Therapy of Occult Hepatitis B Virus Infection and Prevention of Reactivation

Giovanni Raimondo^{a,c} Roberto Filomia^{a,b} Sergio Maimone^{a,b}

^aDivision of Clinical and Molecular Hepatology, ^bDepartment of Internal Medicine, and ^cDepartment of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy

Key Words

Occult hepatitis B virus infection · Hepatitis B virus core antibody · Hepatitis B virus surface antigen

Abstract

Occult hepatitis B virus infection (OBI) is highly prevalent worldwide. In some cases, it is a consequence of infection with variant viruses mutated in the S gene and producing a surface antigen not recognized by diagnostic kits. In most cases, OBI is due to a strong inhibition of hepatitis B virus (HBV) activities exerted by host defense mechanisms. OBI may reactivate in patients undergoing immunosuppressive therapy and/or chemotherapy with the possibility of a consequent development of acute hepatitis that may lead to hepatic failure. Hematological malignancies and therapeutic schedules including rituximab are the conditions most frequently associated with OBI reactivation. However, this event may occur in a large number of additional clinical and therapeutic settings. Identification of patients prone to undergo reactivation is of great importance for promptly starting a proper antiviral therapy that may stop the HBV reactivation and prevent its clinical sequelae.

© 2014 S. Karger AG, Basel

Occult hepatitis B virus infection (OBI) and its clinical implications are becoming one of the most intriguing and important topics in the field of viral hepatitis [1, 2]. In particular, there is growing interest about the risk of OBI reactivation with the possible sequela of acute severe hepatitis [2–5]. This interest is largely justified for at least three main reasons: (1) epidemiological studies have clearly demonstrated that OBI is highly prevalent worldwide [although it is more widespread in the areas where hepatitis B virus (HBV) is endemic] [1, 2], (2) an increasing number of cases of OBI reactivation have been observed recently as a consequence of the availability of new, potent, and efficacious immunological drugs (i.e. targeted immunomodulators or biologics) and complex chemotherapy schedules longitudinally administered through several subsequent cycles in different clinical contexts (i.e. oncology, oncohematology, and autoimmune diseases) [1, 2, 6, 7], and (3) the availability of nucleos(t)ide analogue antivirals specifically inhibiting HBV replication, which (if properly used) represents a tool of utmost importance for preventing OBI reactivation and/or consequent acute hepatitis [8].

The definition of ‘occult hepatitis B virus infection’ groups the clinical/virological conditions in which episomal, free HBV genomes persist for a long time in the hepatocytes of individuals testing negative for HBV sur-

face antigen (HBsAg) [9]. In some cases, the lack of HBsAg detection is the consequence of the infection with variant viruses carrying mutations in the HBV S gene (S-escape mutants) and producing a modified HBsAg that is not recognized by commercially available diagnostic kits [10, 11]. In most cases, OBI is due to replication-competent viruses with a degree and relevance of genetic heterogeneity comparable with the HBV isolates from individuals with HBsAg-positive (namely 'overt') infection [12], but subjected to a potent suppression of the replication activity and gene expression leading to the lack of HBsAg synthesis as well as to the absence (or presence in traces) of HBV DNA in the serum [1, 2]. In the context of this review, it is important to stress that the replication, transcription, and protein synthesis capabilities of HBV isolates from liver of OBI individuals can be fully restored once the viruses are taken out of the host's microenvironment and transfected in hepatoma cells [12]. In fact, the acute hepatitis that may follow OBI reactivation usually shows the typical serological profile of acute hepatitis B, with HBsAg (re)appearance and even HBeAg positivity [1, 3, 13]. Although the mechanisms involved in the strong inhibition of the HBV activities are far from being completely elucidated, it is clear that host factors are largely implicated. In particular, much evidence shows the central role played by immune surveillance in inhibiting HBV replication and gene expression up to the OBI phase development [14–17]. Indeed, OBI reactivation is an event usually occurring in patients immunocompromised because of a disease involving the immune system and/or because therapeutic treatments have considerably weakened the immune response [3, 5–7]. In fact, one may depict a schematic scenario that when a subject with OBI undergoes immunosuppressive treatment, a reactivation of the viral replication and protein synthesis (including HBsAg) may occur as a consequence of the fault of the immunological control, and, once therapy is stopped and immune surveillance reconstituted, a CTL-mediated hepatocyte injury may occur leading to the development of hepatitis. Of note, aside from immunologic mechanisms, there is also evidence that – similar to other DNA viruses (i.e. Epstein-Barr virus and herpesviruses) able to develop chronic silent infections – in the case of OBI, the epigenetic modifications of histones bound to the HBV cccDNA might be a mechanism of transcriptional control and silencing of the viral activity [18]. However, there are only few anecdotal reports and no clear evidence of the possible OBI reactivation due to drugs potentially influencing the epigenetic control of the HBV cccDNA minichromosome [2].

A further point that must be included in these introductory notes concerns the fact that even if the majority of OBI patients are positive for antibodies to the HBV core antigen (anti-HBc) and part of them also for the anti-HBs antibodies, about 20–25% of OBI cases are negative for all HBV serum markers [1, 2]. This last subset of patients is clearly very difficult to recognize as 'OBI carriers' since there is no sign or marker that may lead to suspect the infection and thus to perform an HBV DNA test that might allow identification of the infection. However, apart from a few anecdotal reports concerning HBV reactivation in OBI-positive/HBV-seronegative cases [19], OBI reactivation appears to be an event strictly occurring in anti-HBV antibody-positive subjects. In this context, it is important to stress that there are convincing data showing that the HBV-specific T cell response is much weaker in OBI seronegative individuals than in anti-HBc-positive patients, thus likely insufficient to provoke severe liver injury [20].

OBI Reactivation: Predisposing Conditions and Possible Predictors

Although HBV reactivation in individuals with OBI undergoing immunosuppressive therapies occurs less frequently than in cases with 'overt' infection [5], it has considerable clinical relevance. In fact, considering the enormous number of potential 'OBI carriers' (namely, anti-HBc positive individuals), it represents an everyday challenge in clinical practice. OBI reactivation may be clinically silent, but in some circumstances it may induce acute hepatitis that may have a severe and even fulminant course, or may evolve to rapidly progressive chronic hepatitis [21]. In any case, development of acute hepatitis may determine the interruption of chemotherapy with obvious negative consequences for disease prognosis [22]. To date, no reliable tool for predicting HBV reactivation in OBI patients is available. However, a number of clinical, therapeutic, and immunovirological profiles have been identified that – once cumulatively evaluated – may help to identify individuals at higher and those at lower risk for the occurrence of that event (table 1). The reported frequencies of OBI reactivation in the different populations according to these features are schematically summarized below.

Clinical Profiles

Patients with hematological malignancies (especially non-Hodgkin lymphoma, multiple myeloma, myelomonoblastic acute leukemia, and chronic lymphocytic

Table 1. Risk categories of OBI virological/clinical reactivation*High risk*

Oncohematological malignancies under treatment
R-CHOP treatments
Liver transplantation (from anti-HBc-positive donors)
Hematopoietic stem cell transplantation

Intermediate risk

Rheumatological diseases treated with biological agents or high dosage of steroids for prolonged time
HIV infection
Kidney transplantation (from anti-HBc-positive donors)
Bone marrow transplantation

Low risk

Dermatological and inflammatory bowel diseases treated with biologics
Solid tumors treated with chemotherapy
Organ transplantation other than liver and kidney
Transarterial chemoembolization for treatment of hepatocellular carcinoma

R-CHOP = Rituximab with cyclophosphamide, hydroxydaunorubicin, oncovin, and predniso(lo)ne.

leukemia) have the highest risk of OBI reactivation, especially when treated with schedules including anti-CD20 monoclonal antibody (rituximab) [2, 5–7, 23–25]. Patients undergoing hematopoietic stem cell transplantation also show a high incidence of OBI reactivation [26, 27], which is a frequent occurrence in cases of liver transplantation (but also of kidney) when the recipient is naive for HBV infection and the donor is anti-HBc positive [28, 29].

Patients with rheumatologic diseases have been extensively investigated for evaluation of HBV reactivation. OBI reactivation appears to be an infrequent (but existing) event in individuals undergoing treatments including biologics (mainly anti-CD20 and anti-TNF- α drugs, see below) or with schedules containing high doses of corticosteroids [24, 30, 31]. Only a few cases of OBI reactivation occurring in patients with liver cancer undergoing transarterial chemoembolization and in patients with inflammatory bowel diseases under treatment with biological agents have been reported [2].

Finally, the real risk of OBI reactivation in patients with solid tumor undergoing chemotherapy is debatable [32], and there are no reliable data available about OBI reactivation in other categories of patients, such as individuals with psoriasis, in whom treatments with biological agents are applied.

Immunosuppressive Therapy and Chemotherapy

Therapeutic regimens containing rituximab [especially combinations of rituximab with cyclophosphamide, hydroxydaunorubicin, oncovin, and predniso(lo)ne] provide the highest risk of reactivation in all HBV patients, including those with OBI [5, 21, 23]. Apart from hematological malignancies, rituximab is also widely used in patients with autoimmune inflammatory diseases (i.e. rheumatoid arthritis, inflammatory bowel diseases, etc.). It is a monoclonal antibody directed against the CD20 antigen expressed on the B lymphocyte surface. It seems very important (and also scientifically intriguing) that a drug efficiently depleting B lymphocytes is also the most potent inducer of the restoration of HBV replication in all conditions (of course also including OBI phase) in which it appears to be suppressed (likely because of the immune control exerted by the T lymphocytes). It is thought that the central role played by B lymphocytes in the anti-HBV immune response is related to multiple aspects including, besides the production of antibodies, their activity as antigen-presenting cells and the enhancement of the cytotoxic response of CD8 T lymphocytes [33]. Similarly, ofatumumab – another anti-CD20 monoclonal antibody used for treatment of hematological malignancies – is considered a drug with potential high propensity to induce HBV reactivation [22]. Another biological agent utilized in the field of oncohematologic therapy and recognized as responsible for cases of OBI reactivation is the anti-CD52 monoclonal antibody alemtuzumab [5, 21, 23].

Anti-TNF- α drugs that are widely used in autoimmune inflammatory diseases have been reported to be associated with some cases of OBI reactivation. Of note, TNF- α is a chemokine known to suppress HBV replication [34].

Among the several nonbiologic drugs potentially implicated in HBV reactivation (also in cases with OBI) [2], corticosteroids administered at high doses and for long periods must be listed. In this context, it is worth mentioning that steroids, apart from favoring the establishment of an immunosuppressive status, may directly act by stimulating HBV replication through the glucocorticoid responsive element present in the viral genome [35] (fig. 1).

Virological Profiles

A relevant and debated argument is whether patients positive for anti-HBc alone have a different risk of OBI reactivation compared to those positive for both anti-HBc and anti-HBs, as it was suggested that anti-HBs ex-

Fig. 1. Schematic representation of the glucocorticoid responsive element (GRE) in the HBV genome. 351 and 366: nucleotide positions (nt) of the GRE sequence located in a portion of the S (S gene) and P (Pol gene) overlapping genomic regions. Nucleotide positions are numbered from the EcoRI unique restriction site present in the HBV genome.

erts a protective role against the rebound of HBV active replication. However, recent studies have not confirmed this different behavior of the two subsets (anti-HBs positive and anti-HBs negative) of anti-HBc-positive patients [23, 36]. Indeed, a large body of evidence has demonstrated that anti-HBs/anti-HBc-positive patients undergoing immunosuppression may show a progressive decrease of the titer of anti-HBs that may finally disappear [23, 26, 27]. This phenomenon usually precedes the reappearance of the HBsAg in all cases with complete virological and clinical reactivation.

Similarly debated is whether the presence of minute but detectable amounts of HBV DNA in the serum before starting immunosuppressive therapy is a clear indication for the treatment with antivirals to prevent a possible massive viral reactivation. In this context, it has to be considered that patients with OBI longitudinally followed very often show phases of negativity for serum HBV DNA alternating with phases – or single time points – in which low amounts of HBV DNA are detected. This fluctuating profile has been observed in immunocompetent individuals [37, 38] as well as in patients with solid tumors under chemotherapy; both conditions are usually not followed by clinically relevant viral reactivation [32]. Of note, it has recently been reported that OBI patients with detectable traces of HBV DNA before immunosuppressive therapy

have comparable risks of clinical/virological reactivation as HBV-DNA-negative subjects [36]. In any case, it has to be stressed that HBV DNA testing before starting immune and/or chemotherapies is an undoubtedly important step for at least two main reasons: (1) detection of HBV DNA is a direct, definitive demonstration that a patient is an 'OBI carrier' since the sole detection of anti-HBc is insufficient to prove the occult infection status [9], and (2) assaying HBV DNA is the only test that can identify the infrequent but existing cases of moderate/high levels of viremia (with >200 IU/ml as an arbitrary cutoff, according to the statements from an international expert meeting focused on OBI [9]) that may be due to infection with S-escape virus and that may require therapeutic approaches completely different compared to those adopted in cases of OBI due to suppressed viral activity (fig. 2).

Therapeutic Approaches for the Prevention or the Treatment of OBI Reactivation

The ideal treatment for OBI should rely on a drug capable of eliminating the HBV cccDNA from the hepatocyte nuclei, possibly without killing the cells. Unfortunately, no such drugs are available at present. Consequently, we have to act by trying to prevent OBI reactivation and above all the development of acute hepatitis that may follow viral reactivation, and be aware that such prevention is lifesaving in many cases.

HBsAg-Negative Patients Infected with S-Escape HBV Variants

The clinical/virological features (including serum HBV DNA levels) of these cases are substantially similar to those observed in the different conditions of the 'overt' HBV infection; therefore, the therapeutic approaches should be similar to that adopted in the 'typical' HBsAg-positive forms and patients undergoing chemotherapy and/or immunosuppressive therapies should be treated with entecavir or tenofovir, which are the most potent anti-HBV nucleos(t)ide analogues and (very importantly) which have the highest genetic barrier [8] (fig. 2).

OBI Patients with Suppressed HBV Replication and Gene Expression

This category of patients represents a difficult but frequent challenge for hepatologists. On one hand, there are too many anti-HBc-positive individuals in the world (with the highest prevalence in HBV endemic areas) to propose a preemptive therapy in all cases undergoing immunosup-

Fig. 2. Suggested management of HBsAg-negative/anti-HBc ($\pm$ anti-HBs)-positive patients undergoing immunosuppressive therapy and/or chemotherapy according to serum HBV DNA status. **a** Management of HBV-DNA-positive individuals. * 200 IU/ml of serum HBV DNA levels is an arbitrary cutoff identified in accordance with the statements from the Taormina expert meeting on OBI [9]. **b** Management of HBV-DNA-negative individuals. HBV DNA must be tested by highly sensitive real-time PCR techniques. HSCT = Hematopoietic stem cell transplantation.

pressive therapy. On the other hand, the collaboration between hepatologists and the other specialists taking care of these patients (hematologists, oncologists, rheumatologists, etc.) is often not sufficiently strong enough to guarantee the very narrow biochemical and virological follow-up necessary to identify viral reactivation early enough to start antiviral therapy and prevent acute hepatitis.

Consequently, the following behavior might be suggested for anti-HBc-positive patients undergoing immunosuppressive therapy and/or chemotherapy (fig. 2): (1) all subjects suffering from the above-mentioned diseases at the highest risk of OBI reactivation should be treated with lamivudine, independently of the anti-HBs status and detectable or undetectable serum HBV DNA; (2) similarly, all individuals testing HBV DNA positive and undergoing treatment with biologics (mainly rituximab and other anti-

CD20, but also anti-CD52, and anti-TNF α) and/or with a high dose of corticosteroids should be preemptively treated with lamivudine; (3) in individuals with diseases rarely associated with OBI reactivation, testing HBV DNA positive when untreated with biologics or high doses of steroids should be monitored through evaluations of HBV DNA and aminotransferase (AT) levels every 2–3 months; (4) in individuals with diseases rarely associated with OBI reactivation, testing HBV DNA negative and undergoing treatments with rituximab or other biologics should be monitored through evaluations of HBV DNA and AT levels every 2 months, and (5) all individuals with diseases rarely associated with OBI reactivation, testing HBV DNA negative and undergoing any immunosuppressive therapy or chemotherapy should be monitored by evaluations of HBV DNA and AT levels every 3 months. In individuals at

points 3 and 4, if HBV DNA becomes detectable and/or there is an AT rise, the tests should be quickly repeated to verify the new profile, also including HBsAg testing (and anti-HBs titer in individuals anti-HBs positive at baseline). When the patterns of possible reactivation are confirmed, antiviral therapy with a nucleos(t)ide analogue (preferably entecavir or tenofovir) must be started.

Of note, lamivudine is efficient in preventing HBV reactivation in patients with no or very low serum HBV DNA levels [8], and the use of a very potent nucleos(t)ide analogue does not seem to provide significant advantages [39]. The only warning should be the risk of the selection of lamivudine-resistant viral strains possibly archived in the HBV cccDNA pool and prone to determine a viral reactivation [12]. This eventuality suggests continuing careful monitoring under antiviral treatment, and if the HBV DNA remains detectable (or even increases) during therapy with lamivudine, it is prudent to switch to tenofovir, which is very efficacious in suppressing lamivudine-resistant mutants.

Of great importance, HBV reactivation may occur many months (up to 20 months) after stopping chemotherapy [3, 5, 21, 40]. Consequently, a narrow follow-up for patients not treated with antivirals as well as antiviral prophylaxis for those treated must be continued for a long time (some suggest at least 18 months) after chemotherapy/immunosuppressive therapy discontinuation. In the unfortunate cases in which HBV reactivation is not prevented and acute hepatitis develops, entecavir or tenofovir should be administered as soon as possible since there are reports showing the capacity of these antivirals to avoid the fulminant course in some cases [2]. In cases of liver transplantation (but also of kidney and bone marrow transplantation), when the donor is anti-HBc positive, antiviral prophylaxis is strongly recommended.

Conclusions

Although HBV reactivation in cases with OBI is much less frequent than cases with 'overt' infection, it represents a significant challenge in clinical practice for specialists of different branches. OBI is also a challenge because the number of HBsAg-negative/anti-HBc-positive individuals (potential 'OBI carriers') is considerably higher than HBsAg-positive individuals worldwide. Moreover, while indications for (and schedule of) antiviral treatment in HBsAg-positive subjects undergoing clinical/therapeutic conditions known to predispose to HBV reactivation (i.e. immunosuppressive therapy and/or chemotherapy) are quite well characterized, many doubts still exist about the possible therapeutic approaches in OBI patients undergoing the same conditions. This is mainly due to the fact that not all HBsAg-negative/anti-HBc-positive individuals are 'OBI carriers', and no reliable marker (or strong indicator) of OBI reactivation has been identified so far. Nevertheless, when OBI reactivation occurs, it may determine acute hepatitis that can be fatal for the patient due to its possible fulminant course or the necessity to stop chemotherapy. Development of valid and commercially available assays allowing the certain identification of OBI in all cases in different clinical settings and particularly in conditions known to create risks for HBV reactivation has become a true necessity. In the meantime, international prospective trials involving patients at risk of OBI reactivation should be performed to better define the risk factors, the monitoring and surveillance procedures, the antiviral approaches, and their duration and endpoints.

References

- 1 Torbenson M, Thomas DL: Occult hepatitis B. *Lancet Infect Dis* 2002;2:479–486.
- 2 Raimondo G, Caccamo G, Filomia R, Pollicino T: Occult HBV infection. *Semin Immunopathol* 2013;35:39–52.
- 3 Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, Burra P, Caraceni P, Daniele B, Di M, V, Fabrizi F, Fagiuoli S, Grossi P, Lampertico P, Meliconi R, Mangia A, Puoti M, Raimondo G, Smedile A: Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 2007;39:397–408.
- 4 Kusumoto S, Tanaka Y, Mizokami M, Ueda R: Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. *Int J Hematol* 2009;90:13–23.
- 5 Shouval D, Shibolet O: Immunosuppression and HBV reactivation. *Semin Liver Dis* 2013;33:167–177.
- 6 Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, Chan HL, Hui EP, Lei KI, Mok TS, Chan PK: Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009;27:605–611.
- 7 Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, Kuo CY: Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol* 2010;89:255–262.
- 8 EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167–185.

- 9 Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxi A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trepo C, Villa E, Will H, Zanetti AR, Zoulim F: Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008;49:652–657.
- 10 Allain JP, Belkhir D, Vermeulen M, Crookes R, Cable R, Amiri A, Reddy R, Bird A, Candotti D: Characterization of occult hepatitis B virus strains in South African blood donors. *Hepatology* 2009;49:1868–1876.
- 11 Stramer SL, Wend U, Candotti D, Foster GA, Hollinger FB, Dodd RY, Allain JP, Gerlich W: Nucleic acid testing to detect HBV infection in blood donors. *N Engl J Med* 2011;364:236–247.
- 12 Pollicino T, Raffa G, Costantino L, Lisa A, Campello C, Squadrito G, Levrero M, Raimondo G: Molecular and functional analysis of occult hepatitis B virus isolates from patients with hepatocellular carcinoma. *Hepatology* 2007;45:277–285.
- 13 Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, Kao WY, Chiu CF, Lin SF, Lin J, Chang CS, Tien HF, Liu TW, Chen PJ, Cheng AL: Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. *Hepatology* 2013, Epub ahead of print.
- 14 Penna A, Artini M, Cavalli A, Levrero M, Bertolotti A, Pilli M, Chisari FV, Rehmann B, Del PG, Fiaccadori F, Ferrari C: Long-lasting memory T cell responses following self-limited acute hepatitis B. *J Clin Invest* 1996;98:1185–1194.
- 15 Rehmann B, Ferrari C, Pasquinelli C, Chisari FV: The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996;2:1104–1108.
- 16 Cohen Stuart JW, Velema M, Schuurman R, Boucher CA, Hoepelman AI: Occult hepatitis B in persons infected with HIV is associated with low CD4 counts and resolves during antiretroviral therapy. *J Med Virol* 2009;81:441–445.
- 17 Bes M, Vargas V, Piron M, Casamitjana N, Esteban JL, Vilanova N, Pinacho A, Quer J, Puig L, Guardia J, Saulea S: T cell responses and viral variability in blood donation candidates with occult hepatitis B infection. *J Hepatol* 2012;56:765–774.
- 18 Levrero M, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M: Control of cccDNA function in hepatitis B virus infection. *J Hepatol* 2009;51:581–592.
- 19 Feeney SA, McCaughey C, Watt AP, Agnaf MR, McDougall N, Wend UC, Gerlich WH, Coyle PV: Reactivation of occult hepatitis B virus infection following cytotoxic lymphoma therapy in an anti-HBc negative patient. *J Med Virol* 2013;85:597–601.
- 20 Zerbini A, Pilli M, Boni C, Fiscaro P, Penna A, Di VP, Giuberti T, Orlandini A, Raffa G, Pollicino T, Raimondo G, Ferrari C, Missale G: The characteristics of the cell-mediated immune response identify different profiles of occult hepatitis B virus infection. *Gastroenterology* 2008;134:1470–1481.
- 21 Wursthorn K, Wedemeyer H, Manns MP: Managing HBV in patients with impaired immunity. *Gut* 2010;59:1430–1445.
- 22 Mitka M: FDA: Increased HBV reactivation risk with ofatumumab or rituximab. *JAMA* 2013;310:1664.
- 23 Yeo W, Chan HL: Hepatitis B virus reactivation associated with anti-neoplastic therapy. *J Gastroenterol Hepatol* 2013;28:31–37.
- 24 Coppola N, Tonziello G, Pisaturo M, Messina V, Guastafierro S, Fiore M, Iodice V, Sagnelli C, Stanzione M, Capoluongo N, Pasquale G, Sagnelli E: Reactivation of overt and occult hepatitis B infection in various immunosuppressive settings. *J Med Virol* 2011;83:1909–1916.
- 25 Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, Dai MS, Chiu BC, Fintel B, Cheng Y, Chuang SS, Lee MY, Chen TY, Lin SF, Kuo CY: Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011;22:1170–1180.
- 26 Onozawa M, Hashino S, Izumiyama K, Kahata K, Chuma M, Mori A, Kondo T, Toyoshima N, Ota S, Kobayashi S, Hige S, Toubai T, Tanaka J, Imamura M, Asaka M: Progressive disappearance of anti-hepatitis B surface antigen antibody and reverse seroconversion after allogeneic hematopoietic stem cell transplantation in patients with previous hepatitis B virus infection. *Transplantation* 2005;79:616–619.
- 27 Vigano M, Vener C, Lampertico P, Annaloro C, Pichoud C, Zoulim F, Facchetti F, Poli F, Scalapogna M, Deliliers GL, Colombo M: Risk of hepatitis B surface antigen seroreversion after allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2011;46:125–131.
- 28 Cholongitas E, Papatheodoridis GV, Burroughs AK: Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010;52:272–279.
- 29 Chen GD, Gu JL, Qiu J, Chen LZ: Outcomes and risk factors for hepatitis B virus (HBV) reactivation after kidney transplantation in occult HBV carriers. *Transpl Infect Dis* 2013;15:300–305.
- 30 Lee YH, Bae SC, Song GG: Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2013;31:118–121.
- 31 Giardina AR, Ferraro D, Ciccio F, Ferrante A, Di SR, Craxi A, Triolo G: No detection of occult HBV-DNA in patients with various rheumatic diseases treated with anti-TNF agents: a two-year prospective study. *Clin Exp Rheumatol* 2013;31:25–30.
- 32 Saitta C, Musolino C, Marabello G, Martino D, Leonardi MS, Pollicino T, Altavilla G, Raimondo G: Risk of occult hepatitis B virus infection reactivation in patients with solid tumours undergoing chemotherapy. *Dig Liver Dis* 2013;45:683–686.
- 33 Cooper N, Arnold DM: The effect of rituximab on humoral and cell mediated immunity and infection in the treatment of autoimmune diseases. *Br J Haematol* 2010;149:3–13.
- 34 Guidotti LG, Ishikawa T, Hobbs MV, Matzke B, Schreiber R, Chisari FV: Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity* 1996;4:25–36.
- 35 Tur-Kaspa R, Burk RD, Shaul Y, Shafritz DA: Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc Natl Acad Sci USA* 1986;83:1627–1631.
- 36 Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, Yang MH, Tzeng CH, Lee PC, Lin HC, Lee SD: Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013;31:2765–2772.
- 37 Kannangai R, Vivekanandan P, Netski D, Mehta S, Kirk GD, Thomas DL, Torbenson M: Liver enzyme flares and occult hepatitis B in persons with chronic hepatitis C infection. *J Clin Virol* 2007;39:101–105.
- 38 Chemin I, Guillaud O, Queyron PC, Trepo C: Close monitoring of serum HBV DNA levels and liver enzymes levels is most useful in the management of patients with occult HBV infection. *J Hepatol* 2009;51:824–825.
- 39 Chen FW, Coyle L, Jones BE, Pattullo V: Entecavir versus lamivudine for hepatitis B prophylaxis in patients with hematological disease. *Liver Int* 2013;33:1203–1210.
- 40 Tonziello G, Pisaturo M, Sica A, Ferrara MG, Sagnelli C, Pasquale G, Sagnelli E, Guastafierro S, Coppola N: Transient reactivation of occult hepatitis B virus infection despite lamivudine prophylaxis in a patient treated for non-Hodgkin lymphoma. *Infection* 2013;41:225–229.