated ALT. Besides, moderate or severe liver necroinflammation and accelerated progression of fibrosis can be observed. Phase 3: HBeAg-negative chronic HBV infection, previously termed "inactive carrier" stage. It is characterized by the presence of serum anti-HBeAg antibodies, undetectable or very low HBV DNA ($<$2000 IU/ml) and normal ALT. Only minimal hepatic necroinflammatory activity and low fibrosis can be found. Phase 4: HBeAg-negative chronic hepatitis B. It is characterized by the lack of serum HBeAg with detectable anti-HBe antibodies. Moderate to high levels of HBV DNA ($>$2000 IU/ml) with fluctuating or persistently elevated ALT values could also be observed. The liver pathology demonstrates necroinflammation and fibrosis.

Past HBV infection is defined by negative HBsAg and positive HBcAb.[18] Past HBV infection includes occult HBV infection defined as HBcAb-positivity in the presence of HBV-DNA in blood and/or hepatocyte, and resolved HBV infection defined as the presence of HBcAb with undetectable HBV-DNA.[16,17]

Patients were categorized as having mild hepatitis B flare, severe acute exacerbation of HBV and hepatic decompensation according to the change of biological and virological data after immunosuppressive therapy. At a conference in 2013 on "Reactivation of Hepatitis B" organized by the American Association for the Study of Liver Diseases, standardized nomenclature was proposed. rHBV should be defined as a marked increase in HBV replication ($\geq$2 log increase from baseline levels or a new appearance of HBV DNA to a level of $\geq$100 IU/ml) in a person with previously stable or undetectable level by the American Association for the Study of Liver Diseases.[19,20] Hepatitis B flare should be defined after excluding other liver diseases (e.g., hepatitis C, drug-induced liver injury, alcoholic hepatitis, non-alcoholic fatty liver disease, and autoimmune hepatitis). Mild hepatitis B flare was defined as a five-fold increase in ALT that exceeded the upper limit of normal (ULN). Severe acute exacerbation (SAE) of HBV was defined as a more than ten-fold elevation of ALT that exceeded the ULN or hepatic decompensation.[21]

Risk stratification of rHBV in RA patients

When interpreting data in this review, it was important to bear in mind that the prevalence of HBV infection varies greatly in different areas. The frequency of HBsAg seropositivity in Taiwan was reported to be 15–20% and the

positive rate of HBcAb and/or HBsAb was 80–85%.[3] However, the frequency of HBsAg seropositivity was reported to be 1.5% and the positive rate of HBcAb and/or HBsAb was 23.2% in Japan.[22]

HBV reactivation has been observed in RA patients treated with csDMARDs such as methotrexate, high-dose corticosteroids, biological and targeted DMARDs.[6–8] Among those receiving biological and targeted therapy, the risk of rHBV varies according to the status of HBV infection before therapy and the degree of medication-related immunosuppression.

Risk stratification according to baseline status of HBV infection

Risk categorization of the status of HBV infection before biological and targeted therapy can be accomplished with three serological markers of HBV (HBsAg, HBcAb-IgG, and HBsAb) and HBV-DNA viral loads. Baseline status of HBV infection has been reported to be associated with rHBV in patients receiving chemotherapy or immunosuppressive therapy.[22] Accumulating evidence reveals a marked difference in risk status for HBV reactivation between HBsAg-positive and HBsAg-negative patients receiving immunosuppressive agents, biologics and targeted therapy.[6–8,23]

Among RA patients with chronic HBV infection, the risk of rHBV seems to be highest in those with chronic HBV hepatitis or HBeAg-positive, followed by inactive HBV carrier. Among patients with past HBV infection, the risk of rHBV may be higher in those with occult HBV infection, followed by patients with resolved HBV infection, and may be lowest in patients with high levels of HBsAb.

Risk stratification according to therapy-related immunosuppression

HBV reactivation risk is also determined by host immunity interfered by immunosuppressive agents. Rituximab, a human-mouse chimeric monoclonal antibody that targets the CD20 antigen located on B cells, can induce profound B-cell depletion, resulting in secondary immunosuppression of patients. The data from rituximab-based chemotherapy for lymphoma showed a higher incidence (27–80%) of HBV reactivation without antiviral prophylaxis.[24] Recently, it was reported that rituximab therapy with premedication of corticosteroids was a risk for rHBV in RA patient.[25] In 2013, the US Food and Drug Administration (FDA) issued a safety advisory for rituximab therapy after a review of confirmed rHBV mortality, and warned that rituximab-associated HBV reactivation could occur.[26] Previous studies demonstrated that there was a high risk of rHBV in HbsAg-positive patients treated with TNF-α inhibitors if no antiviral prophylaxis was given.[7,8]

rHBV in HBsAg-positive RA patients receiving biological and targeted therapy

The risk of rHBV is extremely high in HBsAg-positive patients without antiviral prophylaxis, and most reported cases of rHBV were found in HBsAg-positive RA patients receiving biological and targeted therapy.[7,8,27–29] Because there is a strong immunosuppressive effect induced by rituximab therapy, the risk of rHBV may be greatest (up to 50%) in HBsAg-positive RA patients,[29] which is supported by data showing HBV reactivation following rituximab-based chemotherapy for lymphoma.[25] However, more evidences are needed for rHBV following rituximab therapy in RA patients with chronic HBV infection.[26] Regarding the safety of anti-TNF-α therapy, our previous report and other studies found that 6.9–62.5% of HBsAg-positive RA patients had rHBV after anti-TNF-α therapy if anti-viral prophylaxis was not administered.[7,8,28–33] With respect to other biologics, Kim et al. reported the safety data of abatacept in RA patients with positive HBsAg, indicating that all four of the patients without anti-viral prophylaxis experienced rHBV.[34] However, preemptive anti-viral treatment prevented rHBV in another four patients. Another recent report from Taiwan demonstrated that 1 in 2 HBsAg-positive RA patients developed rHBV following abatacept treatment without preemptive anti-viral therapy.[29] The risk for rHBV in HBsAg-positive RA patients receiving tocilizumab were only reported in a few case series and future controlled studies are needed.[26,29,35–37] Tofacitinib have been shown to counteract the suppressive effects of interferon-α on HBV replication.[13] Our recent report also indicates that rHBV may occur after tofacitinib treatment in 33% RA patients with HBV carrier.[38] Close follow up of this high-risk population of RA patients is essential.

A summary of rHBV in HBsAg-positive RA patients receiving biological and targeted therapy is illustrated in Table 1.

rHBV in HBsAg-negative RA patients receiving biological or targeted therapy

For patients with past HBV infection (HBcAb-IgG +), risk of rHBV depends on whether the patients have cleared the viral infection. If the presence of HBV DNA in blood and/or hepatocytes is detectable, these patients should be considered to have occult HBV infection.[17] A meta-analysis of patients with occult HBV infection identified a more than 5-fold increased rate of rituximab-associated HBV reactivation.[24] Although Mitroulis et al. reported no rHBV in twelve RA patients who had past HBV infection and received rituximab therapy, patients with occult HBV infection are still at risk of rHBV.[39] Regarding other biologics, previous reports indicated that the risk of rHBV in RA patients with occult HBV infection following anti-TNF-α therapy is low to moderate.[8,40–42] The risk of reactivation may be related to the persistence of covalently closed-circular HBV DNA (cccDNA) that can serve as template for HBV gene transcription.[17]

For patients with resolved HBV infection with or without detectable HBsAb level, the risk of rHBV following biological or targeted therapy is very low, but not zero.[40] In addition, HBsAb levels could decline and HBsAg seroreversion (i.e., reappearance of HBsAg) was reported following anti-TNF-α or rituximab therapy.[8,33] A summary of rHBV in RA patients who had past HBV infection and received biological or targeted therapy is illustrated in Table 1.

Table 1 The reported data of HBV reactivation in rheumatoid arthritis (RA) patients receiving biological and targeted therapy according to risk status.

	Authors[Ref]	No. of patients	Anti-viral prophylaxis	HBV reactivation
Chronic HBV (HBsAg+)				
Rituximab	Mitroulis et al.[39]	2	+	0 (0%)
	Chen et al.[29]	5	−	3/6 (50%)
Anti-TNF-α	Zingarelli et al.[7]	23	16 (−) 7 (+)	12/16 (75%) 1/7 (14.3%)
	Chung et al.[31]	8	−	1/8 (12.5%)
	Tamori et al.[32]	5	−	2/5 (40%)
	Perez-Alvarez et al.[28]	89	−	35/89 (39%)
	Vassipoulos et al.[33]	14	+	1 (7.1%, LAM resistance)
	Lan et al.[8]	18	10 (+) 8 (−)	0/10 (0%) with NUC 5/8 (62.5%) without NUC
	Ryu et al.[30]	11	−	1/11 (9.1%)
	Chen et al.[29]	28	−	8/26 (30.8%)
Tocilizumab	Nagashima et al.[35]	1	−	1 (100%)
	Tsuboi et al.[36]	1	+	0 (0%)
	Chen et al.[29]	2	−	0 (0%)
Abatacept	Kim et al.[34]	8	4 (+) 4 (−)	0/4 (on NUC Rx.); 4 (100%)/4 without NUC
	Chen et al.[29]	2	−	1/2 (50%)
Tofacitinib	Chen et al.[38]	6	4 (+)	2 (100%)/2 without NUC
Past HBV infection(HBsAg−/HBcAb+)				
Rituximab	Mitroulis et al.[39]	12		0 (0%)
Anti-TNF-α	Mori et al.[23]	60	−	2/60 (3.3%)
	Tamori et al.[32]	45	−	1/45 (2%)
	Vassipoulos et al.[33]	19	−	0 (0%)
	Lan et al.[8]	12	−	1/12 (8.3%)
	Perez-Alvarez et al.[28]	168	−	9/168 (5.0%)
	Lee et al.[41]	327	−	7/327 (2.1%)
	Caporali R et al.[42]	59	−	0 (0%)
Tocilizumab	Nakamura et al.[37]	18	−	2/18 (11.1%)
Abatacept	Nakamura et al.[37]	2	−	0 (0%)
Tofacitinib	Chen et al.[38]	75		0 (0%)
HBV-vaccinated status				
	Vassipoulos et al.[33]	19	−	0 (0%)

HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBcAb: antibody against HBV core antigen; TNF-α: tumor necrosis factor-α; LAM: lamivudine; NUC: pre-emptive nucleotide analogues.

Similar to a previous report for patients with malignant lymphoma,[22] the risk of rHBV can be stratified according to the status of HBV infection and the strength of treatment-related immunosuppression as shown in Fig. 1.

Antiviral prophylactic or preemptive therapy

It is well-recognized that prophylactic or preemptive antiviral therapy can reduce the incidence of rHBV, the severity of associated HBV hepatitis, and mortality.[8,43] The timing of initiating antiviral therapy for hepatitis caused by rHBV (the so-called on demand therapy) may be too late to achieve eradication of virus.[44] Therefore, it would be highly desirable to identify patients in high-risk groups before biological or targeted therapy is needed, as prompt initiation of antiviral prophylaxis of rHBV is critical.[8,14,15] However, risk assessment and management strategies for rHBV in RA patients receiving biological or targeted therapy have not been widely reported.[6,27,45]

The optimal duration of antiviral prophylaxis after completion of biological or targeted therapy has not been determined. Based on the results of previous studies and a meta-analysis in patients receiving chemotherapy for hematological malignancies, six to twelve months of antiviral prophylaxis after completion of rituximab-based chemotherapy may be sufficient.[24,46] The results of a recent study showed that 71% of RA patients who discontinued antiviral prophylaxis developed rHBV three to twenty-one months after discontinuation.[47] However, the optimal duration of antiviral prophylaxis after completion of biological or targeted therapy may vary with different antiviral drugs and treatment used.[41,47]

To date, there is a lack of evidence regarding the choice of antiviral drug to be used for prophylaxis against rHBV. Lamivudine resistance was reported to be 24% at one year for patients with HBV infection,[47] and drug resistance may further increase after long-term treatment. Moreover, recent studies showed that entecavir was more effective than lamivudine with respect to virological response and normalization of hepatic enzymes in HBV-infected patients receiving rituximab-based chemotherapy.[43,46] Although reports on prophylactic antiviral agents have, to date, mainly investigated lamivudine,[48] both entecavir and tenofovir have been recommended as the first-line agents in patients

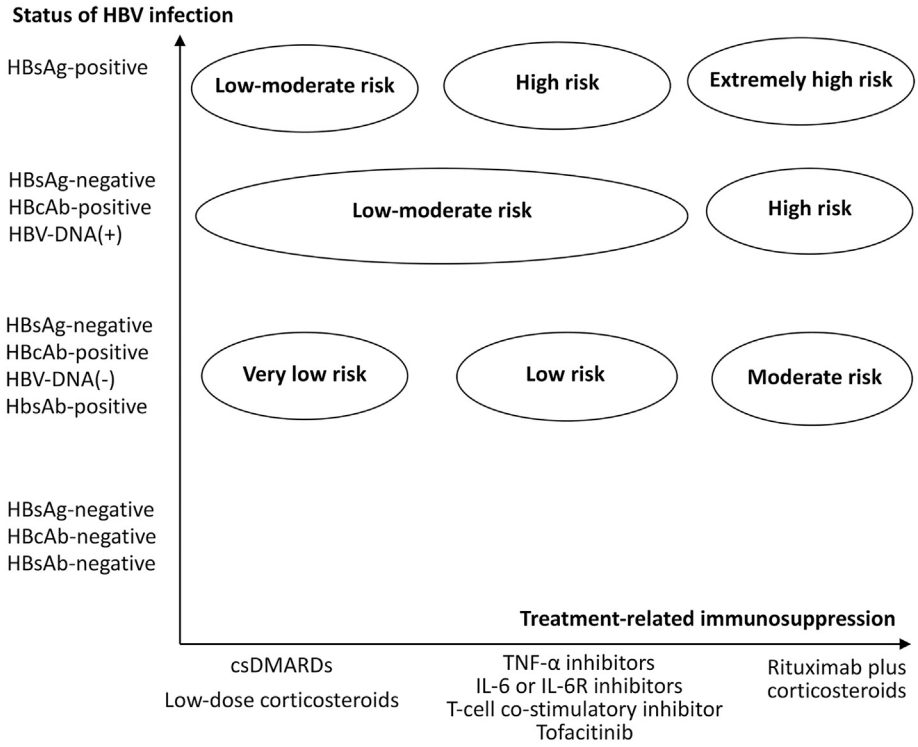

Figure 1. Risk stratification for HBV reactivation in rheumatoid arthritis (RA) patients receiving biological or targeted therapy. The vertical axis shows the status of HBV infection based on HBV serological markers and HBV-DNA before therapy. The horizontal axis shows the conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologics or targeted therapy used. HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBcAb: antibody against HBV core antigen; HBsAb: antibody against HBV surface antigen. This Figure was reproduced by permission and modified from Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. *Int J Hematol* 2009;90:13—23.

receiving chemotherapy.[14,15,18] The choice of appropriate antiviral agents depends on the status of HBV infection and the duration of the scheduled biological or targeted therapy. Therefore, anti-viral agents with higher potency and genetic barrier to resistance, such as entecavir, tenofovir or tenofovir alafenamide fumarate, would be appropriate choices in patients who have chronic HBV hepatitis and are anticipated to receive long-term (≧twelve months) biological or targeted therapy in whom there is a high risk of lamivudine resistance. In contrast, patients with inactive HBV carrier or occult HBV infection, or those receiving short-term (<twelve months) may be treated with lamivudine first, according to recent reviews.[48] Further prospective studies are needed to determine the cost-effectiveness of entecavir or tenofovir as the first-line prophylactic antiviral agents.[49,50]

Risk-stratified management strategies for rHBV

Baseline screening for HBV infection

Given the risk of HBV reactivation and availability of effective antiviral prophylaxis, screening for HBV infection should be conducted in all RA patients scheduled for biological therapy. European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver Disease (AASLD) recommend that HBsAg and HBcAb should be performed in patients who are at risk of rHBV prior to starting chemotherapy or immunotherapy.[14,15,18,27,49] Three serological tests including HBsAg, HBcAb, and HBsAb should be performed before starting biological or targeted therapy, and HBV-DNA viral loads should be examined if evidence of HBV infection exists.[8,27,45,50] In addition, serum levels of ALT and total bilirubin should be checked and HBeAg should be determined if chronic HBV hepatitis exists. For patients who have no evidence of previous HBV infection, completion of vaccination would be suggested before starting biological or targeted therapy.[14,15]

Management strategies for HBsAg-positive patients receiving biological or targeted therapy

Systemic reviews indicated that antiviral prophylaxis should be given in rheumatic patients with HBV infection.[49] A low proportion (0—14%) of RA patients who received antiviral prophylaxis developed rHBV, whereas 24—73% of HBsAg-positive patients without antiviral prophylaxis developed rHBV,[7,8,27] indicating the efficacy of antiviral prophylaxis in preventing rHBV. Considering high risk of rHBV with potential fatal complications in HBsAg-positive patients receiving biological or targeted therapy, antiviral prophylaxis should be initiated one to two weeks before starting therapy and during the period of therapy.[44] In addition,

periodic monitoring of HBV-DNA and ALT levels is necessary after stopping antiviral treatment.[14,15]

Management strategies for HBsAg-negative patients receiving biological or targeted therapy

Management strategies for HBsAg-negative patients receiving biological or targeted therapy have not been established. Antiviral prophylaxis is recommended for occult HBV-infected patients receiving biologics such as rituximab, TNF-α inhibitors, other biologics and targeted therapy.[8,51] Considering the high cost of antiviral therapy and relatively low risk of rHBV, universal antiviral prophylaxis may be impractical in RA patients with resolved HBV infection.[42] However, monitoring of ALT levels and HBV-DNA loads every three months appears to be the most rational approach for preventing rHBV -associated hepatitis.[27,45]

Owing to the high prevalence of HBV infection in Taiwan, the Taiwan Rheumatology Society established a group of experts, including rheumatologists and hepatologists, to assess evidences with a view to develop strategies for rHBV in rheumatic patients on biological therapy. At the end of 2012, such management strategies were proposed and subsequently revised in early 2015. We recommend an algorithm (Fig. 2) which emphasizes appropriate screening of HBV infection and antiviral prophylaxis for those with a risk of rHBV. For HBsAg-positive patients, HBV viral loads should be checked and antiviral prophylaxis be given before starting biological or targeted therapy. For patients with occult HBV infection, antiviral prophylaxis should be given to those at risk. Monitoring of ALT and HBV-DNA should be performed for those with positive HBsAg and occult HBV infection. Among patients with resolved HBV infection with positive HBsAb, antiviral prophylaxis may be unnecessary, but periodic monitoring of ALT levels will still be needed, particularly in HBV endemic areas.

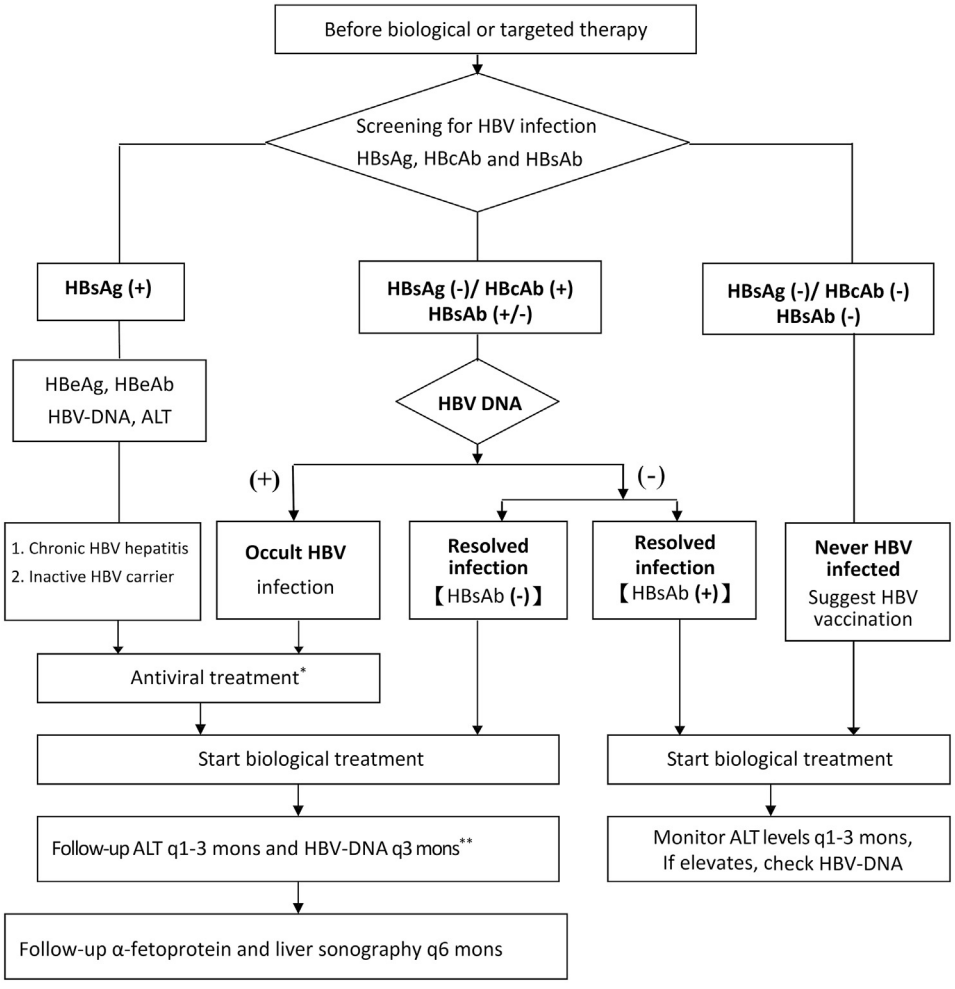

Figure 2. Management strategies for hepatitis B virus (HBV) reactivation in rheumatoid arthritis (RA) patients receiving biological or targeted therapy proposed by the Taiwan Rheumatology Association based on the current treatment guidelines and data presented in previous reports. TNF: tumor necrosis factor; HBsAg: HBV surface antigen; HBsAb: antibody against HBV surface antigen; HBcAb: antibody against HBV core antigen; ALT: alanine aminotransferase. *Antiviral therapy should be given before starting or resuming biologics. Agents with low resistant rate are preferred (eg. entecavir, tenofovir or tenofovir alafenamide fumarate). **The intervals of monitoring HBV DNA may extend to 6—12 months after the first follow-up if choosing entecavir, tenofovir or tenofovir alafenamide fumarate as antiviral agent.

Conclusions

rHBV is a potentially fatal complication after biological or targeted therapy, and the kinetics of reactivation differed by therapeutic agents and baseline HBV status.[45] It is necessary to stratify the risk status of rHBV in RA patients receiving biological or targeted therapy. All patients should be screened to identify risk for rHBV before starting biological or targeted therapy by measuring HBV serological markers including HBsAg, HBcAb, and HBsAb. As rHBV is largely preventable, antiviral prophylaxis should be initiated in patients with risk of rHBV, and regular monitoring of HBV-DNA levels is a reasonable approach. Future prospective studies are needed to investigate the optimal frequency of serum HBV-DNA monitoring, and the duration of antiviral prophylaxis in RA patients during and after biological or targeted therapy.

Conflicts of interest

There are no conflicts of interest.

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