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MINIREVIEWS

Hepatitis B in patients with hematological diseases: An update

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Abstract

Hepatitis B virus (HBV) reactivation (HBVr) in patients undergoing immunosuppressive therapy is still a hot topic worldwide. Its prevention and management still represents a challenge for specialists dealing with immunosuppressed patients. Aim of this paper is to provide a critical review of the relevant information emerged in the recent literature regarding HBV reactivation following immunosuppressive treatments for oncohematological tumors. A computerized literature search in MEDLINE was performed using appropriate terms arrangement, including English-written literature only or additional relevant articles. Articles published only in abstract form and case reports not giving considerable news were excluded. Clinical manifestation of HBVr can be manifold, ranging from asymptomatic self-limiting anicteric hepatitis to life-threatening fulminant liver failure. In clusters of patients adverse outcomes are potentially predictable. Clinicians should be aware of the inherent risk of HBVr among the different virological categories (active carriers, occult HBV carriers and inactive carriers, the most intriguing category), and classes of immunosuppressive drugs. We recommend that patients undergoing immunosuppressive treatments for hematological malignancies should undergo HBV screening. In case of serological sign(s) of current or past infection with the virus, appropriate therapeutic or preventive strategies are suggested, according to both virological categories, risk of HBVr by immunosuppressive drugs

and liver status. Either antiviral drug management and surveillance and pre-emptive approach are examined, commenting the current international recommendations about this debated issue.

Key words: Reactivation; Lymphoma; Hematology; Immunosuppressive therapy; Prophylaxis; Hepatitis B virus; Chemotherapy; Occult/active/inactive carrier; Entecavir; Lamivudine

Core tip: Despite the increasing awareness regarding the issue of hepatitis B virus reactivation (HBVr) in patients undergoing immunosuppressive treatments, there are still some many debated items concerning this potentially fatal but preventable complication. Both hepatitis B surface antigen (HBsAg) patients and subjects with serological signs of previous resolved exposure to the virus (HBsAg negative/anti-core antibody positive patients) are at risk of HBVr. Purpose of our work was to analyze the current international literature and dedicate guidelines, providing evidences and strategies that have been proposed to manage these patients.

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INTRODUCTION

Hepatitis B virus (HBV) infection represents a significant global health problem, since almost one third of the world's population has serological signs of previous or present infection, and that 240 million individuals are chronic hepatitis B surface antigen (HBsAg) carriers[1]. Worldwide, low rates of serological HBsAg positivity (0.2%-0.5%) and signs of previous HBV contact [4%-6% HBsAg negative/anti-hepatitis B core antigen antibodies (anti-HBc) positive subjects] are registered in north western and central Europe, north America and Australia. On the contrary, the highest prevalences are reported in China, Southeast Asia and tropical Africa (chronic infection 8%-20%, and previous exposure 70%-95%, respectively)[2].

It is presently well known that medications such as glucocorticoids and anticancer treatments can interfere with the host immune system and blunt the control that it exerts over HBV replication, with the potential to cause viral reactivation (HBVr) in both HBsAg positive patients and individuals with serological signs of previous resolved HBV exposure. HBVr can assume various manifestations, spanning from asymptomatic hepatitis to life threatening fulminant liver failure. This risk is most common among patients undergoing treatment for hematological tumors or those receiving hematopoietic stem cell transplantation (HSCT). Nevertheless, also patients with solid tumors (such as breast cancer), immunological diseases and inflammatory bowel diseases are exposed to the risk of HBVr[1,3-5].

In this paper, we will critically review the relevant information emerged in the recent international literature regarding HBVr, focusing on patients undergoing immunosuppressive treatments for hematological malignancies.

LITERATURE SEARCH

A computerized literature MEDLINE search was done adopting several combinations of these terms: HBsAg, reactivation, lymphoma, hematology, immunosuppressive therapy, anti-HBc, occult carrier, including only papers in English language. Literature on hematopoietic stem cell transplantation recipients was not considered. Articles published only in abstract form were excluded. Case reports have been included only if adding significant contributions.

HBV INFECTION, HOST IMMUNE RESPONSE AND VIROLOGICAL PROFILES

When the HBV virus encounters the human host, in the presence of a competent immune system, three outcomes relevant to our discussion can be observed: (1) the infection can be rapidly cleared, as it is to be expected in most immunocompetent adults. However, in a part of these individuals, the covalently closed circular (ccc) viral DNA can integrate and persist indefinitely as an immune template in the host hepatocyte; (2) The host immune response might create a dynamic equilibrium in which viral replication either stops or is minimally active; and (3) the host immune system is unable to either eradicate or control viral replication and a state of chronic liver disease ensues, potentially leading to the development of liver cirrhosis and its consequences. These different immunological and clinical scenarios of host-virus interplay constitute the basis to define the corresponding virological HBV categories, summarized in Table 1[5].

Active carriers (AC) are those HBsAg positive patients in whom HBV replication prevails over the control of host immune system, and are characterized by elevated HBVDNA levels ($\geqslant$ 2000 IU/mL). On the other extreme are the occult HBV carriers (OBI), individuals in whom the immune system has successfully cleared the acute viral infection. These individuals however still harbor the viral DNA inside the hepatocytes, integrated in the form of cccDNA but under the effective replicative control of the immune

Table 1 Virological categories of hepatitis B virus infected patients (adapted from[5])

	AC	IC	pOBI
HBsAg	+	+	-
Anti-HBc	+	+	+
Anti-HBs	-	-	-/+
qHBsAg	⩾ 1000	< 1000	-
ALT	Increased	Normal	Normal
HBV DNA in the blood	⩾ 2000	< 2000	-
Liver stiffness (kPa)	> or < 6	< 6	< 6

HBsAg: Hepatitis B surface antigen; AC: Active carrier; IC: Inactive carrier; OBI: Occult hepatitis B virus (HBV) infection; Anti-HBc: Anti-hepatitis B core antigen antibodies; Anti-HBs: Antibodies to HBV surface antigen.

system, only showing serological signs of previous viral exposure (*i.e.*, presence of anti-HBc), very low (< 200 IU/mL) or absent circulating HBVDNA, positive or negative antibodies to HBV surface antigen (anti-HBs), and normal transaminases[6]. The third, more intriguing and elusive category, is currently that of inactive carriers (IC), HBsAg and anti-envelope antigen antibody (anti-HBe) positive patients with indosable or < 2000 IU/mL HBVDNA levels. Their classical definition is completed by the concurrent presence of persistently normal levels of serum transaminases, no signs of HBV-induced liver inflammation/fibrosis and a clinically benign course. The IC state was generally ratified by the stability of these parameters during the course of an extended (usually 12-mo) observation period[7]. However, this lengthy mandatory observation period is awkward in settings requiring a rapid categorization, such in those in which a decision regarding the start of antiviral drugs to protect from HBVr is to be taken.

In the Asian pacific region, the benignity of this entity has been debated, and the term of "low replicative chronic HBV infection" proposed, favored over the "inactive carrier" definition, as the latter can give the patients an incorrect sense of confidence. Considering that hepatitis B infection should be considered a dynamic interplay between the host and the virus, the activity profile can modify over time and virological category can change at different time points[8]. However, this scenario is based on the virological characteristics of the Asian population, while in the Mediterranean basin up to one third of IC individuals present levels of HBVDNA between 2000 and 20000 IU/mL with normal transaminases and absence of liver fibrosis during long term observation. To further sharp the definition of this virological HBV category, recent studies have focused their attention on the role of quantitative HBsAg testing (qHBsAg), HBVDNA cut-offs, and use of fibroelastometry[9-11].

Recent studies have in fact provided data to allow a timely identification of IC group of patients with an acceptable approximation, without the need of a prolonged observation.

In the study by Brunetto *et al*[7], 209 genotype D carriers were enrolled, and the capacity of qHBsAg testing to discriminate between active and inactive HBV carriers and patients with active chronic hepatitis B (CHB) was tested. It was demonstrated that a one-time (so called "spot") quantification of HBVDNA below 2000 IU/mL and HBsAg less than 1000 IU/mL was able to single out IC with good sensitivity, specificity, positive and negative predictive values (91.1%, 95.4%, 87.9%, 96.7% respectively) concluding that this single observation approach obtains the same results of long term monitoring with an acceptable approximation[7]. Raimondo *et al*[6] recently evaluated the reliability of serum HBVDNA and qHBsAg testing, along with liver stiffness measurements (LSM) in identifying the IC status at a spot point investigation among 147 HBsAg and anti-HBe positive patients, including 57 IC and 90 individuals with CHB. The overall evaluation of all parameters allowed to recognize 23 out of 57 (40.3%) ICs, with good specificity, sensitivity, positive and negative predictive values, and diagnostic accuracy (100%, 96%, 100%, 92% and 97%respectively). Even removing from the analysis CHB or cirrhotic patients, the results were similar. It was concluded that combined assessment of HBVDNA level, liver stiffness along with quantitative surface antigen measurements, provide a dependable working instrument, correctly identifying a large portion of IC with a spot assessment only[12]. In genotype B and C patients the validation of a one-time dosage of qHBsAg and HBV DNA to predict IC state was performed in a population of 1529 subjects. When HBsAg < 1000 IU/mL was associated with HBVDNA < 2000 IU/mL, the one-time evaluation was able to discriminate IC from patients with chronic hepatitis B with slightly lower diagnostic accuracy[13]. Thus, it can be concluded by these observations that by using serological and elastographic testing, IC can be currently identified with an acceptable approximation in those instances when prolonged observation is unfortunately not an option.

HBV REACTIVATION AND FACTORS INFLUENCING ITS OCCURENCE

HBVr during immunosuppressive treatments can occur as the result of a loss of control over viral replication induced by these drugs, since they can modify the competence of the host immune system[3]. In this setting, the virus rapidly replicates infecting multiple hepatocytes, however in this phase usually no damage occurs since the immunological response is blunted by immunosuppressive medication. When the immunosuppressive therapy is concluded, a progressively restored immune system can activate the search, destroy and eradication of the HBV infected hepatocytes, and this can cause massive liver necrosis and acute liver failure. This event process can occur at different time points, usually ranging from a few months but also potentially developing years after the end of the immunosuppressive therapeutic cycle, after

Table 2 Incidence of hepatitis B virus reactivation without prophylaxis (adapted from[21])

Disease	HBsAg+ (%)	HBsAg-/anti-HBc+ (%)
Lymphoma	18-73	34-68
Acute leukaemias	61	2.8-12.5
Multiple myeloma	Not available	6.8-8
Breast cancer	21-41	Not available
Hepatocellular cancer (systemic chemotherapy)	36	11
Inflammatory bowel disease	36	0-7
Autoimmune diseases	Not available	17

HBsAg: Hepatitis B surface antigen; Anti-HBc: Anti-hepatitis B core antigen antibodies.

immune response is completely restored[14,15].

HBVr has been variably defined overtime and a consensus has not been reached. According with the American Gastroenterological Association (AGA) guidelines, in HBsAg carriers reactivation occurs when there is either a *de novo* detection of viremia or a one $\log_{10}$ or greater increase in HBVDNA as compared to baseline levels (obtained before starting therapy). Hepatitis flare is considered when there is at least a two-three fold rise of ALT above baseline or a predetermined multiple of the upper normal limit. In HBsAg negative/anti-HBc positive patients reactivation is defined by the reverse seroconversion to HBsAg-positive condition[16]. Similar definitions are also suggested by the Italian association for the study of the liver (AISF).

Since different levels of baseline HBVDNA influence the occurrence of HBVr, the different virological classes, proceeding from OBI to IC and then to AC, are at a progressively higher risk of reactivation. It is in fact widely accepted that subjects with high level of viremia before immunosuppressive therapy are at an increased risk for the development of HBVr as compared to those with undetectable or low levels of HBVDNA[17-19].

Accordingly, many studies have estimated that the risk of HBVr is 5- to 8-fold higher among HBsAg positive patients[20] and that HBeAg positive patients are at higher risk of developing HBVr as compared to HBeAg negative ones[17]. Compared to other diseases groups, patients with hematological malignancies are reported to be those characterized by the highest risk of experiencing HBVr (Table 2)[21] with figures ranging between 24%-88%[22]. It is speculated that this difference could be due to the intrinsic immunosuppression typical of hematological malignancies and to the treatments used to cure them. Interestingly, the first cases of HBVr were actually recorded among patients with lymphoma[23]. In a large multicenter case-control study conducted in Italy, the prevalence of HBsAg positivity among 400 B-cell non-Hodgkin's lymphoma (NHL) cases was higher than in 392 controls (8.5% *vs* 2.8%, respectively)[24]. Thirty-eight to 73% of HBsAg positive NHL cases undergoing chemotherapy for NHL can experience HBVr[25,26].

Also multiple myeloma patients are at risk of HBVr as reported in several recent papers, since in the advanced stages of this disease the occurrence of a more critical immune dysregulation might predispose to the development of viral reactivation[27].

A substantial risk of HBVr, not different from that of lymphoma patients, has also been described among patients undergoing treatment for acute myeloid leukemia. Recently Chen *et al*[28] observed that HBVr and HBV-related hepatitis occurred in 9.5 and 8.3 per 100 person-years, respectively. There is now clear evidence that different classes of immunosuppressive drugs are characterized by different risks of inducing HBVr. Medications used for hematological malignancies are frequently marked by a severe immunosuppressive effect, as the case of rituximab (RTX), an anti-CD20 monoclonal antibody acting as a potent B-cells depleting agent, mostly used in hematological malignancies during the last two decades[29] and well known to increase the chance of HBVr of more than five-fold[30]. This high risk is justified by the marked B-cell reduction, which interferes with the production of anti-HBs and their neutralizing effect on serum HBsAg. Moreover, RTX worsens the imbalance of antigen-presenting B-cells typical of chronic HBV infection, determining a lower activity of CD4 T-cell in generating an adequate immune response[31].

The rate of HBVr inherent to these B-cell depleting agents (RTX, but also ofatumumab) is roughly 16.9% among patients with serological signs of previous HBsAg exposure, and their seroreversion percentage is 20%-40%. With these drugs HBVr can be a late event, even up to 60 mo after the cessation of immunosuppressive therapy, further marking the strong and lengthened influence of these drugs on the recovery of immune competence[16,32,33].

Considering these evidences antiviral prophylaxis of these patients have to be prolonged up to 10-24 mo after the discontinuation of the B-cell depleting agents and a careful surveillance has to be activated after the antiviral therapy withdrawal[3,5]. Among the B-cell depleting agents, more drugs are or will soon be available. A possible example is Obinutuzumab, a new humanized monoclonal antibody to CD20[34] which, in association with other chemiotherapics, has been shown to be more effective than RTX in the treatment of chronic lymphatic leucemia (CLL)[35], but at the cost of determining a more profound immunosuppression than RTX. Even though no HBVr cases have been registered following the use of this drug, it is conceivable that the concerns developed during the experience with RTX should also be extended to the other members of this class of drugs.

Corticosteroids are also widely used in the treatment of hematological malignancies and combined to cytotoxic agents in several therapeutic schedules for the treatment of lymphoma and multiple myeloma. These dugs are able to influence the activity of T-cells but also to directly intensify HBV replication[36]. It has in

Table 3 Risk of hepatitis B virus reactivation according to different immunosuppressive drug classes (adapted from[21])

Risk	Drug class
High (> 10%)	B-cell depleting agents
	Anthracycline
	Corticosteroids high dose
Moderate (1%-10%)	TNFα inhibitors
	Cytokine and integrin inhibitors
	Tyrosine kinase inhibitors
	Corticosteroids moderate dose
Low (< 1%)	Corticosteroids low dose
	Traditional immunosuppression (*e.g.*, azathioprine or methotrexate)

fact been demonstrated that the prolonged assumption of prednisolone increases HBsAg and HBVDNA levels in liver cells, and that the withdrawal of corticosteroid seems to determine a rebound in immune T-cell function resulting in hepatocyte destruction[37]. Corticosteroids have the potential to cause HBVr, but with different percentages of risk depending on dosage, duration of treatment and route of administration; in fact high-dose (> 20 mg/d) prednisolone, and prolonged treatment extension (> 1 mo), correlate with higher risks of reactivation.

AGA evaluated the risk of HBVr according to distinct drug categories, basing its conclusions on an extensive systematic review of the available studies. However, on some medication, data were limited and extrapolated only from either case series or caser reports. This risk stratification is reported in Table 3[21]. A gradation of the HBVr risk (high > 10%, moderate 1%-10% and low < 1%) has been proposed and currently accepted in the western countries[1,3,5].

PREVENTION OF HBVr

To prevent HBVr, it is crucial to identify patients at risk for the development of this potentially severe event before starting immunosuppressive drugs. Most international scientific associations such as the European Association for the Study of the Liver (EASL), AGA, the Asian-Pacific Association for the Study of the Liver (APASL) and AISF suggest to screen for HBV all patients scheduled to undergo immunosuppressive treatment by testing HBsAg, anti-HBc and anti-HBs[1,3,5,8].

On the other hand the American Association for the Study of Liver Diseases (AASLD) and the American Society of Clinical Oncology (ASCO) recommend to limit HBV screening to patients with high or moderate risk of HBVr risk factors[38,39]; for patients at low risk, screening strategies should follow instead the indications produced by the Center for Disease Control and Prevention[40] and the United States Preventive Services Task Force[41,42].

It has been demonstrated in various studies that HBsAg positive patients should undergo antiviral treatment started before (2-4 wk) and continued during chemotherapy, regardless of baseline HBVDNA level, and not on a pre-emptive based strategy, considering that if hepatitis has already developed, it could be more difficult to control the extent of the reactivation process[32,43].

Currently, guidelines worldwide indicate treatment with nucleot(s)ide analogs (NA) for patients with hematological malignancies, positive for the HBsAg and receiving cytotoxic chemotherapeutic drugs[1,3,5,8]. The duration of the antiviral treatment in these patients has been the matter of long debates in the last decade, but actually a higher concordance is registered. In patients with CHB or cirrhosis antiviral therapy has not to be discontinued. However in IC it should be continued during the immunosuppressive treatment and for 12 mo after its discontinuation. Patients with serological signs of resolved past exposure to the virus and detectable viremia should be managed as surface antigen positive subjects, while those with undetectable serum HBVDNA should be carefully followed by ALT, HBsAg and/or HBVDNA testing (regardless of anti-HBs status), and promptly treated with nucleoside analogues upon confirmation of HBV reactivation before ALT elevation. However, when patients with this serological pattern (HBsAg negative/anti-HBc positive) are treated with RTX or similar immunosuppressive drugs, especially when low/absent serum hepatitis B surface antibodies are detected or if close HBVDNA surveillance is not feasible, many experts acknowledge their higher risk of viral reactivation and recommend prophylaxis[8]. In case of monitoring aimed at the prompt activation of pre-emptive therapy, ALT, HBsAg and/or HBVDNA testing is performed every 1-3 mo during the immunosuppressive treatment in the early phase, depending on the type of immunosuppressive drug and comorbidities. When prophylaxis is instead chosen, lamivudine (LAM) is usually suggested[44]. The 2007 Italian AISF guidelines and its recent implementation are in agreement with the international indications previously reported. In particular, among HBsAg-positive patients, AC are treated as their immunocompetent counterparts with the more potent antivirals available, while viremic IC, which received LAM in the past, are now preferentially treated with entecavir (ETV). In these patients monitoring of drug efficacy was performed by HBVDNA and ALT testing. In hematological anti-HBc positive subjects undergoing severely immunosuppressive regimens of various kind (see[4] for a complete list), universal prophylaxis with LAM has been advocated and recently confirmed. In these patients monitoring in prospective of pre-emptive therapy or of response to treatment is advised with ALT and HBsAg testing for their high specificity and maneuverability during the very long period at risk after the immunosuppressive treatment[4,5].

CHOICE OF ANTIVIRAL AGENTS

Regarding the antiviral to use in HBsAg positive sub-

jects, the 2017 American and European guidelines suggest the use of a NA with high potency and high genetic barrier (ETV or tenofovir disoproxil or alafenamde, respectively TDF and TAF)[1,3]. In these patients the role of LAM remains marginal in the very few IC patients without detectable viremia or in developing countries[3,5]. In HBsAg negative/anti-HBc positive subjects with hematological diseases and/or treated with B-cell depleting drugs high barrier antivirals can be obviously considered but the antiviral treatment with LAM is yet accepted[1,5].

In the face of such indications, the most part of data derived from the historical experience with LAM. Seminal papers considered LAM prophylaxis as an efficient agent to decrease the event of reactivation and hepatitis flare, to reduce the risk of HBV-related liver failure, and prevent the delay or discontinuation of chemotherapy as a consequence of HBVr[45]. The influential systematic review by Loomba demonstrated that LAM prophylaxis exerted a protective role against HBVr and death attributable to hepatitis B (relative risk 0.0-0.21 and 0.0-0.2 respectively)[22].

A later review concluded that antiviral LAM prophylaxis during cytotoxic treatment influenced HBVr, determining both a 87% reduction of this event, and a 92% decrease in treatment delay/early interruption of chemotherapy as compared to patients not given prophylaxis[45].

The systematic review and metanalysis of five randomised controlled trials contained in the recent AGA technical review, compared LAM prophylaxis to treatment at the beginning of viral reactivation (pre-emptive strategy)[16,43,46-49]. Antiviral prophylaxis was more effective than the pre-emptive strategy [overall risk ratio (RR) = 0.13], and also determined a significant decrease of hepatitis flare risk (RR = 0.16)[16]. Nevertheless, it has currently been suggested that LAM prophylaxis provides a suboptimal protective action for IC with detectable HBVDNA. The supposed superior efficacy of ETV as compared to LAM in the prevention of HBVr among patients undergoing treatment for hematological malignancies is supported by the results of the registrative studies in patients with CHB[50,51], in which ETV was shown to be more powerful than LAM in terms of histological amelioration, control of viremia, and reversal of ALT values to normal range in either HBeAg positive or negative chronic active hepatitis patients.

Additionally, in patients with NHL has been suggested that LAM provides a suboptimal preventive approach also in low viremic patients. A randomized multicenter study compared the efficacy of prophylactic therapy with LAM and ETV among HBsAg positive subjects and diffuse large B-cell lymphoma treated with RTX-CHOP (Cyclophosphamide, Hydroxydanorubicin, Oncovin, Prednisone); in low viremic (HBVDNA < 2000 IU/mL) patients it was demonstrated that the virological events were significantly lower in the ETV group considering hepatitis (8.2% *vs* 23.3%), HBVr (6.6% *vs* 30%) delayed hepatitis B (0% *vs* 8.3%) and chemotherapy disruption (1.6% *vs* 18.3%). However, at the moment this is the only available prospective study, burdened by some relevant limitations, such as the high prevalence of low viremic HBeAg positive patients in the Asiatic population evaluated[52]. However, a recent systematic review with network meta-analysis has suggested that prophylactic therapy with tenofovir or ETV may represent the most potent intervention to prevent HBVr and HBV-related morbidity and mortality in HBsAg-positive patients undergoing chemotherapy[53]. In two meta-analysis aimed to HBsAg-negative/anti-HBc-positive patients treated with RTX without antiviral prophylaxis, HBVr developed in 6.3%-16.9% of cases[16,54].

LAM was the drug most used for the universal prophylaxis in antiHBc-positive patients with hematological disease. In this setting viral breakthrough and loss of response during the antiviral treatment is very rare, while the risk of HBVr is significant during the first 6-12 mo after the discontinuation[5,16].

A unique randomized prospective study was performed in anti-HBc positive patients treated with RTX, comparing 3 mo of prophylaxis with LAM or ETV. HBVr was significantly higher in the LAM group (P = 0.19); however all the clinical events developed after (0.5-14 mo) the discontinuation of the drug without demonstrating a higher protective effect of ETV during the therapy[46].

LATEST NEWS AND COMPARISON BETWEEN THE MOST RECENT INDICATIONS

As previously reported, in the last few months some relevant indications on the management of HBV reactivation among immunosuppressed patients have emerged and published.

The Italian guidelines[5] are the result of the continuously updated work produced by a team of hepatologists dedicated to the management of immunosuppressed patients at risk for HBV reactivation. Its contents have been widely cited in this paper, as for instance the controversies regarding the best strategies to manage inactive carriers. Guidelines are discussed and developed in single topic events endorsed by AISF. Statements are produced after revision and discussion of the specific literature by hepatologists and other specialists such as hematologists, oncologists, immunoreumathologists, nephrologists and transplantologists. Virological classes and their relative diagnostic criteria are addressed as are screening and diagnostic approaches. Definitions of clinical and virological events are provided. Management and follow up strategies are also thoroughly scrutinized with the aim to promote the awareness regarding this issue, and collaboration among specialists. HBV screening is recommended in all patients undergoing

treatment for hematological malignancies with the use of HBsAg, anti-HBs, and anti-HBc. HBVDNA is then tested to both distinguish AC and IC and to identify potential false OBI. The different classes of risk for HBV reactivation proposed by the 2015 AGA guidelines have been incorporated. For patients with a high risk of reactivation, evaluation by an expert in liver disease is required. For HBsAg positive patients with hematological malignancies the risk of reactivation emerges to be clearly significant (24%-88%, median 50%), and the particular increase of HBVr associated with the use of RTX has been definitely stated. Also, the increased risk of HBVr due to the use of RTX in the OBI group has also been clearly recognized. In this latter virological category, the actual risk of reactivation as the result of treatment with several recently introduced biologics (imatinib, bortezomib, mogamolizumab, ofatumumab, carfilzomib, romidepsin, *etc*.) remains debated. As far as the treatment of HBsAg-positive patients is concerned, even if most available data came from the experience developed with LAM, the presence of newer drugs with greater potency and high genetic barrier, has imposed ETV and tenofovir (especially in the new form to be commercialized in Italy, TAF, with an improved safety profile) as the drugs of choice in viremic patients. In OBI treated with RTX for lymphoma, or with detectable HBVDNA LAM still maintains its role, in the absence of a proven greater protective effectiveness over other antivirals. Antiviral treatment with either ETV or TDF (TAF) is recommended indefinitely for AC patients, while in IC patients, LAM (HBVDNA negative) or ETV (HBVDNA positive) prophylaxis is indicated for at least 12 mo from the end of the immunosuppressive treatment. In OBI subjects duration of LAM prophylaxis it is indicated to extend prophylaxis for at least 18 mo after immunosuppressive regimen has been stopped. In LAM treated pOBI, the monitoring of ALT and HBsAg is indicated every three months. Monitoring in AC during and after the immunosuppressive treatment is similar to that of immune-competent; for IC in prophylaxis, monitoring should be performed dosing ALT and HBVDNA, every 12 wk in the case of LAM; every 6-12 mo, after virological response, with ETV and TDF(TAF). In case of viral breakthrough during prophylaxis or therapy with LAM or ETV, the prompt activation of a rescue therapy with either TDF or TAF is advised; during therapy with TDF/TAF or ETV a partial virological response requires a combined therapy with a nucleoside and a nucleotide. A similar monitoring (HBsAg in OBI and HBVDNA in AC) is recommended in the first month and every three months after the discontinuation of prophylaxis for the first year and every six months thereafter.

Another goal of the team is to provide practical indications for the working physician. To this purpose, statements are then published as a full report illustrating the management of the different subclasses of immunosuppressed patients. These indications have been published for the first time in 2007 and have been constantly updated thereafter during the course of the years. The most recent paper has been published online on the AISF web site in February 2017, and a further meeting is scheduled by the end of this year, with the aim of producing and English version of the newly discussed statements.

The EASL has published in April 2017 the updated guidelines on the management of hepatitis B infection[1]. In this paper, as in its previous 2012 version, the issue of immunosuppressed patients with signs of current or past infection with the HBV are addressed in the section dedicated to the treatment of various special patients groups with HBV infection. Also in this paper, the different classes of risk for HBV reactivation proposed by the 2015 AGA guidelines have been accepted. Vaccination of HBV seronegative immunosuppressed individuals is endorsed. Similarly to the AISF guidelines, it is suggested that all patients scheduled to undergo cytotoxic and/or immunosuppressive treatments should firstly perform a serological screening based on HBsAg, anti-HBs and anti-HBc testing. Evidence and grade of recommendation are very strong. All HBsAg-positive candidates for immunosuppressive therapies should undergo evaluation by a specialist to define their virological class. All HBsAg positive patients should start potent NA as a treatment or prophylaxis. A clear cut approach is proposed for AC, and they should be treated with ETV, TDF or TAF, similarly to the immunocompetent patients. Controversial remains the management of IC. Prophylactic LAM has been shown to obtain a reduction of both HBV reactivation risk and of associated morbidity and mortality. Nevertheless, a residual risk of HBV reactivation remains (approximately 10%) in patients with low viremia (HBV DNA < 2000 IU/mL). Thus, a simplified approach recommends ETV, TDF, TAF in all HBsAg positive patients, both as treatment and prophylaxis (Evidence level Ⅱ-2, grade of recommendation 1). The EASL guidelines also suggest long term prophylaxis (at least 12 mo, and 18 mo in case of rituximab-based regimens) after the cessation of the immunosuppressive treatment, and NA prophylaxis should be stopped only in case the underlying disease is in remission. During prophylaxis, liver function tests and HBVDNA should be tested every 3 to 6 mo. Testing should be performed with the same schedule also after NA withdrawal, since a relevant proportion of HBV reactivations develops after their discontinuation. It is not defined when testing should be stopped.

The risk of HBV reactivation in OBI varies widely according to underlying disease and the type and duration of immunosuppressive regimen. HBVDNA testing should be performed before immunosuppression. If viremic, they should be treated similarly to HBsAg-positive patients. As in the Italian guidelines, in patients at high risk (10%) of HBV reactivation (*i.e.*, anti-HBc

positive subjects undergoing treatment with rituximab in the oncohematological setting; those undergoing stem cell transplantation), antiviral (universal) prophylaxis is recommended. This should be continued for at least 18 mo after stopping immunosuppression and monitoring should continue for at least 12 mo after prophylaxis withdrawal. LAM may be used although cases of HBV reactivation due to LAM resistance have been reported. Interestingly, the EASL guidelines suggest that prophylaxis with ETV or TDF or TAF can also be considered in HBsAg-negative, anti-HBc positive patients receiving highly immunosuppressive regimens of extended duration. So it is concluded that these patients should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level Ⅱ-2, grade of recommendation 1). In isolated anti-HBc positive subjects with either moderate (< 10%) or low (< 1%) risk of HBV reactivation, pre-emptive therapy and not prophylaxis is recommended. Also, the EASL guidelines consider HBsAg reappearance (seroreversion) the main virological event in these patients, constantly associated with hepatitis flare. As also indicated in the Italian guidelines, HBVDNA detection leads to seroreversion and hepatitis in only 50% of cases, thus being less specific as compared to HBsAg testing. However, with an apparent contradiction or a conservative prudence, both HBsAg and/or HBVDNA are monitored every 1-3 mo during and after immunosuppression, and therapy with ETV, TDF or TAF started in case of detectable HBVDNA or HBsAg seroreversion following a pre-emptive strategy. Since after HBsAg seroreversion a severe, even fatal, acute hepatitis could ensue, NA should be started as early as possible, independently of ALT levels. Interestingly the opportunity of using universal prophylaxis rather than pre-emptive therapy is recommended for selected clinical settings, characterized by long duration of immunosuppression, limited compliance to monitoring or unknown risk of viral reactivation for new biological. Limited are the indications on how and when follow-up should be performed after NA withdrawal.

A very recent review by Loomba and Liang[3] also needs to be mentioned. It further stresses and perfects the 2015 position of the AGA regarding patients with signs of current or past HBV infection undergoing immunosuppressive treatments at risk for viral reactivation. The authors accurately scrutinize the most recent data regarding this issue, updating the risk of reactivation associated to other immunosuppressive treatments such as cytokine and integrin inhibitors, immune checkpoint inhibitors such as ipilimumab (anti-CTLA4) and nivolumab (anti-PD-L1), and histone deacetylase inhibitors (HDIs). Complementary information is also provided on tyrosine kinase and proteasome inhibitors. Fine mechanisms of reactivation are reviewed. As in the AISF guidelines, a thorough baseline evaluation of liver status is recommended, and screening for HBV infection by testing HBsAg, anti-HBc and anti-HBs suggested for all patients who are receiving therapies that have either a high or moderate risk of reactivation. Evaluation by a HBV specialist is recommended. Even if LAM might be considered in resource-limited countries, especially in HBsAg-positive individuals with either undetectable or very low HBVDNA serum levels, high potency and high genetic barrier antiviral drugs such as ETV and tenofovir are preferred. Patients with CHB (HBsAg positive HBVDNA ⩾ 2000 IU/mL, elevated transaminases) should be treated as their immunocompetent counterpart. IC (HBsAg positive, HBV-DNA < 2000 IU/mL, normal transaminases) should undergo prophylaxis when exposed to high- and moderate-risk immunosuppressive therapy. Prophylaxis should ideally be initiated 14-30 d prior the initiation of immunosuppressive treatment and maintained for a minimum of 12 mo after its discontinuation.

For IC exposed to low-risk immunosuppressive treatments and OBI patients, surveillance with ALT and HBsAg (adding HBVDNA in those who are HBsAg positive) is recommended. To reduce the event of reactivation, OBI treated with RTX or other high risk treatments should undergo prophylaxis. For OBI at a moderate risk, anti-HBV prophylaxis should be considered, but they could also be monitored for serum ALT and HBsAg levels (and not by HBVDNA testing, similarly to the AISF indications) every 3 mo up to 6 mo after the discontinuation of immunosuppressive treatments. However, since HBV reactivation may occur up to 1-2 years after the last dose of RTX, patients treated with this medication may continue prophylaxis for up to 2 years after its discontinuation.

DISCUSSION AND CONCLUSION

Management of patients with HBV infection undergoing immunosuppressive therapy for hematological malignancies is still a challenge. It is necessary to be aware and vigilant about the risk of HBVr and its potential dire consequences and complications. Baseline screening for HBV infection before treatment initiation it is thus mandatory for these patients. HBV serum markers (HBsAg, anti-HBc and anti-HBs) must be checked, in order to stratify the risk of reactivation and decide which category of patients needs therapy and what is the best option for them.

Management with appropriate antivirals is indicated for their marked propensity to reactivate. Antiviral therapy is necessary in patients with moderate or high risk for reactivation. For HBsAg positive patients antiviral therapy is mandatory; for HBsAg negative/anti-HBc positive patients (OBI) it is possible to consider either prophylactic antiviral management (especially in patients undergoing high-risk therapies), or a pre-emptive approach monitoring ALT, HBsAg and/or HBV-DNA level and starting antiviral therapy as soon as it becomes detectable in the blood.

For several years LAM has been the only antiviral available to treat and manage hepatitis B and its reactivation, but during the last few years several

studies have been published to demonstrate the efficacy of antivirals with superior characteristics of potency and genetic barrier as ETV and TDF (waiting for the availability of TAF, a less nephrotoxic prodrug). Today in the setting of hematology these high barrier drugs have to be used in HBsAg-positive patients and it should be clear that LAM maintains a role only for the universal prophylaxis of HBVr in HBsAg-negative/anti-HBc positive (OBI) patients.

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