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BRIEF REPORT

HBsAg-negative/anti-HBc-positive patients treated with rituximab: prophylaxis or monitoring to prevent hepatitis B reactivation?

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Abstract

Rituximab (RTX) has been classified as a drug associated with a high risk for hepatitis B virus (HBV) reactivation in HbsAg-negative/anti-HBc-positive patients. However, data on frequency of HBV reactivation are limited especially for RTX monotherapy. Several new recommendations for screening, monitoring and prophylactic antiviral treatment have been published recently. Here, we report the real-life experience in the management and reactivation rate of HbsAg-negative/anti-HBc-positive patients treated with RTX with or without chemotherapy from a large cohort and discuss our results in the light of updated recommendations.

Keywords Rituximab · Hepatitis B · Reactivation · Risk groups · Hematologic diseases · Autoimmune diseases · Monotherapy

Introduction

HBV-exposed patients receiving immunosuppressive therapy are at risk of HBV reactivation. Strikingly, HBV does not only flair in a chronic disease state but also after the loss of HBsAg. Despite elimination of the virus from the blood, viral DNA persists in the nucleus of infected hepatocytes and HBV reactivation can occur under immunosuppression. This can lead to symptomatic hepatitis, liver failure or even death [1].

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Therefore, clinicians should be aware of the risk of hepatitis B reactivation and consider screening and initiate preventive measures [2, 3]. In HBsAg-positive patients, initiation of antiviral therapy before immunosuppression is uniformly recommended. In contrast, the management of HBsAg-negative/anti-HBc-positive patients is not well defined.

A broad range of immunosuppressive and targeted immunotherapeutic agents are available for hematologic, autoimmune and infectious diseases. Specific drug classes have different potential to cause hepatitis B reactivation. Recently, the American Gastroenterological Association (AGA) estimated the potential risk of HBV reactivation by drugs based on a comprehensive review of the literature. Based on this analysis, the authors proposed a classification of low- (< 1%), moderate- (1–10%) or high (> 10%)-risk drugs (Table 1) [4, 5].

Rituximab (RTX), a B-cell-depleting agent broadly used in hematological and autoimmune diseases, has been assigned to the high-risk group drugs of HBV reactivation (Table 1) [5]. Reports of severe liver failure after hepatitis B reactivation following RTX treatment have led the FDA to release an alert in 2013, recommending hepatitis B screening before starting rituximab and consulting experts in case of positive HBV serology [6]. Nevertheless, management of HBsAg-negative/anti-HBc-positive patients treated with

Table 1 Risk estimation of different drug groups for hepatitis B reactivation

Risk group	HBV reactivation risk estimates	HBsAg positive/ anti-HBc positive (%)	HBsAg negative/ anti-HBc positive (%)
High-risk group (> 10%)	B-cell-depleting agents (e.g. rituximab, ofatumumab)	30–60	> 10
	Anthracyline derivatives (e.g. doxorubicin, epirubicin)	15–30	
	Corticosteroid therapy for ≥ 4 weeks (moderate/high dose)	> 10	
Moderate-risk group (1–10%)	TNF-α inhibitor (e.g. etanercept, adalimumab)	1–10	1
	Other cytokine inhibitors and integrin inhibitors (e.g. abatecept, ustekinumab)	1–10	1
	Tyrosine kinase inhibitors (e.g. imatinib, nilotinib)	1–10	1
	Corticosteroid therapy for ≥ 4 weeks (low dose)	1–10	
	Corticosteroid therapy for ≥ 4 weeks (moderate/high dose)		1–10
	Anthracyline derivatives (e.g. doxorubicin, epirubicin)		1–10
Low-risk group (< 1%)	Traditional immunosuppressive agents (e.g. azathioprine, methotrexate, 6-mercaptopurine)	< 1	<< 1
	Corticosteroid therapy for ≥ 4 weeks (low dose)		< 1
	Corticosteroid therapy for < 1 week	< 1	<< 1
	Corticosteroid therapy intraarticular	<< 1	<< 1

Table modified from Perrillo et al. [5]

rituximab is not precisely defined as there is a lack of knowledge with regard to rituximab monotherapy.

Therefore, we aimed to retrospectively analyze the real-life management of patients treated with RTX with or without chemotherapy in a cohort of patients with different underlying diseases. Reactivation rate of hepatitis B of HBsAg-negative/anti-HBc-positive patients was analyzed. Furthermore, we will give an overview of published recommendations related to HBV screening and preventive measures with particular attention to RTX in HBsAg-negative/anti-HBc-positive patients as guidelines have been updated recently.

Materials and methods

Patients

This retrospective study was performed in the Department I of Internal Medicine (rheumatology, hematooncology, infectious diseases) of the University Hospital of Cologne, Germany. Outpatients and inpatients receiving RTX between January 2009 and December 2013 were identified by records of the hospital pharmacy and reviewed for available hepatitis B serology (HBsAg, anti-HBc, anti-HBs) and HBV-DNA load. Patients with negative HBsAg and positive anti-HBc were included in the analysis. We documented chemotherapeutical and immunosuppressive co-treatment and antiviral HBV prophylaxis.

HBsAg, HBV-DNA, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST) and serum bilirubin level were checked at baseline and up to 12 months after the end of therapy with RTX. Reactivation of hepatitis B was defined as de novo appearance of HBV-DNA or HBsAg seroreversion.

Molecular and serological HBV testing

HBV testing was performed with commercially available assays according to the manufacturer´s instructions (Abbott, Wiesbaden, Germany). HBV serology was performed on the Architect system (Abbott) with the following chemiluminescence microparticle immunoassays: Architect HBsAg Qualitative II, Anti-HBc II, and (if one of the former assays was reactive) Architect Anti-HBs, HBeAg and Anti-HBe. For HBV-DNA quantification, the Abbott RealTime HBV assay was used (lower and upper limits of quantification: 10 and 10^9 IU/ml).

Ethical considerations and statistics

All patients were treated on the wards or the outpatient department of the clinic I of Internal Medicine of the University Hospital of Cologne. No identifying data were used for the patient's characterization in this strictly retrospective study. According to § 15 subparagraph 1 (code of medical ethics for physicians in the state of North Rhine-Westphalia) and § 6 subparagraph 2 (health privacy law for the state of

North Rhine-Westphalia), no ethics committee approval and informed consent were necessary for this study.

Data analysis was performed using GraphPad5 software (GraphPad, San Diego, CA). The statistical significance of differences between two groups was evaluated by Mann–Whitney test. $p < 0.05$ was considered to be statistically significant.

Selection of updated guidelines

We reviewed the leading American, Asian and European gastroenterology associations—namely the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), the Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of the Liver (EASL) for an update of the existing or for new guidelines since 2014, after the FDA alert related to hepatitis B reactivation in HBsAg-negative/anti-HBc-positive patients receiving immunosuppressive therapy with particular regard to rituximab was published [6]. Furthermore, we checked for recent recommendations from an Infectious Diseases Perspective including the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

Results

Cohort

In our study, 87% (861/986) of the patients treated with RTX with different underlying diseases were screened for hepatitis B virus. 11% (94/861) of the patients were anti-HBc positive. We found 9% (79/861) to be HBsAg negative/anti-HBc positive and this subgroup was followed for reactivation (Fig. 1).

Table 2 shows the baseline characteristics of the HBsAg-negative/anti-HBc-positive patients. Most patients (73%) were male, 60% had a high anti-HBs titer > 100 IU/l and nearly half (45%; n = 36) received antiviral prophylaxis. Lamivudine was the most frequently applied antiviral drug (68%; 21/36), followed by tenofovir (n = 11) and entecavir ($n = 4$). Sixty-two patients (79%) received RTX with chemotherapy and 17 (21%) without chemotherapy. All patients except for one (EBV reactivation) received steroids in addition to RTX. RTX was administered with a dose of 375 mg/m² except for patients with rheumatoid arthritis and Felty syndrome. They received a higher dose of 500 mg/m².

Patients with antiviral prophylaxis showed no significant differences compared to patients without prophylaxis related to the sex, age, underlying disease, rituximab given in combination with chemotherapy and anti-HBs-titer > 100 IE/ml (Table 2).

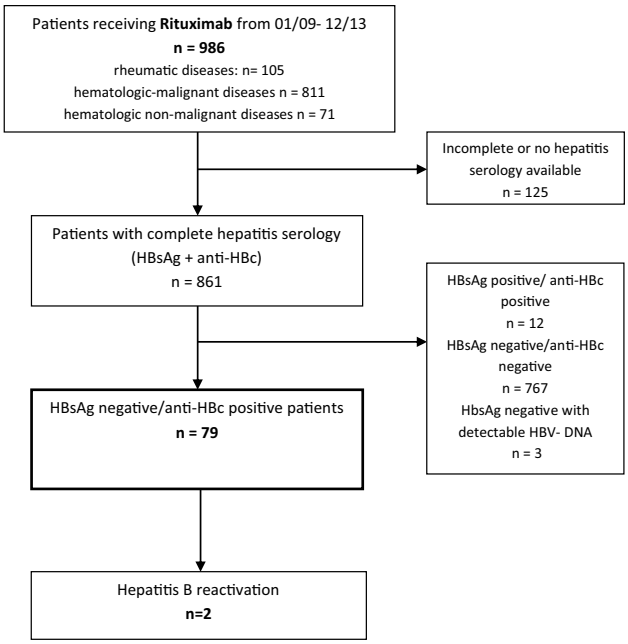

Fig. 1 Flow diagram

In our cohort, in 2 out of 79 patients hepatitis B reactivation was observed (Fig. 1). Both patients had a high-grade non-Hodgkin lymphoma and received RTX with polychemotherapy. Patient no. 1 had no HBV chemoprophylaxis. His HBV was reactivated 10 months after the end of RTX with severe hepatitis and HBsAg seroreversion, and distinct increase of HBV-DNA (viral load 5×10^5 copies/ml). He recovered completely under antiviral therapy with entecavir (0.5 mg/day) and lost HBsAg and detectable HBV-DNA after 5 months. HBV of patient no. 2 was reactivated despite antiviral prophylaxis with tenofovir (245 mg/day) 4 months after the start of RTX therapy. HBV-DNA increased slightly (viral load 180 copies/ml), but neither elevated liver enzymes nor HBsAg were detected. HBV-DNA disappeared spontaneously without change of antiviral therapy after 1 month.

Guidelines

Since 2014, American, Asian and European gastroenterology associations have published new guidelines related to the management of hepatitis B; while the American Gastroenterological Association (AGA) drafted a new specific guideline for the "Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy" [4], the European Association for the Study of the Liver (EASL) [7] and the Asian Pacific Association for the Study of the Liver (APASL) [8] included some new details in their general guidelines, and the American Association for the Study of Liver Diseases (AASLD) [9] did not change their

Table 2 HBsAg-negative/anti-HBc-positive patients with and without HBV chemoprophylaxis

Baseline characteristics	All ($n=79$)	With HBV chemoprophylaxis ($n=36$)	Without HBV chemoprophylaxis ($n=43$)	p
Age [median (IQR)]	61 (48–70)	62 (46–70)	61 (50–71)	0.85
Gender				
Male	58 (73%)	27 (75%)	31 (72%)	0.78
Anti-HBs (IU/l) ($n=70$) (median (IQR))	186 (23–663), $n=70$	157 (51–866), $n=31$	203 (19–543), $n=39$	0.65
> 100 (IU/l)	42 (60%)	20 (65%)	22 (56%)	0.50
Underlying disease (indication for RTX)				
Hematologic—malignant[a]	59 (74%)	26 (72%)	33 (77%)	0.65
Hematologic—non-malignant[b]	9 (11%)	3 (8%)	6 (14%)	0.44
Rheumatologic[c]	4 (5%)	3 (8%)	1 (2%)	0.23
Others[d]	7 (9%)	4 (11%)	3 (7%)	0.53
Therapy regimen[e]				
RTX with chemotherapy[f]	62 (79%)	29 (81%)	33 (77%)	0.67
RTX without chemotherapy[g]	17 (21%)	7 (19%)	10 (23%)	0.69

Data are presented as numbers (percentages), unless indicated otherwise. The statistical significance of differences between the groups with and without HBV chemoprophylaxis was evaluated by Mann–Whitney test. $p<0.05$ was considered to be statistically significant

RTX rituximab, *HBV* hepatitis B virus

[a]Leukemias ($n=14$); lymphoma ($n=44$); lymphoproliferative disease ($n=1$)

[b]Autoimmune hemolytic anemia ($n=2$), idiopathic immune thrombocytopenia ($n=7$)

[c]Rheumatoid arthritis ($n=3$); Felty syndrome ($n=1$)

[d]EBV-viremia ($n=3$); graft versus host disease ($n=4$)

[e]Chemotherapy or immunosuppressive therapy ≤ 1 year before or after RTX administration was included

[f]Including 14 patients with hematopoetic stem cell transplantation (HSCT) [autologous ($n=7$), allogenic ($n=6$), autologous and allogenic ($n=1$)]

[g]Including four patients with immunosuppressives [azathioprine (50 mg/day), leflunomide (10 mg/day), cyclophosphamide (50 mg/day), methotrexate (15 mg/week); each $n=1$]

recommendations related to the management of HBsAg-negative/anti-HBc-positive patients treated with immunosuppressive drugs or chemotherapy (Table 3).

HBsAg and anti-HBc screening is recommended by all associations before immunosuppressive therapy or chemotherapy, whereat AGA and APASL advise additional HBV-DNA testing in case of anti-HBc positivity.

Specific references to RTX are only included by AGA and EASL [AGA: RTX is classified in the "high-risk" group (Table 1); EASL: "new biological response modifiers risk of reactivation can be high, particularly for rituximab (alone or with steroids)"].

Recommendations related to monitoring are rather unspecific, with most details proposed by EASL (parameter: ALT, HBV-DNA; interval: 1–3 months; duration: at least 12 months after withdrawal of immunosuppression). Specific recommendations related to RTX are not listed.

Prophylaxis is not recommended by AASLD and APASL but by EASL and AGA. Both stratify the indication on the basis of the risk classification of AGA [5] in which RTX is classified in the "high-risk" group (Table 1), but EASL adds a further specification ["including those treated with rituximab in the onco-hematological setting (or those undergoing stem cell transplantation")]. AGA recommends only antiviral drugs with a high barrier of resistance formation but EASL lists lamivudine as first choice. Both associations advice a prolonged duration of prophylaxis with EASL in general for 18 months after withdrawal of immunosuppressive therapy and AGA for at least 12 months with the use of RTX.

The ESCMID Study Group for Infections in Compromised Hosts (ESGICH) released a consensus document analyzing the safety of specific targeted and biological therapies, and suggesting preventive recommendations [10] (Table 3). Here, strategies to prevent HBV reactivation when initiating treatment with CD20 monoclonal antibodies, including RTX, are established. They recommend screening for chronic or resolved HBV infection before starting treatment. In HBsAg-negative/anti-HBc-positive patients, they recommend to offer a prophylaxis usually with lamivudine. Further information related to the duration of prophylaxis and monitoring in HBsAg negative/anti-HBc positive is not given. They further refer to the increased risk of other infections.

In our department, we recommend to measure HBsAg and anti-HBc before initiation of RTX and—in case of

Table 3 Guidelines related to the management of HBsAg-negative/anti-HBc-positive patients with immunosuppressive therapy

Society	ESCMID Study Group for Infections in Compromised Hosts (ESGICH)	American Association for the Study of Liver Diseases (AASLD)	American Gastroenterological Association (AGA)	Asian Pacific Association for the Study of the Liver (APASL)	European Association for the Study of the Liver (EASL)
Year of publication	2018	2016	2015 (specific)	2016	2017
Former Year of publication		2009		2012	2012
Screening					
Patient group	Patients before being treated with anti-CD20 monoclonal antibodies	Patients with high risk of HBV infection[a] before initiation of chemotherapy or immunosuppressive therapy	Patients at moderate or high risk[b] who will undergo immunosuppressive drug therapy	All patients before initiation of chemotherapy and immunosuppressive therapy	All patients before initiation of chemotherapy or immunosuppressive therapy New biological response modifier risk of reactivation can be high, particularly for rituximab (alone or with steroids)
Parameter	For chronic and resolved Hepatitis B; not specified	HBsAg, anti-HBc	HBsAg, anti-HBc If positive HBV-DNA	HBsAg, anti-HBc If positive HBV-DNA	HBsAg, anti-HBc, anti-HBs If positive HBV-DNA
Monitoring					
Patient group	No recommendation for monitoring	Undergoing chemotherapy or immunosuppressive therapy	No recommendation for monitoring	Undergoing chemotherapy or immunosuppressive therapy	Undergoing chemotherapy and/or immunosuppressive therapy (regardless of anti-HBs status)
Parameter		No specification		ALT, HBV-DNA	ALT, HBV-DNA
Interval		No specification		No specification	Range 1–3 months
Duration		No specification		No specification	At least 12 months after prophylaxis withdrawal
Prophylaxis					
Indication	Prophylaxis should be offered (treatment with anti-CD20 antibodies)	Not enough information to recommend routine prophylaxis (treatment when HBV-DNA becomes detectable)	High risk (including B-cell-depleting agents as rituximab) prophylaxis Moderate risk: prophylaxis Low risk: no prophylaxis	No prophylaxis (be aware of risk in lymphoma patients with rituximab—further studies needed to compare efficacy and cost-effectiveness for prophylaxis versus monitoring)	High risk (analog AGA) (including those treated with rituximab in the onco-hematological setting (or those undergoing stem cell transplantation)[c]: prophylaxis Moderate/low risk: no prophylaxis
Drug	Usually with lamivudine (treatment with anti-CD20 antibodies)	n.a	Antiviral drug with high barrier		Lamivudine (ETV or TDF or TAF can be considered in patients receiving highly immune-suppressive regimens of extended duration)

Table 3 (continued)

Society	ESCMID Study Group for Infections in Compromised Hosts (ESGICH)	American Association for the Study of Liver Diseases (AASLD)	American Gastroenterological Association (AGA)	Asian Pacific Association for the Study of the Liver (APASL)	European Association for the Study of the Liver (EASL)
Duration	Not specified	n.a	High risk: at least 6 months after discontinuation of immunosuppressive therapy; at least 12 months for B-cell-depleting agents Moderate risk: at least 6 months after discontinuation of immunosuppressive therapy		At least 18 months after stopping immunosuppression

n.a. not applicable, *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

[a]Groups at high risk for HBV infection: areas of high or intermediate prevalence rates, infants whose parents were born in regions with high HBV endemicity (8%), household and sexual contacts of HBsAg-positive persons, persons who have ever injected drugs, persons with multiple sexual partners or history of sexually transmitted disease, men who have sex with men, inmates of correctional facilities, individuals with chronically elevated ALT or AST, individuals infected with HCV or HIV, patients undergoing renal dialysis, all pregnant women, persons needing immunosuppressive therapy

[b]High risk: B-cell-depleting agents (e.g. rituximab, ofatumumab) defined as high-risk group > 10%; see also Table 1

[c]Former wording in the guidelines from 2012: "some experts recommend prophylaxis in patients who receive rituximab and /or combined regimens for hematological malignancies, if they are anti-HBs negative and/or if close monitoring of HBV-DNA is not guaranteed"

positivity—additionally HBV-DNA. HBsAg positive, but also HBsAg-negative/anti-HBc-positive patients receive prophylaxis with highly potent nucleoside/nucleotide analogs during treatment with RTX and for further 18 months after end of RTX treatment. Subsequently, we continue our monitoring for another 12 months to exclude late reactivation.

Discussion

Between 2009 and 2013, 986 patients with hematologic and rheumatologic diseases were treated RTX at the University Hospital of Cologne. The HBV screening rate was 85% (861/986); 11% (94/861) of the screened patients were anti-HBc positive and 9% (79/861) were HBsAg negative/anti-HBc positive. 62 of these patients received RTX in combination with and 17 without chemotherapy. 45% ($n=36$) received antiviral prophylaxis and two patients reactivated—one with and one without prophylaxis.

In our cohort, the overall screening rate for hepatitis B was high (85%), considering that the black box warning for RTX was published after our study period. A relevant proportion (11%) of patients had been infected with hepatitis B in the past, although the study was performed in a low-incidence western country [6]. Consistently, all cited guidelines now recommend screening before immunosuppressive or chemotherapy independent of the risk of exposure to hepatitis B.

Our study reflects the broad spectrum of indications for RTX either as a monotherapeutic drug or in combination with chemotherapy. RTX has been assigned by Perrillo et al. to the high-risk group drugs for HBV reactivation but the authors differentiated between HBsAg positive and negative patients (Table 1, [5]). In patients who are HBsAg negative/anti-HBc positive, the risk of HBV reactivation by RTX is rated > 10% which is just at the threshold for moderate risk (up to 10%). As RTX is given frequently in combination with chemotherapy in the hemato-oncologic setting, most available data are for combination therapy. For RTX monotherapy or RTX given with low-risk immunosuppressives, only case reports exist. It could, therefore, be hypothesized that the risk for reactivation might be lower in this setting.

Two different strategies exist to prevent hepatitis B reactivation—either prophylactic or pre-emptive antiviral therapy [3]. Prophylactic therapy is initiated before immunosuppressive therapy and pre-emptive therapy later when monitoring shows an increase of liver enzymes and/or HBV-DNA levels without clinical signs of liver failure. For RTX, routine prophylactic antiviral therapy is recommended by AGA and EASL, and pre-emptive therapy by APASL and AASLD. When choosing pre-emptive therapy, monitoring is important to detect reactivation before liver failure occurs; nevertheless, recommendations are quite unspecific related to the precise time interval and duration of monitoring. Only the EASL includes details about the intervals and duration but only a range of 1–3 months is listed concerning the monitoring interval. It is important to note that reactivation can occur late after application of RTX; one of our two patients reactivated with severe liver disease 10 months after discontinuation of RTX.

For antiviral prophylaxis lamivudine, entecavir and tenofovir are available. The use of lamivudine has been mostly superseded by entecavir and tenofovir as rates of HBV-resistance are lower for the latter and they have been shown to be safe and effective [11].

Definition of hepatitis B reactivation is not standardized; mostly it is defined as HBsAg seroreversion and/or de novo HBV-DNA appearance. Additionally, a rise in HBV-DNA of at least 1 log (tenfold) IU/ml or above an arbitrary cutoff with biochemical worsening is applied as definition [11]. In our study, one patient showed HBsAg seroreversion with liver failure and one patient only detection of HBV-DNA without liver failure.

Conclusion

RTX can induce hepatitis B reactivation with severe liver failure also in HBsAg-negative/anti-HBc-positive patients. Recommendations related to screening, monitoring and prophylaxis of this patient group have been updated recently.

Nevertheless, data for RTX applied without chemotherapy are rare and preventive measures are less clear. Therefore, studies for this field of RTX application are needed.

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Compliance with ethical standards

Conflict of interest None to declare. LD, KT, GF, JF, VS, UW, JR, DN stated no conflicts of interest related to the article. JJV has served at the speakers bureau of Pfizer, Merck, Gilead, Basilea and Astellas, received research funding from Astellas, Gilead, Infectopharm, Merck/MSD, Basilea and Pfizer, has received travel assistance from Astellas, Gilead, Merck/MSD and Basilea, and is a consultant to Astellas, Gilead, Basilea and Merck/MSD. MH has received consultancy fee, speaker`s honoraria and research support from Roche/Gentech. CL has received travel grants from Gilead and BMS and speaking honorarium from Gilead, Janssen, ViiV and Abbvie. NJ has received lecture fees from Labor Stein, Novartis, Gilead, MSD, Infectopharm and travel grants from Gilead, Novartis and Basilea.

References

1. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol. 2016;22:219–37.
2. Perrillo RP, Martin P, Lok AS. Preventing hepatitis B reactivation due to immunosuppressive drug treatments. JAMA. 2015;313:1617–8.
3. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nat Rev Gastroenterol Hepatol. 2014;11:209–19.
4. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:215–9.
5. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:221–44.
6. Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. JAMA. 2013;310:1664.
7. EASL. Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–98.
8. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
9. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261–83.
10. Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernandez-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect. 2018;24(Suppl 2):71–82.
11. Gonzalez SA, Perrillo RP. Hepatitis B virus reactivation in the setting of cancer chemotherapy and other immunosuppressive drug therapy. Clin Infect Dis. 2016;62(Suppl 4):306–13.