World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i12.1563

World J Gastroenterol 2011 March 28; 17(12): 1563-1568
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Juan-Ramón Larrubia, PhD, *Series Editor*

Management of occult hepatitis B virus infection: An update for the clinician

José Luis Lledó, Conrado Fernández, María Luisa Gutiérrez, Sara Ocaña

José Luis Lledó, Conrado Fernández, María Luisa Gutiérrez, Gastroenterology Unit, Hospital Universitario Fundación Alcorcón, Av Budapest-1, 28922 Alcorcón, Madrid, Spain
Sara Ocaña, Laboratory Unit, Hospital Universitario Fundación Alcorcón, Av Budapest-1, 28922 Alcorcón, Madrid, Spain
Author contributions: Lledó JL, Fernández C, Gutiérrez ML and Ocaña S contributed towards the conception and design and wrote the review; Fernández C revised it critically.
Correspondence to: José Luis Lledó, PhD, Gastroenterology Unit, Hospital Universitario Fundación Alcorcón, Av Budapest-1, 28922 Alcorcón, Madrid, Spain. jllledo@fhalcorcon.es
Telephone: +34-916-219705 Fax: +34-916-219975
Received: August 6, 2010 Revised: September 18, 2010
Accepted: September 25, 2010
Published online: March 28, 2011

Abstract

Occult hepatitis B virus (HBV) infection (OBI) is defined by the presence of HBV DNA in the liver tissue of individuals who test negative for hepatitis B surface antigen (HBsAg). Patients who have recovered from acute hepatitis B can carry HBV genomes for a long time and show histological patterns of mild necro-inflammation, even fibrosis, years after the resolution of acute hepatitis, without showing any clinical or biochemical evidence of liver disease. At least in conditions of immunocompetence, OBI is inoffensive itself, but when other relevant causes of liver damage are present it might make the course of the liver disease worse. The risk of HBV transmission through transfusion is related to blood donations negative for HBsAg that have been collected during the pre-seroconversion period or during chronic OBI. Use of HBV nucleic acid amplification testing and multivalent anti-HBs antibodies in the HBsAg assays is recommended for detection of true and false OBI, respectively. It is not known if prior hepatitis B immunization with an optimal anti-HBs response in cases of HBV transmission through organ transplantation can effectively modulate or abort the infection. Use of antiviral agents as prophylaxis in patients with serological evidence of past HBV infection prevents reactivation of OBI after transplantation in most cases. Reactivation of OBI has been observed in other conditions that cause immunosuppression, in which antiviral therapy could be delayed until the HBV DNA or HBsAg becomes detectable. OBI might contribute to the progression of liver fibrosis and hepatocellular carcinoma development in patients with chronic liver disease.

Key words: Occult hepatitis B; Management; Blood transfusion; Organ transplantation; Virus reactivation; Chronic liver disease; Hepatocellular carcinoma

Peer reviewers: Ballarin Roberto, MD, Liver and Multivisceral Transplant Center and HPB surgery, University of Modena and Reggio Emilia, # 71, Via del Pozzo, 41100 Modena, Italy; Robert Christiaan Verdonk, MD, PhD, Department of Gastroenterology and Hepatology, University Medical Centre Groningen, Hanzeplein 1, Groningen, 9700 RB, The Netherlands

Lledó JL, Fernández C, Gutiérrez ML, Ocaña S. Management of occult hepatitis B virus infection: An update for the clinician. *World J Gastroenterol* 2011; 17(12): 1563-1568 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i12/1563.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i12.1563

INTRODUCTION

Occult hepatitis B virus (HBV) infection (OBI) is defined by the presence of HBV DNA in the liver tissue of individuals who test negative for hepatitis B surface antigen (HBsAg), by currently available assays, regardless of the detection of HBV DNA in the serum. When detectable, the level of HBV DNA in the serum is usually very low (< 200 IU/mL). Depending on the HBV antibodies detected, OBI may be seropositive [anti-hepatitis B core (HBc)

and/or anti-HBs positive] or seronegative (anti-HBc and anti-HBs negative) (> 20 %)[1].

The molecular basis of OBI is linked to the intrahepatic persistence of covalently closed circular DNA and to strong suppression of viral replication activity and gene expression. Host immune response, co-infection with other infectious agents, and epigenetic factors probably play a relevant role in HBV inhibition. This suppression of HBV activity is responsible for the very low or undetectable levels of serum HBV DNA in OBI cases[2,3]. If serum HBV-DNA levels are similar to those detected in serologically evident HBV infection, it should be considered as false OBI, usually due to infection by HBV variants with mutations in the S gene. These variants produce a modified HbsAg that is not recognized by commercially available detection assays[1]. OBI is more prevalent among subjects at high risk for HBV infection and with liver disease[1].

The gold standard for diagnosis of OBI is the analysis of HBV-DNA extracts from the liver and blood samples. As liver samples are only available in a minority of cases, the most common diagnosis of OBI is based on the analysis of serum samples[1]. In all cases, it is recommended to use a highly sensitive and specific test, like HBV nucleic acid amplification testing (NAT), a PCR technique with detection limits of < 10 copies HBV DNA per reaction. Only if this highly sensitive HBV-DNA testing is not possible, should anti-HBc be used to identify potential seropositive OBI cases[1].

OBI is a complex entity that comprises many conditions and different situations. The evidence of its potential relevance is the reason for the growing interest in this topic. The purpose of this review is to synthesize the current evidence regarding OBI management, with special emphasis on strategies for prevention of OBI transmission in different scenarios (Table 1).

Table 1 Scenarios in which occult hepatitis B virus infection is of clinical importance

After acute hepatitis B
Blood donation
Organ transplantation
Immunosuppression
Cryptogenic chronic liver disease
Hepatocellular carcinoma development

OBI AFTER ACUTE HEPATITIS

Patients who have recovered from acute hepatitis B might carry HBV genomes for several years without showing any clinical or biochemical evidence of liver disease[4-6]. The question is if patients with this disorder are at risk for transmitting infection to others or for progression of their disease.

In a woodchuck model of OBI, maternal-fetal transmission has been observed from mothers with occult infection. Low levels of virus were detected in peripheral blood mononuclear cells and liver of newborns that had recovered from hepatitis, and this was associated with liver injury that occasionally led to hepatocellular carcinoma (HCC) development[4,7-9].

In immunocompetent humans who have developed anti-HBc and anti-HBs following acute hepatitis B, no transmission of HBV has ever been demonstrated in blood donations[10]. The persistence of virus-specific cytotoxic T lymphocytes as a consequence of stimulation by viral replication and gene expression in this population is necessary to control HBV infection and maintain the long-term persistence of anti-HBc and anti-HBs in these patients[9]. Mild necro-inflammation, even fibrosis, has been observed in patients who have recovered from acute hepatitis B for several years after resolution of hepatitis[11,12].

With regard to the management of these patients, we know that, at least in conditions of immunocompetence, OBI is innocuous in itself, but when other relevant causes of liver disease are present, mild liver damage produced by the occult virus might contribute to making the course of the liver disease worse[2,13].

OBI AND BLOOD DONATIONS

HBsAg-negative blood donations that contain HBV DNA are considered infectious and might transmit HBV that usually induces typical type B hepatitis in recipients[14]. Nowadays, OBI is the major cause of post-transfusion hepatitis B in western countries[15] and in countries like India and Taiwan where the incidence of this problem is considerable[16,17]. Although post-transfusion hepatitis B is rare in western countries[15], the risk of transmission of HBV by transfusion is probably higher than for hepatitis C virus or human immunodeficiency virus (HIV)[18].

The risk of HBV transmission through transfusion is related to blood donations that have been collected during the so-called pre-seroconversion period or during chronic OBI[10]. The risk of transmission is high with blood that lacks anti-HBs, but it might not reach 100%. There are several possible explanations as to why not all recipients of HBV-DNA-positive, HBsAg-negative blood develop hepatitis[9]: (1) vaccination or prior disease in recipients can induce immunity to HBV; (2) concurrent infusion of anti-HBs in another blood component; (3) presence of immune complexes; (4) inocula below the minimum infectious dose of HBV; (5) presence of defective or replication-incompetent virions; and (6) viral interference from another pathogen. The risk of transmission is insignificant when anti-HBs is present in the blood, regardless of anti-HBc status[19,20]. The concentration of anti-HBs which makes transfusion safer is a matter of debate. However, caution is recommended when immunodeficient patients receive anti-HBc-positive, anti-HBs-positive donations. This is important if we consider that almost 50% of transfused blood in Western Europe is given to immunodeficient patients[20].

With regard to the management of these patients, the use of multivalent anti-HBs antibodies in the HBsAg assays is strongly recommended for detection of false OBI[1]. In cases of pre-seroconversion period donation, HBsAg or anti-HBc screening cannot detect OBI, and we

must use HBV-DNA NAT[10]. NAT detects potentially infectious blood units before donation and consequently reduces the risk of transmitting HBV through blood transfusion. In HBV-endemic regions of the world, where a universal hepatitis B vaccination program is not available, NAT has higher potential benefit for reducing this risk. However, in low-prevalence countries, the availability of highly sensitive and specific HBsAg and anti-HBc assays limits the benefit of NAT[9,10,21].

OBI AND ORGAN TRANSPLANTATION

Grafts from donors who are HBsAg-negative and anti-HBc-positive might transmit HBV to recipients after organ transplantation; particularly in the case of orthotopic liver transplantation (OLT), and especially if the recipient is negative for all HBV serum markers, because of the presence of viral strains in the hepatocytes, which can be reactivated during immunosuppression[22-24]. In OLT, this occurs in 17%-90% of cases[24]. Transmission of occult infection from HBV-seronegative (anti-HBs negative/anti-HBc-negative) individuals is uncertain. There is no evidence of this theoretical possibility, which is probably underestimated by a regular allocation to *de novo* HBV infection after transplantation[1].

The risk of occult HBV transmission is very low after kidney, heart or bone marrow transplantation[25,26]. Reactivation of OBI is possible in liver transplant recipients with a serological profile of past exposure to hepatitis B (anti-HBc positive), as a consequence of immunosuppression after transplantation[27]. Hepatitis B infection usually has a benign course and is often less severe following solid organ transplantation obtained from anti-HBc positive donors when compared to hepatitis B that develops as a result of recurrent disease[22,28].

With regard to the management of these patients, it is not known if prior hepatitis B immunization with an optimal anti-HBs response can modulate or abort the infection[9]. Prophylaxis with antiviral agents prevents reactivation of OBI in most of these cases[24].

REACTIVATION OF OBI

The risk of HBV reactivation is well documented in HBsAg-positive patients who receive chemotherapy and/or with hemato-oncologic diseases, and there is consensus that these patients require prophylaxis with an antiviral agent[29,30]. However, the risk of HBV reactivation in OBI is less defined[31-33]. The state of strong suppression of viral replication and gene expression activity by the host immune system in OBI patients might be discontinued, which leads to the development of a classical hepatitis B that often has a severe clinical course[2]. This situation has been observed in several conditions including HIV infection[34,35], hematological malignancies[29], patients undergoing chemotherapy[36,37], transplantation (bone marrow, liver, or kidney)[38-40], and treatment with potent immunosuppressive drugs like rituximab (anti-CD20), alemtuzumab (anti-CD52) or infliximab (anti-tumor necrosis factor)[41-43].

Various mechanisms are involved in HBV reactivation[9]: (1) immunosuppression with cytotoxic agents can enhance HBV replication and lead to direct hepatic damage; (2) cytotoxic/immunosuppressive agents can suppress T-cell function and/or deplete B cells; and (3) suppressed immunological response leads to widespread HBV infection of hepatocytes. Once recovery is achieved following withdrawal of cytotoxic agents and immune surveillance is reconstituted, a rebound in cytotoxic-T-cell response is induced that leads to the development of cellular injury and hepatitis.

The clinical significance of HBV reactivation in HIV-positive patients is uncertain[44-46]. Severe HBV reactivation has been reported after withdrawal of antiretrovirals that are active against HBV[35].

Graft reinfection and reactivation of OBI is possible in liver transplant recipients with a serological profile of past exposure to hepatitis B (anti-HBc positive)[27,47]. OBI patients with cirrhosis need close monitoring because the mortality rate following reactivation approaches 5%-40%[9].

All patients who receive chemotherapy and immunotherapy should be tested for HBV serology and/or viremia before starting therapy, especially if they are positive for antibody to viral antigens, and monitored for several months or years after stopping treatment[2,29]. Early identification of virological reactivation is essential to start antiviral therapy and prevent the occurrence of hepatitis B, which can be very dangerous in these patients[2,32,48].

Use of antiviral agents as prophylaxis against HBV in HBsAg-positive patients who are undergoing cytotoxic chemotherapy is a standard strategy[9,30,49]. However, for patients with OBI and those who are serologically HBV-DNA-negative but anti-HBc-positive, current data are insufficient to recommend routine prophylaxis and antiviral therapy could be delayed until the HBV DNA becomes detectable[9,49-51].

For those with OBI, especially in the absence of anti-HBs, a prudent therapeutic approach is to initiate HBV antiviral therapy (lamivudine, telbivudine, adefovir, entecavir or tenofovir) prior to chemotherapy. This should be continued for $\geq$ 6 mo after stopping immunosuppressive treatment. If long-term treatment (> 12 mo) is predicted, then adefovir, entecavir or tenofovir should be chosen, and if a more rapid response is needed, then entecavir or tenofovir could be considered. Antiviral therapy is usually unsuccessful if started after alanine aminotransferase becomes elevated[9].

For those patients who are HBV-DNA-negative and anti-HBc-positive, the following approach could be considered based on the kinetics of reactivation[9,32]: (1) monitor at 4-wk intervals with HBV-DNA NAT (low limit of detection < 10 IU/mL) and begin antiviral therapy when the result is > 30 IU/mL; or (2) monitor at 4-wk intervals with a highly sensitive HBsAg assay (low limit of detection < 0.1 ng/mL) and begin antiviral therapy when the test becomes positive. Further studies are needed to clarify the clinical usefulness, safety and cost-effectiveness of these strategies in OBI. In HIV-positive patients, the risk

of HBV sero-reversion is low; therefore, it does not justify any prophylaxis.

OBI AND CHRONIC LIVER DISEASE

OBI has been detected in patients with cryptogenic chronic liver disease[52-54] and could be associated with progression of liver fibrosis and cirrhosis development in these patients[52,55,56]. HBV-infected patients might present with progressive reduction of viral replication and serum HBsAg levels. HBsAg might disappear over time, despite the presence of severe liver injury that has been provoked by overt hepatitis B, and then maintained once the occult HBV status has been established[2,57].

It has been reported that close monitoring of serum HBV-DNA levels and liver-enzyme levels could be useful in the management of patients with OBI and cryptogenic liver disease in two respects[58]: (1) to predict the risk of cirrhosis or HCC; and (2) to decide on the possibility of antiviral treatment to prevent HBV reactivation or transmission in the case of transplantation. However, the role of OBI in accelerating the development of cirrhosis is still unresolved. Prospective studies using well-defined selection criteria of patients and standardized laboratory techniques are needed[1,56,59].

OBI AND HCC DEVELOPMENT

Many epidemiological and molecular studies have indicated that OBI is a potential risk factor for HCC development. OBI seems to maintain HBV oncogenic mechanisms such as the capacity to be integrated in the host genome, and production of transforming proteins[1,52,59-68]. This pro-oncogenic role is not only the consequence of the integration of viral DNA into the host genome. Other factors might contribute[2]: (1) persistence of replicating virus might induce mild liver necro-inflammation that continues for life; (2) occult strains usually persist as free genomes, and maintain the capacity to transcribe and replicate[68-70]; and (3) OBI might contribute to progression towards cirrhosis, which is the most important risk factor for HCC development. However, further molecular pathogenesis studies and prospective molecular epidemiological studies are needed to reach the conclusion that OBI plays a major role in hepatocellular transformation. Until then, it is premature to recommend testing all HBsAg-negative patients with HCC for OBI[62].

CONCLUSION

OBI is a complex entity that comprises many conditions and different situations. Patients who have recovered from acute hepatitis B can carry HBV genomes for a long time, and the virus might aggravate the course of their liver disease, when other causes of liver damage are present. Use of HBV-DNA NAT and multivalent anti-HBs antibodies in the HBsAg assays is recommended for detection of true and false OBI, respectively, and to minimize the risk of HBV transmission through transfusion. It is not known if prior hepatitis B immunization with an optimal anti-HBs response can effectively modulate or abort the infection in the case of HBV transmission through organ transplantation. In patients with serological evidence of past infection with hepatitis B, prophylaxis with antiviral agents prevents reactivation of hepatitis B after transplantation in most cases. Reactivation of OBI has been observed in several other conditions that cause immunosuppression in which antiviral therapy could be delayed until HBV DNA or HBsAg becomes detectable. OBI might contribute to the progression of liver fibrosis and HCC development in patients with chronic liver disease. However, further studies are needed to clarify the clinical usefulness, safety and cost-effectiveness of strategies for management of OBI.

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