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Reactivation of hepatitis B virus during targeted therapies for cancer and immune-mediated disorders

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Review

Reactivation of hepatitis B virus during targeted therapies for cancer and immune-mediated disorders

ABSTRACT

Introduction: Targeted therapies have gained popularity in the treatment of several oncologic and immune-mediated diseases. Immunosuppression caused by these drugs has been associated to reactivation of hepatitis B virus (HBV) in both hepatitis B surface antigen (HBsAg) positive patients (overt infection) and HBsAg negative/anti-hepatitis B core antigen (anti-HBc) positive carriers (resolved infection), leading to premature discontinuation of therapy and potentially fatal hepatitis.

Areas covered: This review summarizes the evidence of HBV reactivation in patients with overt or resolved HBV infection undergoing targeted therapies for cancer or immune-mediated disorders, providing recommendations for the management of these patients.

Expert opinion: The risk of HBV reactivation relies on the immunosuppressive potency and duration of these therapies, the underlying disease and the virological patient's profile. However, HBV reactivation is preventable by screening for HBV markers in all patients scheduled to receive targeted therapies, assessing the virological profile and patient's clinical state, followed by appropriate antiviral treatment or prophylaxis in those patients at high risk of HBV reactivation. Close monitoring of HBV carriers at low risk of reactivation is warranted with the aim to start antiviral therapy as soon as HBV reactivates.

Keywords: anti-TNF-±, antiviral therapy, biological therapy, cancer, hepatitis B reactivation, monoclonal antibodies, rituximab, targeted therapy

1. INTRODUCTION

Targeted therapies, which include both biologics and small molecule inhibitors, have been a breakthrough in the management of many oncologic and immune-mediated disorders and in recent years these drugs have gained popularity with the expectation of a continuous market growth in the near future. These therapies, in fact, are a potent treatment strategy as they directly counteract the pathogenic mechanisms responsible for autoimmune or oncologic diseases. One major caveat of targeted therapies, however, is their ability to increase susceptibility of reactivation of concurrent infections as a consequence of the impaired immune response. In this context, hepatitis B virus (HBV) reactivation was a relevant adverse event that may occur both in patients with overt infection, i.e. HBsAg positive patients, and those with resolved HBV infection, i.e. HBsAg negative, anti-HBc positive with or without antibodies against HBsAg (anti-HBs). Indeed, the management of these patients differs across national and international guidelines (1-7). This is not a trivial point considering that worldwide 400 million persons carry chronic HBV infection and approximately 2 billion subjects have serum markers of resolved HBV infection (8). The mechanism of HBV reactivation during targeted therapies is an impaired balance between HBV and the host, taking place in both overt carriers of HBV and those with resolved HBV infection (9,10). The immunosuppression induced by targeted therapies removes the immune surveillance pressure against HBV and enhances HBV viral replication. The ‘‘first phase’’ of HBV reactivation which kick offs when the patient starts targeted therapy is characterized by the absence of any sign of liver damage but an increase in serum HBV DNA levels. After withdrawal of the targeted agents, there is a ‘‘second phase’’ characterized by recovery of host immunity and rapid T-cells mediated damage of the infected hepatocytes, resulting in the onset of hepatitis with elevation of serum alanine aminotransferase (ALT) and development of constitutional symptoms. This event may evolve to full recovery or an accelerated progression to chronic hepatitis/cirrhosis or even to liver failure (9,11). The severity of reactivation is driven by the stage of baseline liver disease, the extent of liver damage caused by HBV reactivation, the concomitant exposure to hepatotoxic drugs and the

presence of co-morbidities. Reactivation of HBV impacts patient care and survival since it may influence the continuation of specific treatments while preventing the use of further drugs or immunosuppressive agents (9,11). Despite the progress in the diagnosis of virological and clinical profiles associated with HBV and the availability of effective antiviral treatments to prevent HBV reactivation, the increased access of patients to targeted therapies coupled with insufficient awareness on the risk of HBV reactivation among caregivers, have frequently resulted in patients experiencing HBV reactivation.

We review here the clinical impact of targeted therapies for cancer or immune-mediated disorders in chronic HBV carriers with the aim to provide practical insights on how to screen and manage patients in need of such drugs.

2. METHODS

Articles, case series and reports concerning the use of targeted therapies in patients with overt or resolved HBV infection were searched in PUBMED, MEDLINE, EMBASE, COCHRANE, focusing on: safety, risk for hepatitis reactivation, prophylaxis, treatment and patient management. Search terms included: viral infection, hepatitis B virus, HBV, hepatitis reactivation, monoclonal antibodies, kinase inhibitors, mTOR inhibitors, proteasome inhibitors, biological therapies, targeted therapies. English-language articles published between 2001 and 2015, as well as conference proceedings from the annual meetings of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) were reviewed. Primary relevance was given to prospective studies, where available; review articles were used only to identify primary papers.

3. HEPATITIS B

3.1 The virus

HBV is a leading cause of acute and chronic liver disease and anticipated liver-related death (8). Prevalence of HBV infection varies greatly throughout the world, being between low (<1%) and moderate (1-2%) in Western countries whereas in Asia and in most parts of Africa it is much higher (>8%) (8). As a consequence, the risk of HBV reactivation very much depends on HBV prevalence within the general population.

HBV efficiently replicates into hepatocytes and in parallel integrates within the host DNA, the natural course of HBV infection being determined by the interplay of viral replication and host immune response and evolving through five phases (4). The first phase of infection, characterized by the presence of hepatitis B envelope antigen (HBeAg) and high levels of HBV DNA in serum, is defined as "immune tolerant"; it is associated with normal ALT levels and absence of significant liver injury and significant fibrosis progression. In the second phase, immune tolerance is lost leading to appearance of humoral and histological signs of necro-inflammatory liver injury, the so called ‘‘immune reactive HBeAg positive phase’’. In this phase levels of ALT are fluctuating and liver disease can advance to significant fibrosis. Upon progression of immune reactivity against HBV infected liver cells, HBeAg is lost whereas the appearance of antibodies against HBeAg (anti-HBe) can lead to ‘‘inactive carrier state” (third phase). In this phase histological signs of hepatitis progressively vane in the presence of persistently low (usually <2000 IU/mL) or undetectable serum levels of HBV DNA, ALT levels are below the upper limit of normal (ULN). In the fourth phase, i.e. “HBeAg negative chronic hepatitis”, despite the absence of HBeAg, active liver disease ensues with intermittently or persistently high HBV DNA and ALT levels, progressive liver injury and high risk of developing advanced hepatic fibrosis, cirrhosis and liver-related complications. Complete clinical recovery from HBV infection (fifth phase) is associated with clearance of serum HBsAg with or without development of anti-HBs, even though low-level HBV replication persists with detectable HBV DNA in the liver. Generally, HBV DNA is not detectable in the serum, while anti-HBc antibodies are present (10).

3.2 Definition of HBV virological profile before targeted therapies

The correct identification of the virological and clinical profile of HBV patients is mandatory prior to start targeted therapies, since the baseline status of the infection is crucial with respect to the choice of which strategy to adopt, not to mention that the risk of complications is related to the severity of the underlying liver disease (1). Patients with ongoing HBV infection, i.e. HBsAg positive carriers are defined as active carriers if they circulate e2000 IU/mL HBV DNA, ALT > ULN and have signs of hepatic disease (first, second and fourth phase of HBV infection). HBsAg positive individuals are classified as inactive carriers if they circulate anti-HBe, persistently normal ALT levels and HBV DNA <2000 IU/mL (third phase of HBV infection). Patients with resolved HBV infection are HBsAg negative carriers with anti-HBc with or without anti-HBs (fifth phase). In the latter individuals, an occult HBV infection is defined as evidence of intrahepatic and/or detectable serum HBV DNA in the absence of active liver disease. Characteristically, the ongoing low-level transcription and replication of HBV in the liver poses these patients at risk of reactivation upon immunosuppression (10).

3.3 Definition and outcome of HBV reactivation

All the above mentioned virological conditions may change during targeted therapies. Active carriers may have HBV reactivation with significant increase of serum HBV DNA and ALT levels leading to worsening of the pre-existing liver disease. Inactive carriers may convert to active carriers as HBV DNA replication and ALT levels increase leading to hepatic damage. Patients with resolved HBV infection may face an increase of serum HBV DNA with or without HBsAg seroreversion (re-emergence of HBsAg) and ALT flares. HBV reactivation may impact patient care as it may lead to either transient interruption or premature discontinuation of chemo-immunosuppressive therapy compromising patient survival. The spectrum of HBV reactivation varies from an asymptomatic increase in serum HBV DNA to hepatitis flares and even acute liver

failure. The severity of HBV-related hepatitis is related to the pre-treatment profile of HBV infection, the underlying liver disease, the patient's age and the general health status.

4. HBV REACTIVATION DURING DIFFERENT TARGETED THERAPIES

4.1 Monoclonal antibodies

Monoclonal antibodies (MAbs) recognize and bind to specific cellular proteins. Each MAb recognizes one particular protein and works in different ways depending on the protein they are targeting.

4.1.1 Rituximab

Rituximab (RTX), a chimeric mouse anti-human CD20 MAb, is indicated for the treatment of patients with non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), microscopic polyangiitis and rheumatoid arthritis (RA) refractory to tumor necrosis factor-inhibitors. This MAb is also increasingly being used to treat a number of other autoimmune conditions such as systemic lupus erythematosus, idiopathic thrombocytopenic purpura, auto-immune haemolytic anemia, pemphigus vulgaris, Sjogren's syndrome, graft versus host disease, mixed cryoglobulinaemia, multiple sclerosis, membranous nephropathy, auto-immune hepatitis and dermatomyositis (12). Since 1999, several cases of HBV reactivation were reported in HBsAg positive patients with hematological malignancies who were treated with RTX-combined chemotherapy or RTX monotherapy, in the absence of anti-HBV prophylaxis (13). The rates of HBV reactivation among HBsAg positive patients with hematological malignancies treated with RTX-based chemotherapy without any anti-HBV prophylaxis ranges from 40% to 80%. HBV reactivated from a few to up 28 months from start of therapy, most often in patients affected by lymphoma. Despite onset of antiviral therapy at the time of HBV reactivation, up to 40% of patients ultimately died as a consequence of acute liver failure (ALF) (14-39). HBV reactivation was also reported in lymphoma patients with a resolved infection who were treated with a RTX-based therapy. Prospective studies

reported a 20% risk of HBV reactivation, showing that RTX increases by 6 times this risk compared to patients treated without it (13,40). A recent systematic review including 578 patients from 15 studies reported a 6.3% risk of clinical HBV reactivation defined as ALT >3 ULN coupled with HBV DNA increase or HBsAg seroreversion (41).

Despite the use of lamivudine (LMV) for preventing chemotherapy-induced HBV reactivation in HBsAg positive patients undergoing RTX-based therapy for onco-hematological disease, this drug is burdened by the high incidence of LMV-resistant (R) mutations limiting its long-term efficacy (13,42). Alternative nucleos(t)ide analogs (NUCs) with stronger antiviral activity and better resistance profiles such as entecavir (ETV) provided better efficacy than LMV (37,38). No cases of HBV-related hepatitis were reported among HBsAg positive patients with lymphoma undergoing RTX-based chemotherapy in combination with ETV compared to a 12%/13% rates of HBV reactivation among patients who received LMV therapy (43,44).

There is no standard management to prevent HBV reactivation in HBsAg-negative, anti-HBc-positive patients undergoing RTX plus corticosteroid-containing chemotherapy (R-CHOP) for B-cell NHL. Two options are available in such patients: 1) the “pre-emptive anti-HBV therapy” based on monitoring of HBV DNA and/or HBsAg in all patients followed by rescue with anti-HBV drugs in the few cases who reactivate HBV, 2) the “anti-HBV prophylaxis”, based on the administration of anti-HBV drugs to all patients during and for some time after chemotherapy with the aim to prevent HBV reactivation.

As far as the “pre-emptive anti-HBV therapy” strategy is concerned, in a Japanese multicenter prospective observational study in 269 patients with resolved HBV infection undergoing R-CHOP for NHL who were monitored monthly for serum HBV DNA [low limit of quantification (LLOQ): 11 IU/ml], 22 (8%) patients had an increase of HBV DNA levels (median HBV DNA levels: 27 IU/mL, range: 11 and 432 IU/mL). HBV-related hepatitis was fully prevented due to the prompt start of ETV treatment (45). A single centre Japanese prospective long-term study with monthly monitoring of serum HBV DNA (LLOQ: 2.1 log copies/mL) in 28 patients with resolved HBV

infection undergoing R-CHOP for NHL, reported 2 (7%) cases of HBV reactivation (serum HBV DNA levels of 5.4 and 3.6 log copies/mL, respectively), who were promptly rescued by ETV before the onset of HBV-related hepatitis (46). A prospective study from Taiwan described the efficacy of ETV as "pre-emptive anti-HBV therapy" in 150 lymphoma patients with resolved HBV infection undergoing R-CHOP (47). During 27 months of follow-up, HBV reactivation occurred in 17 patients (11%) (12 of them had also HBsAg seroreversion), HBV-related hepatitis flares (> 3-fold increase in ALT exceeding 100 IU/L) were reported in 10 patients (7%) while a severe HBV-related hepatitis (ALT >10 fold of ULN) occurred in 4 patients (3%) despite ETV treatment. A randomized controlled study from Taiwan in patients with resolved HBV infection undergoing RTX-based chemotherapy for lymphoma compared the use of ETV as either "anti-HBV prophylaxis" (n=41) started in all patients within 1 week before the first course of chemotherapy and continued until 3 months after completing chemotherapy or "pre-emptive anti-HBV therapy" (n=39) started at the time of HBV reactivation, defined as an increase of serum HBV DNA to greater than 2000 IU/mL, and HBsAg seroreversion or at time of HBV DNA >2000 IU/mL accompanied by ALT greater than 100 U/L (48). During 18 months of follow-up, one patient in the "prophylactic" group and 7 patients in the "pre-emptive therapy" group had HBV reactivation (2.4% vs 18%, p=0.027) whereas HBsAg seroreverted in none of the former group compared to 4 patients in latter group (0% vs 10%, p=0.052). Only one patient randomized in the "pre-emptive anti-HBV therapy" group had an HBV-related hepatitis (ALT: 117 U/L).

No properly sized studies using LMV as either "anti-HBV prophylaxis" or " pre-emptive anti-HBV therapy" in patients with resolved HBV infection undergoing R-CHOP for NHL are available. However, we recently reported neither increase of serum HBV DNA nor HBsAg seroreversion among 67 such patients undergoing LMV prophylaxis (49).

HBV reactivation during RTX therapy has been also reported in non onco-hematological settings such as RA, both in HBsAg positive patients without HBV prophylaxis but also in some patients with resolved infection (50-53). On the other hand, HBV reactivation among rheumatic patients

treated with RTX-based therapy was never reported in HBsAg carriers who underwent anti-HBV prophylaxis and only in one out of 59 (1.7%) patients with resolved HBV infection without antiviral prophylaxis (54-56).

The current label for RTX includes a black box warning about the risk of HBV reactivation, which in some patients has resulted in ALF and death, while it recommends that all patients undergo screening for serum markers of HBV infection before starting RTX therapy and be monitored during and after treatment (57).

4.1.2 Tumor necrosis factor-alpha (TNF-±) antagonists

Tumor necrosis factor alpha (TNF-±) is one of the most important cytokine in the pathogenesis of many inflammatory diseases. Anti TNF-± agents such as Infliximab (IFX), Adalimumab (ADA), Etanercept (ETN), Certolizumab Pegol (CZP), Golimumab (GOL) are indicated to treat different pathological conditions as RA, ulcerative colitis, Crohn's disease and psoriasis (58). The interruption of TNF-± signal may increase HBV replication and viral reactivation. The risk of HBV reactivation is higher with IFX, maybe due to the more pronounced inactivation of TNF-± induced by IFX that is cytotoxic for TNF-expressing cells and binds both soluble and membrane-bound TNF-± in comparison with ETN that can only bind soluble TNF-± (59,60). Liver deterioration occurring either as early as the first dosing or as late as 2 years after starting IFX, almost universally in association with other immunosuppressors, suggests a relationship between degree of immunosuppression and risk of viral reactivation (61).

Perez Alvarez et al. reported in a series of 89 HBsAg positive patients and in 168 patients with resolved HBV infection undergoing different anti-TNF-± treatments (50% IFX, 33% ETN and 17% ADA), that the rates of HBV reactivation were 39% and 5%, respectively. Interestingly, only 25% of the patients who developed HBV reactivation had received antiviral prophylaxis, compared to 62% of those who didn't experience viral reactivation (62). Similar data were confirmed by Lan et al. in 12 HBsAg positive patients and in 70 patients with resolved HBV infection (HBsAg

negative/anti-HBc positive) undergoing anti-TNF-± treatments for RA with rates of HBV reactivation of 62% and 1%, respectively (63).

A recent systematic review and meta-analysis from 10 studies reported that the risk of HBV reactivation among patients treated with anti-TNF-± was 3% for patients with resolved infection and 15% for overt infection. Due to the significant risk of HBV reactivation, anti-HBV prophylaxis was recommended in the latter group of patients (64).

A prospective study in 14 HBsAg positive patients (8 inactive carriers and 6 active carriers) treated with anti-TNF showed that anti-HBV drugs may prevent viral reactivation though one active carrier developed HBV reactivation 3 years after the start of antiviral treatment due to the occurrence of LMV-resistance (R) (65). A recent prospective study in 37 HBsAg positive patients with inflammatory arthritis reported a reactivation rate of 33% without antiviral therapies compared to no cases of HBV reactivation in patients treated with antiviral therapies (66). Chung et al. among 8 inactive carriers treated with anti-TNF agents, reported one (12%) patient only with HBV reactivation after the third infusion of IFX, thus requiring anti-TNF withdrawal and ETV treatment initiation (67).

Overall, among HBsAg carriers treated with anti-TNF without anti-HBV drugs, HBV reactivation was reported in up to 60% of patients, having high serum HBV DNA levels, the exposure to more than one immunosuppressant agent and prolonged treatment duration as the most important factors associated with HBV reactivation. Otherwise, the risk of HBV reactivation in patients with resolved HBV infection undergoing anti-TNF administration for rheumatologic disorders or inflammatory bowel disease is very low (1-5%) (61-64).

The current label of IFX includes a warning about the risk of HBV reactivation, recommending that all patients undergoing this drug need to be screened for serum markers of HBV infection before starting the drug and monitored during and after treatment (68).

Small studies in HBsAg carriers exposed to anti-TNF treatment showed the efficacy of LMV to control viral replication for a short period of time in inactive carriers, however, the efficacy of LMV

in active carriers is significantly compromised by the emergence of LMV-R (4,61). Therefore, in active carriers, third generation NUCs, i.e. ETV or tenofovir disoproxil fumarate (TDF) should be preferred to LMV (69).

4.1.3 Ustekinumab

Ustekinumab, a human MAb against interleukin (IL)-12 and 23, is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and for those with active psoriatic arthritis, alone or in combination with Methotrexate. HBsAg positive patients treated with Ustekinumab in combination with antiviral prophylaxis did not show HBV reactivation whereas two out of the seven (29%) patients who did not receive antiviral prophylaxis exhibited HBV reactivation during treatment (70,71). Conversely, no viral reactivation was observed in 26 patients with resolved HBV infection who underwent Ustekinumab without any anti-HBV prophylaxis (71-73).

4.1.4 Alemtuzumab

Alemtuzumab, a humanized MAb against CD52 epitopes on lymphocytes cells, is indicated for the treatment of patients with CLL. One subject with CLL and resolved HBV infection developed a full blown hepatitis with HBsAg seroreversion after four weeks of Alemtuzumab therapy rescued by LMV. Another patient with resolved HBV infection was kept under prophylaxis with LMV up to three months after Alemtuzumab. Two months after LMV withdrawal clinical and laboratory features of acute hepatitis B developed requiring LMV restart. Antiviral therapy achieved a prompt recovery with also HBsAg clearance (74). One HBsAg positive man treated with LMV plus adefovir dipivoxil (ADV) combination therapy maintained control of viral replication during long-term chemotherapy with Alemtuzumab for CLL (75).

4.1.5 Ipilimumab

Ipilimumab, a MAb that inhibits the cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) receptor on cytotoxic T lymphocytes resulting in immune-mediated tumor cell death, is increasingly used in the treatment of metastatic melanoma. Rarely liver toxicity necessitating cessation of treatment has been reported. Limited data exist regarding the safety of Ipilimumab in patients with HBV infection as such patients were excluded from registration trials. Four patients with chronic hepatitis B (CHB) who received Ipilimumab in combination with third generation NUCs didn't report liver disease deterioration (76,77). However, one unrecognized HBsAg carrier who started Ipilimumab without antiviral prophylaxis developed severe HBV reactivation requiring ETV rescue therapy (Viganò personal communication), emphasizing the risk of viral reactivation among HBsAg positive patients due to the increased T-cell activation and proliferation induced by Ipilimumab by blocking the inhibitory action of the negative T-cell regulator CTLA-4 (78). Otherwise, one patient with resolved HBV infection who received Ipilimumab without antiviral prophylaxis didn't report liver disease deterioration (77).

4.1.6 Ofatumumab

Ofatumumab is a fully human MAb for the CD20 protein which appears to inhibit early-stage B lymphocyte activation approved in 2009 for treating CLL that is refractory to Fludarabine and Alemtuzumab and has also shown potential in treating follicular NHL, diffuse large B cell lymphoma, RA and relapsing and remitting multiple sclerosis.

In 2013, the US Food and Drug Administration (FDA) is alerting physicians and patients that individuals undergoing treatment with Ofatumumab have an increased risk of HBV reactivating recommending that all patients undergo screening for serum markers of HBV infection before starting Ofatumumab and be monitored during and after treatment (79).

4.1.7 Tocilizumab

Tocilizumab (TCZ), a humanized MAb against IL-6 receptor, is currently used for RA treatment. RA patients co-infected with HBV were not included to clinical studies with TCZ, therefore data on the safety of TCZ in patients infected with HBV are scarce. Nagashima et al. reported that TCZ was administered safely in a RA patient with CHB without antiviral therapy (80). Safe TCZ use with no cases of HBV reactivation among CHB patients undergoing antiviral prophylaxis were also reported (81,82). A recent retrospective study from Nakamura et al. among 18 RA patients with a resolved HBV infection undergoing TCZ treatment without antiviral prophylaxis reported two cases of HBV reactivation (11%) after two infusion of TZC with slight increase of serum HBV DNA but without liver function tests deterioration (83).

4.1.8 Other monoclonals

No cases of HBV reactivation were reported yet with the following MAbs: Basiliximab, Belimumab, Bevacizumab, Blinatumomab, Brentuximabvedotin, Canakinumab, Cetuximab, Epratuzumab, Gemtuzumabozogamicin, Ibritumomab, Natalizumab, Nivolumab, Obinutuzumab, Panitumumab, Pertuzumab, Ramucirumab, Ranibizumab, Secukinumab, Sifalimumab, Siltuximab, Tositumomab, Trastuzumab, Vedolizumab.

4.2 Abatacept

Abatacept (ABA) is currently approved to treat RA. By mimicking the CTLA4, a negative regulator of T-cell co-stimulation, mainly prevents the activation of the T-cell compartment. A retrospective analysis of 8 patients with RA and HBV infection (2 active and 6 inactive carriers) treated with ABA showed that none of the 4 patients on anti-HBV prophylaxis (3 ETV, 1 TDF) had HBV reactivation compared to the remaining 4 patients developing HBV reactivation while not on antiviral prophylaxis (84). HBV reactivation occurring several months after the first ABA infusion without antiviral prophylaxis was also reported in patients with resolved HBV infection (85,86).

4.3 Tyrosine kinase inhibitors (TKI)

4.3.1 Imatinib

Imatinib mesylate, a tyrosine kinase inhibitor (TKI) that blocks the ATP-binding site of BCR/ABL, is recommended as the first line therapy for chronic myeloid leukemia (CML) and for unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). In 2006, Ikeda et al. reported the first case of fatal HBV reactivation occurred during treatment of CML with Imatinib in a CHB patient (87). Afterwards, 7 cases of HBV reactivation (two of whom required liver transplantation) among CHB patients who underwent Imatinib treatment for CML without antiviral prophylaxis, were reported (88-91) and recently, the first case of ALF due to HBV reactivation in a patient receiving Imatinib as adjuvant therapy for a GIST has been reported (92). The mechanism of TKI-induced HBV reactivation remains unclear. However, the observation that HBV reactivation occurred after a tumor response, supports the hypothesis of immune restoration leading to HBV reactivation. In vitro studies have in fact reported that Imatinib can inhibit T cell activation and proliferation thus restoring the function of plasmacytoid dendritic cells, the well-known crucial effectors in innate immunity (93,94).

4.3.2 Dasatinib

Dasatinib is a small-molecule inhibitor of the TKs SRC and ABL that has been approved for the treatment of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia. Reactivation of resolved HBV infection in a CML patient receiving Dasatinib has been recently reported (95). Although Dasatinib is not recognized as an immunosuppressant, this report suggests that the drug may enhance HBV replication inducing its reactivation in immunocompetent patients.

4.3.3 Other kinase inhibitors

No cases of HBV reactivation were reported yet with Afatinib, Axitinib, Bosutinib, Crizotinib, Erlotinib, Gefitinib, Ibrutinib, Lapatinib, Nilotinib, Pazopanib, Sorafenib, Sunitinib.

4.4 Proteasome inhibitors

4.4.1 Bortezomib

Bortezomib (BOR), which inhibits reversibly proteasomes and disrupts cell-signaling pathways, is indicated for treatment of patients with multiple myeloma (MM) and with mantle cell lymphoma. BOR may alter the number and function of specific lymphocyte subsets, especially CD8 T cells and CD56 natural killer cells (96-98). Some cases of HBV reactivation after BOR therapy have been reported both among HBsAg positive patients but also among patients with resolved HBV infection (99-101).

4.4.2 Carfilzomib

Carfilzomib is a selective proteasomes inhibitor that differs structurally and mechanistically from BOR. It is approved for relapsed and refractory MM. Although no cases of HBV reactivation have been reported, the risk of viral reactivation may be considered similar to BOR.

4.5 mTOR inhibitors

4.5.1 Everolimus

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor approved in renal cell carcinoma, neuroendocrine tumours and breast cancer. Two cases of HBV reactivation in CHB patients (one fatal) treated with Everolimus for renal cell carcinoma were reported (102,103).

4.5.2 Other mTOR inhibitors

No cases of HBV reactivation were reported yet with the other mTOR inhibitors such as Deforolimus, Sirolimus, Temsirolimus.

5. CONCLUSIONS

Biologic therapies are of strategic importance in the management of patients with cancer or inflammatory diseases, yet they often subvert host immunocompetence to the point of inducing HBV reactivation and/or acceleration of a pre-existing liver damage. In the absence of antiviral therapy, the majority of patients with an overt HBV infection following biologic therapies will experience an increase of viral load and ALT flares. HBV reactivation may occur with a wide variety of immunosuppressive therapies employed to treat both benign and malignant diseases. Owing to the lack of randomized control studies on viral reactivation prevention in patients with an overt or resolved HBV infection exposed to targeted therapies, current recommendations have been designed largely on the basis of small cohort studies, case reports and expert opinions (Table 1). Owing to the high prevalence of HBV among the general population, the increasing use of these drugs and the risk of severe, sometimes fatal, reactivation of HBV, all patients scheduled to receive these drugs should be screened for HBsAg and anti-HBc before start of therapy (4-7). It is clinically important for physicians to be aware that all patients with a resolved HBV infection (HBsAg negative/anti-HBc positive), but particularly those with detectable serum HBV DNA who prevail in high endemic countries such as Southeast Asia, are at risk of reactivation upon immunosuppression.

All patients with an overt or resolved infection should be referred for additional assessment and medical management since appropriate treatment of such patients is not only effective but also cost-saving. The choice on the best strategy to use, i.e. anti-HBV therapy versus anti-HBV prophylaxis versus pre-emptive anti HBV-therapy is based on the clinical setting, the virological patient's profile and the drug used.

6. EXPERT OPINION

All active carriers need anti-HBV therapy with third-generation NUCs, i.e. ETV or TDF, independently of the immunosuppression. NUCs should be started prior to any biologic therapies and maintained long-term, perhaps indefinitely, due to the high risk of relapse after withdrawal, unless HBsAg serocoversion takes place (Figure 1). Patients should be monitored as recommended

by international guidelines (2-4) in order to evaluate efficacy, safety and tolerability of NUC therapy.

Inactive carriers are indicated to "anti-HBV prophylaxis" with LMV for at least 12/18 months after the end of targeted therapies. In such patients serum HBV DNA should be tested every 3/4 months both during prophylaxis due to emergence of LMV-R or after LMV withdrawal, to promptly start rescue with TDF monotherapy. However, in inactive carriers who received RTX plus other combination therapies with or without high doses of steroids, those with onco-hematological diseases, those for whom long-term biologic therapy can be anticipated, those with moderate levels of HBV DNA or whenever regular HBV DNA monitoring cannot be implemented, ETV or TDF should be preferred instead of LMV (Figure 1).

For patients with resolved HBV infection the best anti-HBV strategy remains unknown. In high-risk patients such as those with hematological malignancies undergoing RTX-based chemotherapy, BOR or Carfilzomib treatment, two strategies could be used: "pre-emptive anti-HBV therapy" with ETV or "anti-HBV prophylaxis" with LMV. Both strategies have pros and cons. The former strategy, which is based on intensive monitoring of serum HBV DNA with a sensitive PCR assay in all patients to identify the few cases with HBV reactivation to be rescued by potent NUC is challenged by the need of patient's adherence, the cost of the strategy and the residual risk of hepatitis (2-7%) (45-48). On the other hand, the latter strategy which is based on the administration of LMV to all patients during immunosuppression and for a 18-month consolidation time, has the potential advantages of high efficacy and simple and less labor intensive management although it is so far supported by fewer clinical data (49).

By converse, pre-emptive anti-HBV therapy is likely to be the best strategy for patients at low risk of HBV reactivation, i.e. those receiving all the other targeted therapies for cancer or immune-mediated disorders (Figure 1). In these patients close monitoring of HBV DNA and/or HBsAg every 3/4 months to start anti-HBV drugs following HBV DNA increase and/or HBsAg seroreversion before clinical evidence of hepatitis reactivation, may be cost-effective. Whenever

regular HBV DNA and/or HBsAg levels monitoring cannot be implemented in these patients “anti-HBV prophylaxis” with LMV should be started.

ARTICLE HIGHLIGHTS

- Targeted therapies are increasingly popular for the treatment of several oncologic and immune-mediated diseases. However, HBV reactivation may occur with a wide variety of immunosuppressive therapies in benign or malignant disease both in patients with overt and resolved infection.
- HBV reactivation may induce not only premature discontinuation of targeted therapies and progression of the underlying disease but, more importantly, potentially fulminant and even fatal hepatitis. However, this complication is preventable by screening for HBV markers (HBsAg, anti-HBc, anti-HBs) all patients scheduled to receive these therapies and by referring those with overt or resolved infection for the proper management.
- Long-term anti-HBV therapy with ETV or TDF is recommended in all active HBV carriers in need of targeted therapies.
- All inactive carriers undergoing targeted therapies for cancer or immune-mediate disorders must undergo anti-HBV prophylaxis. For most of these carriers, LMV for at least 12/18 months after completion of immunosuppressive therapy is the recommended strategy. By converse, for inactive carriers who receive RTX plus other combination therapies with or without high doses of steroids, those with onco-hematological diseases, those for whom long-term biologic therapy can be anticipated or whenever regular HBV DNA monitoring cannot be implemented, ETV or TDF should be preferred.
- Patients with resolved HBV infection receiving RTX, BOR or Carfilzomib for onco-hematological disease both the “anti-HBV prophylaxis” with LMV for at least 12/18 months after the end of chemotherapy or the “pre-emptive anti-HBV therapy” with ETV could be

recommended, whereas for all the other settings at low risk of reactivation the “pre-emptive anti-HBV therapy” is the best strategy.

DECLARATION OF INTEREST

P Lampertico has received funding for participation in speaking bureaus and advisory boards for Bristol-Myers Squibb, Roche, Gilead, MSD and GlaxoSmithKline. M Viganò has received funding for speaking and teaching from Roche, Gilead and Bristol-Myers Squibb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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*=of importance

**= of considerable importance

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FIGURE LEGEND

Figure 1. Algorithm for screening and treatment of hepatitis B virus infection before starting targeted therapies for cancer and immune-mediated disorders.

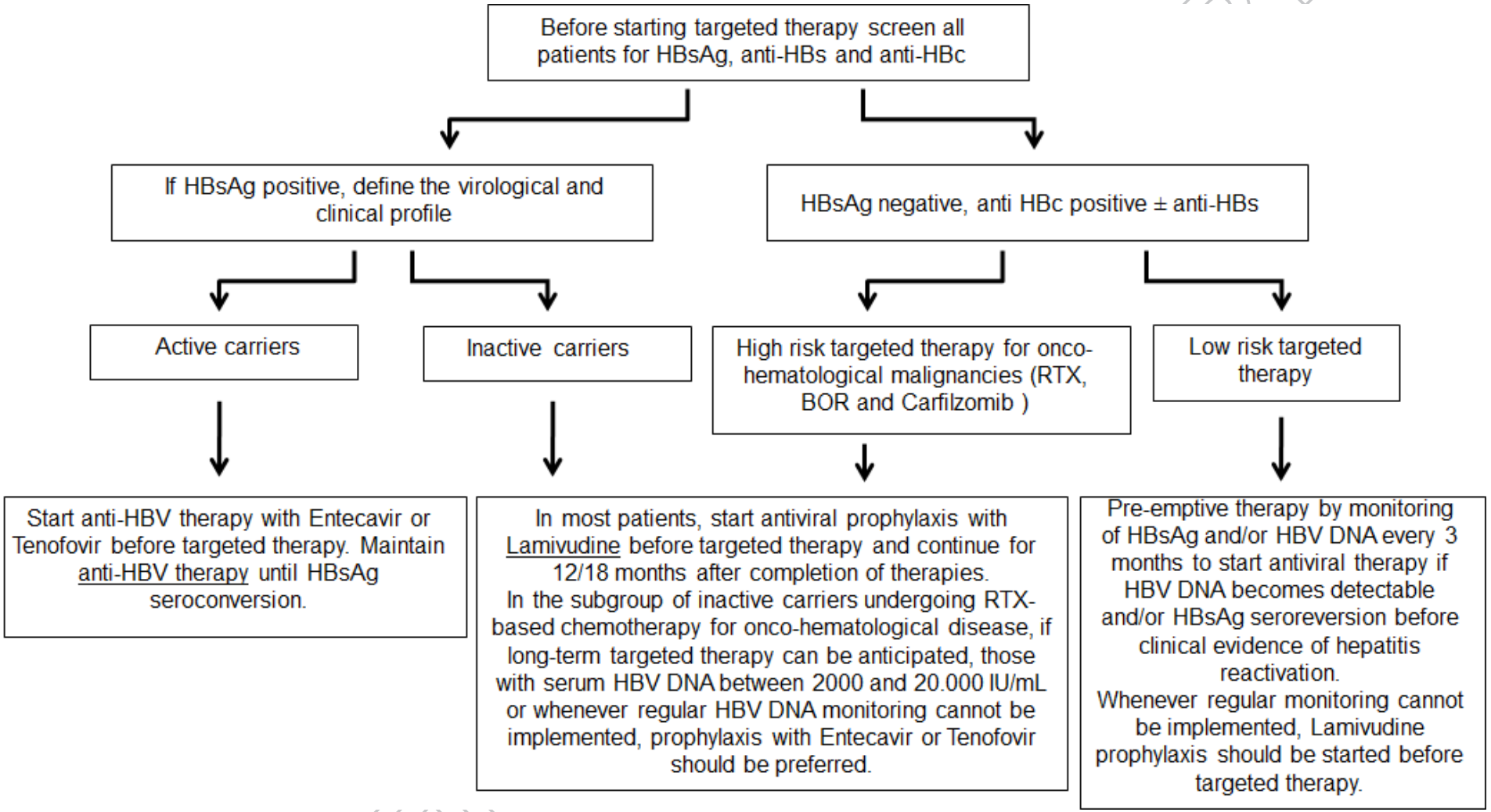

Table 1. Studies on the risk of hepatitis B reactivation during biologic therapies.

		HBsAg positive		HBsAg negative
Drug	**Year***	**Active carriers**	**Inactive carriers**	**Anti-HBc positive**
Rituximab	1997	RCT (17,38,58) R (13,15,24,36) CR (14,18,19,23,26,27,29) RS (28,30,33-35,37-39,43)	RCT (38,58) R (13,24,36) CR (20-22,25,31,32,43) RS (28,30,33-35, 37,43,54,55)	RCT (48) R (13,24,36) RS (28,30,35,39,54, 56) CR (51,52) PS (40)
TNF-alfa antagonists	1998	R (59-61) RS (62,63) PS (65,66)	R (60,61) RS (62,63,66) PS (65,66)	R (61) RS (63) PS (66,67)
Ustekinumab	2009	RS (70,71)	No studies	RS (71-73)
Alemtuzumab	2001	CR (75)	No studies	CR (74)
Ipilimumab	2011	CR (76,77)	No studies	CR (77)
Tocilizumab	2010	CR (80-82)	No studies	RS (83)
Abatacept	2015	RS (84)	RS (84)	CR (85,86)
Imatinib	2001	CR (88,92)	CR (87,89,90)	CR (91)
Dasatinib	2006	No studies	No studies	CR (95)
Bortezomib	2003	CR (101) RS (98,100)	No studies	CR (97,99)
Everolimus	2009	CR (102)	CR (103)	No studies

*Year of approval by Food and Drug Administration

Type of study (references): CR=case report; RS=retrospective study; PS=prospective study; R=review; RCT=randomized control study