ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2017 June 28; 23(24): 4317-4472

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 23 Number 24 June 28, 2017

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Yuan Qi, Vice Director
Ze-Mao Gong, Vice Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
June 28, 2017

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: http://www.f6publishing.com

World J Gastroenterol 2017 June 28; 23(24): 4317-4323

DOI: 10.3748/wjg.v23.i24.4317

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C

Ioanna Aggeletopoulou, Christos Konstantakis, Spilios Manolakopoulos, Christos Triantos

Ioanna Aggeletopoulou, Christos Konstantakis, Christos Triantos, Department of Gastroenterology, University Hospital of Patras, 26504 Patras, Greece

Spilios Manolakopoulos, 2nd Department of Internal Medicine, Hippokration General Hospital of Athens, 11527 Athens, Greece

Author contributions: Aggeletopoulou I collection data and drafting the manuscript; Konstantakis C collection data; Manolakopoulos S interpretation of the data, drafting the manuscript, and revision of manuscript for important intellectual content; Triantos C interpretation of the data, drafting the manuscript, and revision of manuscript for important intellectual content

Conflict-of-interest statement: Spilios Manolakopoulos has received research grants from Gilead Sciences and Bristol-Myers Squibb and fees for lectures and being an advisory board member from Gilead Sciences, Bristol-Myers Squibb, Janssen, AbbVie and MSD. Christos Triantos has received fees as a speaker/advisory board member and research/travel grants from MSD, Roche, AbbVie, Janssen, Bristol-Myers Squibb, Bayer and Gilead Sciences.

Manuscript source: Invited manuscript

Correspondence to: Christos Triantos, MD, Department of Gastroenterology, University Hospital of Patras, D. Stamatopoulou 4, Rio 26504, Patras, Greece. chtriantos@hotmail.com
Telephone: +30-697-2894651
Fax: +30-261-0625382

Received: January 27, 2017
Peer-review started: February 4, 2017
First decision: February 27, 2017
Revised: March 28, 2017
Accepted: May 9, 2017
Article in press: May 9, 2017
Published online: June 28, 2017

Abstract

The recent introduction of direct-acting antiviral drugs (DAAs) for treatment of the hepatitis C virus (HCV) has greatly improved the management of HCV for infected patients. These viral protein inhibitors act rapidly, allowing HCV clearance and increasing the sustained virological response rates. However, hepatitis B virus (HBV) reactivation has been reported in HCV/HBV co-infected patients. Hepatitis B reactivation refers to an abrupt increase in the HBV and is well-documented in patients with previously undetected HBV DNA due to inactive or resolved HBV infection. Reactivation can occur spontaneously, but in most cases, it is triggered by various factors. Reactivation can be transient, without clinical symptoms; however, it usually causes a hepatitis flare. HBV reactivation may occur regardless of HCV genotype and type of DAA regimen. HBV screening is strongly recommended for co-infected HCV/HBV patients before initiation and during DAA therapy regardless of HBV status, HCV genotype and class of DAAs used. HBV reactivation can be prevented with pretreatment screening and prophylactic treatment when necessary. Additional data are required to evaluate the underlying mechanisms of HBV reactivation in this setting.

Key words: Hepatitis B; Hepatitis C; Hepatitis B virus reactivation; Direct-acting antivirals; Pretreatment screening

Core tip: Hepatitis B reactivation is related to an abrupt increase in hepatitis B virus (HBV) replication in patients

with inactive or resolved hepatitis B. Most cases of HBV reactivation resolve spontaneously, but the existence of continuous immune suppression leads to hepatitis flare development and then to progressive acute hepatic injury. The introduction of direct-acting antiviral drugs (DAAs) treatment increases the risk of HBV reactivation in hepatitis C virus (HCV) /HBV co-infected patients. The high incidence of HBV reactivation in these patients highlights the necessity for HBV pretreatment screening before initiation and during DAA therapy.

Aggeletopoulou I, Konstantakis C, Manolakopoulos S, Triantos C. Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C. *World J Gastroenterol* 2017; 23(24): 4317-4323 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i24/4317.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i24.4317

INTRODUCTION

Epidemiological studies suggest that approximately 240 million people worldwide are infected with the hepatitis B virus (HBV)[1,2]. The clinical course of HBV infection varies and may include asymptomatic carriage, acute hepatitis or chronic active hepatitis, which can progress to cirrhosis and hepatocellular carcinoma[2,3].

HBV reactivation is characterized by an increase of HBV DNA in the serum and is well documented in patients with previously undetected HBV DNA, due to inactive or resolved HBV infection[4-6]. Reactivation is usually followed by the reappearance of HBV activity (HBV DNA recurrence or increase > 1 log) or a flare of hepatitis in previously minimal or inactive disease[5]. HBV reactivation mainly occurs in patients who receive immunosuppressive or cytotoxic chemotherapy for various malignancies[6-8] and autoimmune diseases[9-12] or in patients who undergo solid organ transplantation[13,14]. The reappearance of serum HBV DNA has also occasionally been observed in patients with the hepatitis B surface antigen (HBsAg) seroclearance, suggesting that HBV reactivation occurs in patients who have recovered from hepatitis B and have antibodies for the hepatitis B core antigen (anti-HBc) but have no detectable serum HBsAg[15,16].

Hepatitis with alanine transaminase (ALT) elevation due to reactivation of HBV has been reported in HCV/HBV co-infected patients who were treated with direct-acting antiviral (DAA) regimens for chronic hepatitis C virus (HCV) infection[17-23]. Patients with HCV/HBV coinfection have a significantly higher risk of developing hepatic cirrhosis and hepatocellular carcinoma[24]. In HCV/HBV coinfection, HCV has been shown to suppress HBV replication, resulting in decreased HBV antigen levels[21,25]. The administration of HCV treatment may lead to an increase in HBV replication and in lower rates of HBV DNA clearance. Pegylated interferon-based treatments could suppress both HCV and HBV replication[26,27]. However, the development of interferon-free treatments with DAA agents has changed the course of treatment for chronic HCV infection[28]. DAAs constitute new therapeutic agents with great efficacy for the treatment of HCV infection, and they can be used safely in HCV naïve-treatment patients or in patients who have been treated unsuccessfully, thus decreasing the duration of therapy, improving the sustained virological response rates and reducing the side effects[28-30].

PATHOGENESIS OF HBV REACTIVATION

Chronic HBV infection is defined as persistent circulating serum HBsAg for more than 6 mo[31,32]. In the initial stages of immune tolerance, HBV replication is enhanced by the presence of increased levels of HBeAg and active infection of hepatocytes[31,33]. The maturation of the immune system leads to the clearance phase, which is characterized by T cell mediated damage of infected hepatocytes through immune surveillance and the development of hepatitis flares[31,33]. Spontaneous HBeAg clearance is followed by the suppression of HBV DNA and the increase of circulating ALT levels[31,33]. During the immune control phase, some patients achieve HBV DNA clearance and develop immunoprotection[31]. However, when a patient is exposed to immunosuppressive agents or has concomitant infection with HIV, HCV, HAV or HDV, loss of immune control occurs, and there is an increased risk of HBV reactivation. HBV reactivation may be spontaneous and is divided into 3 different phases[4,5,31-35]. An abrupt increase of HBV replication occurs with a concomitant development of an infection in the hepatocytes and with the reappearance of HBV markers (HBsAg and HBeAg). At the second phase, immunosuppression is reduced and hepatocytes are targeted and damaged, causing liver injury that can range from mild to fulminant, or fatal hepatitis. This phase is followed by the recovery phase, in which liver damage is resolved[4,5,31-35]. HBV reactivation can lead to progressive hepatic injury and even hepatic decompensation[16].

REACTIVATION OF HEPATITIS B IN HCV INFECTED PATIENTS

Recent studies have shown that there is a risk of HBV reactivation in patients with HCV and HBV coinfection, who receive treatment with direct-acting antivirals[17-21,23]. There are 5 case reports[17-21], 1 observational study[23] and 1 letter to the editor[22] that describe the HBV reactivation in HCV/HBV co-infected patients following the use of DAA regimens. The clinical characteristics of the patients involved in these studies are shown in Table 1. Collins *et al*[21] reported 2 cases of HBV reactivation during HCV treatment using

Table 1 Overview of clinical characteristics in patients with hepatitis C virus/hepatitis B virus coinfection who had hepatitis B virus reactivation during direct-acting antiviral drugs - based hepatitis C virus treatment

Patients' characteristics					HCV Treatment		HBV Infection			
Ref	Gender	Age	HIV coinfection	HCV genotype	Previous treatment	DAA regimen	Profile before DAAs[1]	HBV DNA (IU/mL) before/after DAAs[2]	ALT levels (IU/L) before/after DAAs[3]	Week[4]
Collins *et al*[21]	M	55	No	1a	IFN/ribavirin	Sofosbuvir/ simeprevir	Inactive carrier	2.300/ 22 million	62/1.495	8
Collins *et al*[21]	M	57	No	1a	IFN/ribavirin	Sofosbuvir/ simeprevir	Occult infection	20/11.255	Within normal limits	4
Ende *et al*[20]	F	59	No	1b	IFN/ribavirin	Sofosbuvir/ simeprevir/ ribavirin	Resolved infection	Undetectable/ 29 million	168/2.263	11
Takayama *et al*[17]	M	69	No	1b	No treatment	Daclatasvir/ asunaprevir	Inactive carrier	310/10 million	94/237	6
De Monte *et al*[19]	M	53	Yes	4d	IFN/ribavirin	Sofosbuvir/ ledipasvir	Resolved infection	Undetectable/ 960 million	Within normal limits /1.026	6
Hayashi *et al*[18]	F	83	No	1b	No treatment	Daclatasvir/ asunaprevir	Unclear	Undetectable/ 1.000.000	Within normal limits/1.066	48
Madonia *et al*[22]	F	62	No	2	No treatment	Sofosbuvir/ ribavirin	Resolved infection	Undetectable/ 2.080.000	34/1.896	36

[1]Profile of HBV infection according to HBV viral load and HBs antigen detection; [2]HBV viral load before DAA treatment and at initiation of HBV reactivation; [3]ALT levels before DAA treatment and at initiation of HBV reactivation; [4]Weeks after the initiation of DAA treatment. HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBV: Hepatitis B virus; IFN: Pegylated interferon; ALT: Alanine transaminase; DAA: Direct-acting antiviral drugs.

sofosbuvir and simeprevir regimens. At the initiation of the treatment, the HBV DNA viral load was 2.300 IU/mL for the first patient and was under the lower limit of 20 IU/mL for the second patient. At 4 wk, HCV clearance had been achieved in the first patient, but at week 8, the HBV viral load had significantly increased to 22 million IU/mL. At week 2, the second patient had an undetectable HCV viral load, but at week 4, the HBV viral load increased to 11.255 IU/mL. Both patients received HBV treatment consisting of either tenofovir/emtricitabine or tenofovir[21]. Ende *et al*[20] described a case of HBV reactivation in an HCV patient who was HBsAg negative but anti-HB core positive. The patient received HCV treatment with sofosbuvir, simeprevir and ribavirin and had an HCV viral load below the level of quantification at 4 wk after treatment. The HBV viral load was undetectable before the initiation of the treatment, but at week 11 of a planned 12-wk course, the patient developed severe hepatitis B with a viral load of 29 million IU/mL and started a treatment using tenofovir[20]. Takayama *et al*[17] reported one case of HBV reactivation in a patient who was an inactive carrier of HBV with a viral load of 310 IU/mL prior to HCV treatment. He received a combination of daclatasvir/asunaprevir and the HCV RNA on day 15 was undetectable. On day 43, serum HBV DNA increased to 10 million IU/mL. A hepatitis flare due to HBV reactivation was diagnosed and the patient received entecavir[17]. De Monte *et al*[19] reported a case of HBV reactivation in a patient who had a resolved HBV infection and chronic HCV/HIV coinfection and was on a treatment combination of DAAs (sofosbuvir/ledipasvir). Upon initiation of the treatment, the patient had an undetectable HBV viral load. At week 6, the HBV viral load had increased (960 million IU/mL) and tenofovir was introduced[19]. Hayashi *et al*[18] reported a case of a patient with unclear HBV infection status who was infected with HCV. The patient received an HCV treatment consisting of daclatasvir/asunaprevir, and 4 wk after initiation of the treatment, the HCV RNA became negative. Five months after treatment began, the patient developed acute hepatitis B and initiated treatment with entecavir for suspected liver failure due to HBV reactivation[18]. Madonia *et al*[22] reported a case of HBV reactivation in a patient with HCV infection and isolated anti-HBc, who was being treated with sofosbuvir/ribavirin. Thirty-six weeks after the initiation of the DAA therapy, the patient developed a hepatitis flare and started tenofovir treatment[22]. The incidence of HBV reactivation in HCV/HBV co-infected patients was further confirmed in an observational study that was conducted in China[23]. Ten patients in the study were HBsAg positive before initiation of the HCV treatment, and 3 (30%) of them developed HBV reactivation after the use of DAA regimens[23]. In contrast, none of the 124 patients with occult HBV infection developed HBV reactivation during the use of DAA regimens[23].

DISCUSSION

Various concerns have been raised in relation to the reappearance of hepatitis B due to HBV reactivation after successful clearance of hepatitis C through the use of DAA therapy in patients with HCV/HBV coinfection[17-23,36,37]. Recently, clinical and *in vitro* studies

have been carried out to elucidate the virological and molecular aspects of the HCV/HBV coinfection[17-23]. The clinical characteristics of the patients in these studies vary, as they were infected with different HCV genotypes, received different oral DAA regimens and presented with various states of HBV infection[17-23]. However, none of the patients received HBV treatment concurrently with DAA therapy, and all of the patients had increased serum HBV DNA after or at the end of the HCV treatment[17-23]. This suggests that HCV RNA clearance may be associated with HBV reactivation, regardless of HCV genotype and type of DAA regimen.

There are data supporting that there is a significant increase in hepatitis due to HBV reactivation in HCV patients who are also HBsAg positive and are being treated with DAA therapy[23]. Wang *et al*[23] reported that HCV patients with HBV or occult HBV infection who are receiving DAA therapy may develop a biochemical flare that is unrelated to HBV reactivation[23]. Other causes, such as ingesting herbs and binge drinking alcohol were the main causes of hepatitis development in these cases.

The molecular aspects related to HCV/HBV interferences remain controversial, as patients with HCV/HBV coinfection show a high range of virological profiles. Several studies have described an inverse relationship between the DNA levels of the two viruses in cases of coinfection, suggesting potential direct or indirect viral interference in their life cycle[19,26,38-40]. In particular, most HBV-infected individuals who develop HCV have decreased HBV replication due to the suppression effect of HCV on HBV infection[39,41]. Similarly, suppression in HCV replication occurred in patients who developed an HBV superinfection[38,41]. Other studies have reported HBV reactivation in patients with HCV/HBV after treatment with peginterferon/ribavirin[42,43]. In addition, studies that included *in vitro* experiments with HCV/HBV co-transfection in the same cell culture system, have shown that HCV and HBV were able to replicate in the same hepatocyte without evidence of interference[44,45]. Lastly, another study supports the theory that in the chronically HCV-infected liver, the HCV-induced IFN-α/β response creates an antiviral state that limits both the initiation of HBV infection and the replication of HBV in the cells whose type I interferon-stimulated gene expression profile does not preclude HBV infection[16]. The above data suggest that the viral interference and the various dominance phases in co-infected patients may occur due to an indirect mechanism mediated by host immune regulation[26].

The HBV reactivation in the examined studies was a retrospective diagnosis in most cases[17-22]. Collins *et al*[21] described two different cases of HBV reactivation that occurred in the same medical unit. In the second case, diagnosis was earlier due to a previous case of HBV reactivation. After initiation of the DAA treatment, the HBV DNA concentrations were prospectively monitored at 2-week intervals, and when HBV replication had logarithmically increased, anti-HBV therapy was initiated[21]. Consequently, the HBV viral load should be closely monitored during HCV treatment using DAAs in patients that have an HCV/HBV coinfection to prevent the progression to HBV reactivation. Moreover, the observational study done by Wang *et al*[23] prospectively evaluated the incidence of HBV reactivation in Chinese patients who were HCV/HBV co-infected and receiving DAA treatment regimens. Wang *et al*[23] concluded that patients with HCV infection and HBsAg positivity are at greater risk of developing HBV reactivation, and thus they strongly suggest that HBsAg status be checked before the initiation of pan-oral DAA therapy. However, it is worth-mentioning that we did not find any cases with fatal outcomes due to reactivation.

The cases of HBV reactivation in co-infected HCV/HBV patients who are undergoing DAA treatment support the theory of reciprocal HCV/HBV interference and suppression of HBV replication due to HCV infection. Interferon-based anti-HCV therapies have rarely led to HBV reactivation due to their suppression effect on both HBV and HCV replication[27]. The introduction of DAA treatment increased the risk of HBV reactivation because of HCV clearance and lack of anti-HBV activity. This eliminates the inhibitory effects of HCV on HBV, leading to HBV reactivation. These data suggest that after initiation of DAA treatment, HBV infection should be closely monitored in co-infected patients by checking the HBV viral load, the HBsAg and the aminotransferase levels, regardless of the type of DAAs and the HCV genotype. In patients with positive anti-HBc and negative HBsAg and anti-HBs, the HBV viral load could be measured before the initiation of DAAs and should be monitored during the treatment. Anti-HBV therapy should be considered when the HBV viral load is detected after the initiation of DAA therapy. Patients with liver cirrhosis or impaired liver function are at greater risk and an HBV reactivation occurrence may be fatal. Therapy with nucleoside/nucleotide analogues (NAs) could prevent adverse effects, such as severe liver failure, when the HBV reactivation is diagnosed at an early stage. Recent guidelines on this issue have been introduced by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)[36,37]. EASL guidelines suggest that patients should be tested for HBs antigen, anti-HBc and anti-HBs antibodies before the initiation of DAA therapy[36]. If HBs antigen is present, or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients ("occult" hepatitis B), then concurrent HBV NA therapy is indicated[36,46]. AASLD suggests that all HCV patients who are about to initiate DAA therapy should be assessed for HBV coinfection by checking for the presence of HBsAg, anti-HBs and anti-HBc[37]. In addition, patients with positive HBsAg should be tested for HBV DNA viral load prior to the initiation of DAA therapy[37]. The patients who meet the criteria

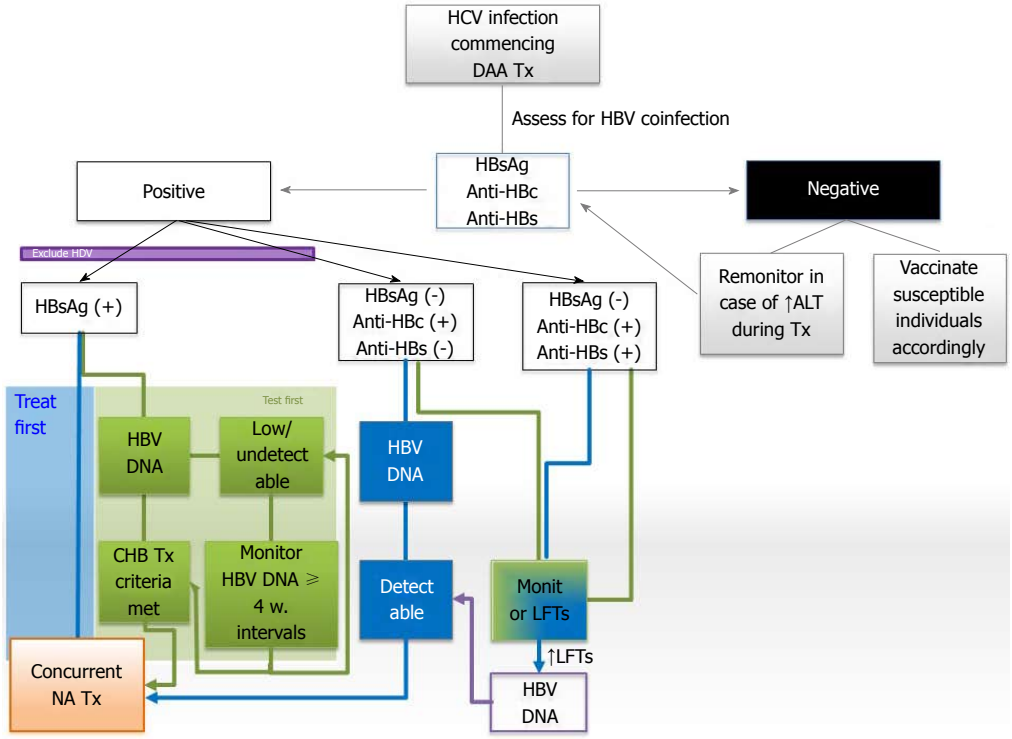

Figure 1 Treatment algorithm. Therapeutic options for HCV-HBV co-infected patients. All HCV patients who are about to commence DAA therapy should be assessed for HBV coinfection and accordingly for HDV. Patients who are negative for HBV will be monitored using liver function tests (LFTs) during and after the end of DAA therapy. A flare in ALT/liver biochemistry during this timeframe should prompt the treating physician to reconsider the possibility of an occult HBV infection and to re-test for HBV infection (HBsAg and/or HBV DNA)[36]. Management options for patients who are positive for HBV vary according to their serology results. HBsAg positive patients have the following two options: the "treat first" approach (blue pathway), where HBsAg positive are treated with NA agents (commencing NA therapy even before the start of DAA treatment), or the "test first" option (green pathway) where patients are monitored with HBV DNA and are treated according to the detected levels. Both treatment options are viable and are supported by clinical guidelines[36,37]. HCV: Hepatitis C virus; HBV: Hepatitis B virus; DAA: Direct-acting antiviral; Tx: Therapy; HDV: Hepatitis D virus; CHB: Chronic hepatitis B infection; HBsAg: Hepatitis B surface antigen; anti-HBs: Hepatitis B surface antibody; anti-HBc: Total hepatitis B core antibody; NA: Nucleoside/nucleotide analogue; LFTs: Liver function tests; ALT: Alanine transaminase. Blue pathway, options in accordance with EASL guidelines; green pathway, options in accordance with AASLD - IDSA guidelines.

for HBV treatment due to active HBV infection should initiate the HBV treatment before or during the HCV treatment[37]. The patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually no more than once every 4 wk) for HBV reactivation, and the patients with HBV DNA levels that meet treatment criteria should initiate HBV therapy[37]. For those patients with positive anti-HBc or anti-HBs and anti-HBc, there are no sufficient recommendations; however, there is a risk of HBV reactivation in the case of elevated liver enzymes during or after DAA therapy[37]. In everyday clinical practice, patient characteristics [age, co morbidities (especially liver-related, such as alcohol use and obesity), performance status, liver function status/presence of cirrhosis, HIV status] and institutional/national regulations and insurance policies are critical for decisions regarding treatment. Moreover, that HBV reactivation does not occur during DAA treatment as often as with other immunosuppressive therapies, should further impact the decision for treatment. Taking the safety of the patients into serious consideration, we could propose the "treat first" strategy for patients with poor performance status and advanced fibrosis (Figure 1).

CONCLUSION

Generally, HBV reactivation is a severe, life-threatening consequence of chemotherapy and immunotherapy in patients with chronic hepatitis B infection. The severity of HBV reactivation ranges from mild with asymptomatic elevation of aminotransferases to fulminant liver failure. Recent evidence suggests that reactivation may be associated with DAA therapy in patients with HCV/HBV coinfection. HBV screening is recommended for patients both before the initiation and during DAA therapy. HBV reactivation can be prevented through the use of pretreatment screening and anti-HBV prophylactic treatment. Existing evidence is not enough to support pre-emptive therapy in all patients with HBsAg or occult hepatitis B. Additional studies are needed to investigate the duration of HBV treatment and the potential alternative HCV antiviral treatments in HCV/HBV co-infected patients to eliminate the risk of HBV reactivation. Moreover, further studies should be conducted to evaluate the underlying mechanisms of HBV reactivation during DAA therapy that is deemed necessary. Until then, careful monitoring for HBV reactivation should be

mandatory both before and during anti-HCV therapy with DAA.

REFERENCES

1 **World Health Organization**. Hepatitis B. Available from: URL: http://wwwwhoint/mediacentre/factsheets/fs204/en 2015
2 **Ott JJ**, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30**: 2212-2219 [PMID: 22273662 DOI: 10.1016/j.vaccine.2011.12.116S0264-410X(11)02077-9]
3 **Juszczyk J**. Clinical course and consequences of hepatitis B infection. *Vaccine* 2000; **18** Suppl 1: S23-S25 [PMID: 10683539]
4 **Bessone F**, Dirchwolf M. Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations. *World J Hepatol* 2016; **8**: 385-394 [PMID: 27004086 DOI: 10.4254/wjh.v8.i8.385]
5 **Hoofnagle JH**. Reactivation of hepatitis B. *Hepatology* 2009; **49**: S156-S165 [PMID: 19399803 DOI: 10.1002/hep.22945]
6 **Huang YW**, Chung RT. Management of hepatitis B reactivation in patients receiving cancer chemotherapy. *Therap Adv Gastroenterol* 2012; **5**: 359-370 [PMID: 22973419 DOI: 10.1177/1756283X12450245 10.1177_1756283X12450245]
7 **Dervite I**, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 2001; **344**: 68-69 [PMID: 11187122 DOI: 10.1056/NEJM200101043440120]
8 **Yeo W**, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299-307 [PMID: 11055239 DOI: 10.1002/1096-9071(200011)62]
9 **Kato M**, Atsumi T, Kurita T, Odani T, Fujieda Y, Otomo K, Horita T, Yasuda S, Koike T. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in Hepatitis B surface antigen-negative cases. *J Rheumatol* 2011; **38**: 2209-2214 [PMID: 21844146 DOI: 10.3899/jrheum.110289]
10 **Calabrese LH**, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis* 2006; **65**: 983-989 [PMID: 16627542]
11 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601 DOI: 10.1136/gut.2004.040675 53/9/1363]
12 **Tsai FC**, Hsieh SC, Chen DS, Sheu JC, Chen CH. Reactivation of hepatitis B virus in rheumatologic patients receiving immunosuppressive agents. *Dig Dis Sci* 2006; **51**: 1627-1632 [PMID: 16927141 DOI: 10.1007/s10620-006-9074-8]
13 **Knöll A**, Boehm S, Hahn J, Holler E, Jilg W. Reactivation of resolved hepatitis B virus infection after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 925-929 [PMID: 15004543 DOI: 10.1038/sj.bmt.17044571704457]
14 **Dickson RC**, Everhart JE, Lake JR, Wei Y, Seaberg EC, Wiesner RH, Zetterman RK, Pruett TL, Ishitani MB, Hoofnagle JH. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. *Gastroenterology* 1997; **113**: 1668-1674 [PMID: 9352871]
15 **Terrault NA**, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; **63**: 261-283 [PMID: 26566064 DOI: 10.1002/hep.28156]
16 **Nakamura M**, Kanda T, Nakamoto S, Haga Y, Sasaki R, Jiang X, Yasui S, Arai M, Yokosuka O. Reappearance of serum hepatitis B viral DNA in patients with hepatitis B surface antigen seroclearance. *Hepatology* 2015; **62**: 1329 [PMID: 25573053 DOI: 10.1002/hep.27693]
17 **Takayama H**, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. *Hepatol Res* 2016; **46**: 489-491 [PMID: 26297529 DOI: 10.1111/hepr.12578]
18 **Hayashi K**, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Nishimura D, Goto H, Hirooka Y. A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis? *Clin J Gastroenterol* 2016; **9**: 252-256 [PMID: 27329484 DOI: 10.1007/s12328-016-0657-410.1007/s12328-016-0657-4]
19 **De Monte A**, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, Cottalorda J, Ollier L, Giordanengo V. Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol* 2016; **78**: 27-30 [PMID: 26967675 DOI: 10.1016/j.jcv.2016.02.026S1386-6532(16)30017-8]
20 **Ende AR**, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J Med Case Rep* 2015; **9**: 164 [PMID: 26215390 DOI: 10.1186/s13256-015-0630-810.1186/s13256-015-0630-8]
21 **Collins JM**, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, Farley MM. Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir. *Clin Infect Dis* 2015; **61**: 1304-1306 [PMID: 26082511 DOI: 10.1093/cid/civ474civ474]
22 **Madonia S**, Orlando E, Madonia G, Cannizzaro M. HCV/HBV coinfection: The dark side of DAAs treatment? *Liver Int* 2016; Epub ahead of print [PMID: 27966812 DOI: 10.1111/liv.13342]
23 **Wang C**, Ji D, Chen J, Shao Q, Li B, Liu J, Wu V, Wong A, Wang Y, Zhang X, Lu L, Wong C, Tsang S, Zhang Z, Sun J, Hou J, Chen G, Lau G. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. *Clin Gastroenterol Hepatol* 2016; **5**: 30370-30376
24 **Kruse RL**, Kramer JR, Tyson GL, Duan Z, Chen L, El-Serag HB, Kanwal F. Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. *Hepatology* 2014; **60**: 1871-1878 [PMID: 25065513 DOI: 10.1002/hep.27337]
25 **Biliotti E**, Kondili LA, Furlan C, Ferretti G, Zacharia S, De Angelis M, Guidi S, Gusman N, Taliani G. Acute hepatitis B in patients with or without underlying chronic HCV infection. *J Infect* 2008; **57**: 152-157 [PMID: 18538412 DOI: 10.1016/j.jinf.2008.04.006S0163-4453(08)00157-6]
26 **Konstantinou D**, Deutsch M. The spectrum of HBV/HCV co-infection: epidemiology, clinical characteristics, viralinteractions and management. *Ann Gastroenterol* 2015; **28**: 221-228 [PMID: 25830779]
27 **Yu ML**, Lee CM, Chen CL, Chuang WL, Lu SN, Liu CH, Wu SS, Liao LY, Kuo HT, Chao YC, Tung SY, Yang SS, Kao JH, Su WW, Lin CL, Yang HC, Chen PJ, Chen DS, Liu CJ. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. *Hepatology* 2013; **57**: 2135-2142 [PMID: 23322699 DOI: 10.1002/hep.26266]
28 **Alexopoulou A**, Karayiannis P. Interferon-based combination treatment for chronic hepatitis C in the era of direct acting antivirals. *Ann Gastroenterol* 2015; **28**: 55-65 [PMID: 25608803]
29 **Webster DP**, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet* 2015; **385**: 1124-1135 [PMID: 25687730 DOI: 10.1016/S0140-6736(14)62401-6]
30 **Jazwinski AB**, Muir AJ. Direct-Acting Antiviral Medications for Chronic Hepatitis C Virus Infection. *Gastroenterol Hepatol* 2011; **7**: 154-162 [PMID: 21528041]

31 **Post A**, Nagendra S. Reactivation of hepatitis B: pathogenesis and clinical implications. *Curr Infect Dis Rep* 2009; **11**: 113-119 [PMID: 19239801]

32 **Samal J**, Kandpal M, Vivekanandan P. Molecular mechanisms underlying occult hepatitis B virus infection. *Clin Microbiol Rev* 2012; **25**: 142-163 [PMID: 22232374 DOI: 10.1128/CMR.00018-1125/1/142]

33 **Visram A**, Feld JJ. Defining and grading HBV reactivation. *Clin Liver Dis* 2015; **5**: 35-38

34 **Bessone F**. Re-appraisal of old and new diagnostic tools in the current management of chronic hepatitis B. *Liver Int* 2014; **34**: 991-1000 [PMID: 25098191 DOI: 10.1111/liv.12499]

35 **Roche B**, Samuel D. The difficulties of managing severe hepatitis B virus reactivation. *Liver Int* 2011; **31** Suppl 1: 104-110 [PMID: 21205146 DOI: 10.1111/j.1478-3231.2010.02396.x]

36 **European Association for the Study of the Liver**. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017; **66**: 153-194 [PMID: 27667367 DOI: 10.1016/j.jhep.2016.09.001]

37 **Diseases AAftSoL**, America IDSo. Recommendations for testing, managing, and treating hepatitis C. Updated July 6, 2016

38 **Coffin CS**, Mulrooney-Cousins PM, Lee SS, Michalak TI, Swain MG. Profound suppression of chronic hepatitis C following superinfection with hepatitis B virus. *Liver Int* 2007; **27**: 722-726 [PMID: 17498260]

39 **Dai CY**, Yu ML, Chuang WL, Lin ZY, Chen SC, Hsieh MY, Wang LY, Tsai JF, Chang WY. Influence of hepatitis C virus on the profiles of patients with chronic hepatitis B virus infection. *J Gastroenterol Hepatol* 2001; **16**: 636-640 [PMID: 11422616]

40 **Sagnelli E**, Coppola N, Marrocco C, Onofrio M, Sagnelli C, Coviello G, Scolastico C, Filippini P. Hepatitis C virus superinfection in hepatitis B virus chronic carriers: a reciprocal viral interaction and a variable clinical course. *J Clin Virol* 2006; **35**: 317-320 [PMID: 16316779]

41 **Liaw YF**, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Gastroenterology* 2004; **126**: 1024-1029 [PMID: 15057742]

42 **Hamzaoui L**, El Bouchtili S, Siai K, Mahmoudi M, Azzouz MM. Hepatitis B virus and hepatitis C virus co-infection: a therapeutic challenge. *Clin Res Hepatol Gastroenterol* 2013; **37**: e16-e20 [PMID: 22959099 DOI: 10.1016/j.clinre.2012.08.001S2210-7401(12)00200-8]

43 **Potthoff A**, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, Spengler U, Gruengreiff K, Kaeser T, Schuchmann M, Bergk A, Forestier N, Deterding K, Manns MP, Trautwein C. The HEP-NET B/C co-infection trial: A prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008; **49**: 688-694 [PMID: 18490077 DOI: 10.1016/j.jhep.2008.03.028S 0168-8278(08)00282-1]

44 **Eyre NS**, Phillips RJ, Bowden S, Yip E, Dewar B, Locarnini SA, Beard MR. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. *J Hepatol* 2009; **51**: 446-457 [PMID: 19596477 DOI: 10.1016/j.jhep.2009.04.025S0168-8278(09)00367-5]

45 **Bellecave P**, Gouttenoire J, Gajer M, Brass V, Koutsoudakis G, Blum HE, Bartenschlager R, Nassal M, Moradpour D. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference. *Hepatology* 2009; **50**: 46-55 [PMID: 19333911 DOI: 10.1002/hep.22951]

46 **European Association for Study of Liver**. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015; **63**: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]

P- Reviewer: Akamatsu N, Allison WE, Kanda T, Su WW, Lee HC
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

ISSN 1007-9327