sciendo

Case series

DOI:10.2478/rrlm-2020-0039

Rapid loss of HBs antigen in patients with HBV reactivation and high level of transaminases during immunosuppressive therapy - case series

Violeta Molagic[1*], Cristina Popescu[1,2], Catalin Tiliscan[1,2], Victoria Arama[1,2], Stefan Sorin Arama[1,2]

1.Infectious Diseases, "Prof. Dr. Matei Bals" National Institute for Infectious Diseases, Romania

2. Infectious Diseases, "Carol Davila" University of Medicine and Pharmacy, Romania

Abstract

Reactivation of hepatitis B virus (HBV) infection has been described in patients with HBsAg negative and antiHBc positive (occult hepatitis B infection -OBI) receiving immunosuppressive therapy (IST). The lack of proper monitoring of patients with this HBV infection during IST can result in viral reactivations with high level of transaminases, jaundice and even acute liver failure. In these situations, it is mandatory to start antiviral therapy with nucleot(s)ide analogs (NA) which produce a strong viral suppression. We report a series of five cases of OBI patients with severe HBV reactivation during IST. One patient was diagnosed with hematologic malignancy (non-Hodgkin lymphoma), two with rheumatoid arthritis, one with psoriasis and one patient with renal transplant. All the patients were evaluated and treated for the reactivation of HBV in the Prof. Dr. Matei Bals National Institute of Infectious Diseases, a tertiary care hospital from Bucharest, Romania. At the time of HBV reactivation diagnosis, 3 patients were asymptomatic and two developed jaundice. All had acute ALT flares (more than 10 times the upper limit of normal range - ULN), very high HBV viral loads and anti-HBc serum IgM antibodies. All patients were immediately treated with ETV 0.5 mg /day and if it was possible, IST was stopped. In all cases was obtained quickly HBsAg loss under antiviral therapy.

Received: 24th July 2020; Accepted: 5th November 2020; Published: 29th December 2020

Background

Patients with HBV infection, especially those with OBI defined by serum negative surface antigen (HBsAg) and presence of hepatitis B core antibodies (anti-HBc), should be carefully monitored during IST used for hematologic or rheumatologic diseases, because of the significant potential of reactivation. The risk of HBV reactivation depends on the immunosuppressive regimen used and the HBV serological and viro-

* **Corresponding author**: Violeta Molagic, Infectious Diseases, "Prof. Dr. Matei Bals" National Institute for Infectious Diseases, Bucharest, Romania. E-mail: violeta_molagic@yahoo.com

logical profile. Anti-B-cell agents, such as Rituximab, have a high risk of HBV reactivation because they induce a broad and deep B-cell depletion (1).

The lack of proper monitoring of patients with OBI during IST can result in viral reactivations with high level of ALT, jaundice and even acute liver failure. In these situations, it is mandatory to start antiviral therapy with nucleot(s)ide analogs (NA) which produce a strong viral suppression.–

All international guidelines (2,3) recommend prophylactic therapy regardless of HBsAg status to all patients receiving anti-CD20 therapy or undergoing stem cell transplantation. OBI patients may be at risk of reactivation and should undergo either monitoring (if they have high HBsAb titers) or prophylactic NA therapy with Entecavir (ETV), Tenofovir disoproxil fumarate (TDF) or Tenofovir disoproxil alafenamide (TAF); Lamivudine is no longer recommended as it has a low barrier to resistance.

The aim of our communication is to present a series of OBI patients with severe HBV reactivation during IST, treated with ETV, who experienced rapid HBsAg loss under antiviral therapy. All patients signed the informed consent before the inclusion, according to the latest version of World Medical Association Declaration of Helsinki.

Case description

We present five cases, three males and two females (mean age of 57.4 years), one patient with a hematologic malignancy, two with rheumatoid arthritis, one with psoriasis, and one patient with renal transplant. All the patients were evaluated and treated for the reactivation of HBV in the Prof. Dr. Matei Bals National Institute of Infectious Diseases, a tertiary care hospital in Bucharest, Romania.

Prior to IST, all the patients had negative serum HBsAg and positive IgG HBc antibodies. Two patients were negative for HBsAb, two had HBsAb titers above 10 UI/ml, and in one case no prior quantification of HBsAb was performed. In one patient, HBV DNA was measured prior to IST and the result was negative. Before initiating IST all patients had normal ALT .

Table I presents the most important clinical, biological, and virusological characteristics of our patients.

At the time of HBV reactivation diagnosis, 3 patients were asymptomatic and two developed jaundice. All had acute ALT flares (> 10 times the upper limit of normal range - ULN), high HBV DNA and positive IgM HBc. Four patients were HBeAg positive. The epidemiological inquiry for other recent viral parenteral transmission was negative. All patients received ETV 0.5 mg /day and, if possible, IST was stopped.

The first patient was a 48-year-old female, with a severe form of psoriasis under therapy with methotrexate and cyclosporin for one year. At the start of IST, the patient was screened for HBV and was HBsAg and HBsAb negative but IgG HBc positive. Because of severe fatigue during IST (which was started one year before), the ALT was checked and a high level of ALT was discovered. The patient's HBV profile revealed: HBsAg and HBeAg positivity, IgM HBc antibodies, and HBV DNA= 16 million UI/ml. IST was stopped and ETV was started. The outcome was good with HBeAg loss after 4 months and HBsAg clearance after 6 months of therapy. The patient continued ETV one year after IST cessation without HBsAb seroconversion.

The second patient was a 66-year-old female, with rheumatoid arthritis and who was enrolled in a clinical trial with a biological agent (Baricitinib). The HBV profile was at the start of IST:

HBsAg negativity, IgG HBc antibodies positive, HBsAb positive (titer > 1000ui/ml). After 6 months of IST, the patient developed jaundice, a high level of ALT with HBsAg, IgM HBc and HBeAg positive with HBV DNA > 170 million UI/ml. The investigational product was stopped and ETV was started with HBeAg loss after 4 months and HBsAg clearance after 6 months. After 2 months of ETV, adalimumab was started and the patient continued ETV, with persistence of HBsAg negativity, but no HBsAb were subsequently detected.

The third patient was a 35-year-old male who had kidney transplantation 2 years before HBV reactivation. He had been receiving tacrolimus since transplantation. The HBV profile was: negative HBsAg and HBsAb, but had positive IgG HBc antibodies. Because at that time the local guidelines for patients with solid organ transplantation were not recommending prophylaxis for HBV reactivation in this situation, the patient did not receive any medication for HBV. After two years, he developed jaundice with a high level of ALT and was referred to our clinic. The profile of HBV was: HBsAg, IgM HBc antibodies and HBeAg positive with viral load 1.3 million UI/ml. ETV was started with HBe seroconversion and HBsAg clearance after 6 months and with HBs seroconversion after 12 months of antiviral treatment. The patient continues to receive ETV and is monitored in our clinic every 6 months.

The fourth patient was a 69-year-old male with B-cell non-Hodgkin lymphoma treated with Rituximab-containing regimens (R-CHOP). The HBV profile was: HBsAg, HBsAb and HBeAg negative, but IgG HBc positive. He received R-CHOP for 6 months without any antiviral prophylaxis. The HBV reactivation occurred during the 7th cycle of IST, with ALT > 10ULN, reverse seroconversion of HBsAg, HBeAg, IgM HBc antibodies and HBV DNA > 38 million UI/ml. The patient received ETV with ALT normalization after two months and had HBs seroconversion with HBsAb titer of 200 mUi/ml and undetectable viral load after 6 months of therapy.

The fifth case was a 69-year-old male diagnosed with rheumatoid arthritis, for 6 years on anti-TNF-alpha therapy (Infliximab, followed by Adalimumab). The anti-TNF-alpha therapy was followed by Rituximab from December 2009 until March 2015. Prior to the start of Rituximab he was negative for HBsAg, but positive for IgG HBc and HBsAb (35 mUI/ml). After 12 cycles of Rituximab his ALT level was high and he was admitted to our hospital. The viral pattern showed HBsAg, IgM HBc and HBeAg positive, HBsAb negative and HBV DNA >14 million UI/ml.

He received Entecavir 0.5 mg/day with normalization of ALT level and HBe seroconversion after four months. After six months, the viral load became undetectable and he achieved HBs seroconversion with positive HBsAb (263mUI/L).

Discussions

HBV reactivation may occur either spontaneously, after discontinuation of antiviral therapy or in patients with conditions requiring IST (4,5). The evolution depends on the complex interplay between the host's immune response and viral replication. HBV reactivation was reported during IST both in patients with HBsAg positive chronic HBV infection and with OBI. We present **5 cases** with OBI who had HBV reactivation, all with acute hepatitis flares (defined as an an abrupt ALT elevation > 5 x ULN) (6), serum presence of IgM HBc antibodies, and reverse seroconversion from HBsAg negative to HBsAg positive due to different causes of iatrogenic immunosuppresion. All patients achieved HBsAg loss and had a favourable clinical outcome after stopping IST and received ETV treatment, which signified the return to the initial HBV status, prior to the initiation of IST. None of the pa-

Table I. Clinical, biological and virusological characteristics of our patients

Gender/ age	Disease/ Chemotherapy or Immu-no-suppressive therapy	HBV serol-ogy prior CHT	HBV serology at time of reactiva-tion	HBV serolo-gy after one month	2 mo ETV	4 mo ETV	6 mo ETV	Observation
F/48 year	Psoriasis/ Methotrexat and cyclosporin	HBsAg neg-ative IgG HBc positive HBsAb neg-ative	HBsAg positive QHBsAg - 5400 HBeAg positive IgM HBc positive ALT – 760 ui/ml BT- 1.3mg/dl **STOP IST**	HBsAg positive HBeAg positive IgM HBc pos-itive ALT -1013UI/ ml BT – 2mg/dl HBV-DNA= 16 million UI/ml **START ETV**	HBsAg positive HBeAg positive IgM HBc pos-itive ALT- 401UI/ml BT – 2mg/dl	HBsAg pos-itive Q HBsAg 340 HBeAg neg-ative HBeAb neg-ative IgM HBc negative ALT= 65 UI/ ml BT = 2mg/dl	HBsAg negative HBsAb negative HBeAb positive ALT= 23UI/ml BT=0.7mg/dl HBV-DNA neg-ative	ETV contin-ued for 12 months after HBsAg neg-ative Did not de-velop HBsAb Did not recur HBsAg
F/66 year	Rheumatoid arthritis / Baricitinib	HBsAg neg-ative IgG HBc positive HBsAb pos-itive HBV-DNA negative	HBsAg positive Q HBsAg = 5600 IgM -HBc positive HBeAg positive ALT= 1000UI/ml BT =5.6mg/dl HBV-DNA >170 milions UI/ml **STOP IST**	HBsAg positive IgM HBc pos-itive HBeAg positive ALT= 346UI/ml BT =5.6mg/dl **START ETV**	Q HBsAg= 340 HBeAg nega-tive HBeAb positive IgM HBc neg-ative ALT= 23UI/ml BT=0.7mg/dl **START Adalimumab**	Q HBsAg=190 IgM HBc negative HBeAg neg-ative HBeAb positive ALT=25UI/ ml BT=0.6mg/dl	HBsAg negative HBsAb negative ALT= 23UI/ml BT = 0.5mg/dl HBV-DNA= 47 UI/ml	After one year of ETV HBsAg negative with HBsAb negative and HBV-DNA <15 UI / ml **Continue ETV**

M/35 year	Kidney transplantation/ Tacrolimus	HBsAg negative IgG HBc positive	HBsAg positive QHBsAg= 4460 HBeAg positive HBeAb negative ALT= 961ui/ML BT = 3.3mg/dl HBV-DNA= 1.3 million UI/ml **START ETV**	HBsAg positive IgM HBc positive HBeAg positive ALT= 354UI/ml BT =1.9mg/dl	HBsAg positive Q HBsAg=120 HBeAg positive HBeAb negative ALT=32UI/ml BT=0.9mg/dl	-	HBsAg negative HBeAb negative HBsAb=100UI/l ALT=23UI/ml BT=0.6mg/dl HBV-DNA negative	**Continue ETV** Afer one year HBsAb positive= 190 UI/L
M/69 year	B-cell non-Hodgkin lymphoma (NHL)/ Rituximab	HBsAg negative IgG HBc positive HBsAb negative	HBsAg positive IgM HBc positive HBeAb positive HBV-DNA= 38,700,000 UI/ml ALT=457UI/ml BT= 1.9mg/dl **Start ETV** **Stop IST**	HBsAg positive IgG HBc positive ALT=230UI/ml BT=1 mg/dl HBV-DNA=2,300UI/ml	HBsAg positive ALT=30 UI/ml	-	HBsAg negative HBsAb positive=200 UI/l HBV-DNA=negative	Continue ETV Hematological remision
M/69 year	Rheumatoid arthritis / 6 years with Adalimumab/ Infliximab Rituximab (6,5 years) and metotrexat 12 years	HBsAg negative IgG HBc positive HBsAb positive 35 mUI/ml	HBsAg positive QHBsAg=230 HBeAg positive IgM HBc positive HBsAb negative HBV-DNA= 14,135,879UI/ml ALT= 658UI/ml BT=1.8mg/dl **Stop IST** **Start ETV**	HBsAg positive HBeAg positive HBV-DNA= 267,908UI/ml ALT= 2183UI/ml BT= 1.3mg/dl	HBsAg positive HBeAg positive HBV-DNA= 188 UI/ml ALT=206UI/ml BT=1.5mg/dl	HBsAg positive HBeAg negative HBeAb negative ALT=44UI/ml BT= 1.2mg/dl	HBsAg negative HBsAb positive= 263UI/L HBeAb positive HBV-DNA negative ALT= 20UI/ml BT= 1.5mg/dl	Continue ETV Continue Rituximab Still HBsAb positive =260 UI/L

HBV=hepatitis B virus; IST=immunosuppressive therapy; ETV=entecavir; CHT=chemotherapy; HBsAg= Hepatitis B surface antigen; QHBsAg= quantitative hepatitis B surface antigen; HBsAb=antibody against hepatitis B surface antigen; HBeAg=Hepatitis B e antigen; HBeAb= antibody against hepatitits B e antigen; IgM HBcAb= Hepatitis B core antibodies IgM; IgG HBcAb= Hepatitis B core antibodies IgG; ALT: Alanine aminotransferase; BT=total bilirubin; ULN= upper limits of normal

tients developed liver failure and no death was recorded.

We hypothesize that the restoration of immune antiviral responses after IST cessation led to achieving again viral control and HBsAg loss for all cases and presence of HBsAb in three patients. Interestingly, one patient who initially had serum HBsAb failed to develop them after one year since the moment of IST cessation and initiation of ETV treatment, while two other patients, negative for HBsAb before IST achieved seroconversion to HBsAb following reactivation. One patient had prior serum HBsAb and managed to reacquire HBsAb, with a higher titer, after HBV reactivation and treatment. In one case no prior HBsAb testing was performed, which represents a limitation of the present study. All of our patients achieved HBeAg clearence and had normal ALT after 4 months of ETV therapy. HBsAg clearence occured within 6 months of therapy and HBV viral load became also undetectable in less than 6 months after the initiation of antiviral treatment.

The prevalence estimates for OBI vary widely between 1% to 87% according to different studies in various geographical regions of the world and many clinical and pathogenic characteristics of OBI are still incompletely defined (7-9). In spite of strong immune responses, that limit HBV replication, in OBI patients HBV DNA is preserved in the nuclei of hepatic cells as covalently-closed-circular DNA (cccDNA).

OBI is increasingly recognized as having a major clinical relevance, especially in patients during IST, when loss of immune surveillance may lead to significant HBV replication, with rapid viral protein expression in hepatocytes, causing their direct distruction (10).

Another major mechanism of hepatic distruction, which may significantly increase the risk of hepatic decompensation and failure is the immune restoration syndrome, following cessation of IST. Rapid reconstitution may lead to exaggerated immune responses against hepatocytes that express hepatitis B viral proteins, with potential major necrosis of liver cells (11).

Considering these pathogenic mechanisms, the management of HBV reactivation must include both cessation of IST (which permits the restoration of antiviral immune responses) (12) and direct antiviral treatment (which limits the initial uncontrolled viral replication, the expression of hepatitis B-associated viral proteins and decreases the cythopathic effect associated with rapid immune restoration). Immune recovery after stopping IST has the potential of achieving better viral control, as observed in our case series in two patients that achieved HBsAg seroconversion after OBI reactivation.

HBV reactivation associated with IST may appear in the first months of therapy or can be delayed; it may even be observed a long time after cessation of immunosuppresion intervention. Muraishi et al. (13) reported OBI reactivation in a 68-year-old man with lymphoma, which occurred 27 months after the end of rituximab-associated chemotherapy. Rituximab is associated with prolonged immunosuppresion, due to major B-lymphocyte depletion effects (14), followed by a delayed immune restoration phase, which may explain why in Rituximab-based regimens HBV reactivation may be observed more than 12 months after the end of IST(15).

In our case series, all patients had HBV reactivation after more than 6 months of IST, including two patients with Rituximab-containing regimens.

A few other studies reported that an ALT level of more than 200 UI/l was associated with HBsAg clearancce (16,17). Ueda et al. in Japan and Sanchez et al. in Spain (2009) reported HBsAg loss after 2 and 6 months of Entecavir treatment in patients who received chemotherapy for B-cell lymphoma (18,19). Brost et al. (20) reported in

Germany four cases with hematological malignancies and HBV reactivation. All were associated with rapid ALT normalisation and undetectable viral load between 3 and 13 months of antiviral treatment. In a retrospective study of 392 HBV patients followed for more than 5 years, Shinya N et al. observed that hepatic flares promote rapid and greater reduction of HBsAg levels in patients with HBsAg seroclearance (21).

International guidelines recommend HBV screening for all patients receiving IST. This should include evaluation of HBsAg, IgG HBc, and HBsAb. HBV reactivation prophylaxis must be recommended to patients with positive HBsAg and also to those who only have positive IgG HBc. Current guidelines recommend the use of Entecavir or Tenofovir for prophylaxis of HBV reactivation (2,3).

We emphasize that in contrast to HBV chronic hepatitis treated with NA, severe OBI reactivation has a particular outcome, with a higher rate of HBsAg clearence. According to our experience, the rate of HBsAg loss in patients with chronic HBV hepatitis undergoing NA therapy is under 5% (22,23). All of our OBI patients with severe reactivation cleared AgHBs. Further studies in this direction could be important.

There are studies who have shown that atypical serological profiles and high HBV viral load may be an indicator of S gene mutations causing OBI, HBV reactivations and progress to severe forms of liver damage which is why it is important to detect gene mutations by molecular analysis and monitor them (24).

In summary, screening for HBV (HBsAg, HBsAb, HBcAb) should be performed in all patients who need IST, followed by prophylaxis, when required, and careful monitoring, as reactivation in OBI patients may occur even late after the start of immunosuppresion regimen. OBI reactivation may occur during various IST regimens and ETV treatment and cessation of IST both contribute to rapid viral control and may induce HBsAg seroconversion.

Abbreviations

HBV=hepatitis B virus
IST=immunosuppressive therapy
ETV=entecavir
CHT=chemotherapy
HBsAg= Hepatitis B surface antigen
QHBsAg= quantitative hepatitis B surface antigen
HBsAb=antibody against hepatitis B surface antigen
HBeAg=Hepatitis B e antigen
HBeAb= antibody against hepatitits B e antigen
IgM HBcAb= Hepatitis B core antibodies IgM
IgG HBcAb= Hepatitis B core antibodies IgG
ALT: Alanine aminotransferase
BT=total bilirubin
ULN= upper limits of normal

Acknowledgements

This work is part of “Carol Davila” University of Medicine and Pharmacy doctoral programme.

Authors’ Contributions

VM (Conception and design; Acquisition of data; Analysis and Interpretation of data; Writing Manuscript; Final approval), CP (Conception and design; Acquisition of data; Analysis and Interpretation of data; Writing Manuscript; Final approval); CT (Conception and design; Acquisition of data; Analysis and Interpretation of data; Writing Manuscript; Final approval), VA (Conception and design; Acquisition of data; Analysis and Interpretation of data; Writing Manuscript; Final approval), SSA (Conception and design; Acquisition of data; Analysis and Interpretation of data; Writing Manuscript; Final approval).All the authors had equally contributed in elaborating the paper.

Conflict of Interest

None to declare.

References

1. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute Technical Review on Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology. 2015 Jan 1;148(1):221-244.e3. DOI: 10.1053/j.gastro.2014.10.038
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
3. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol Baltim Md. 2018;67(4):1560-99. DOI: 10.1002/hep.29800
4. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. Gastroenterology. 1984 Feb;86(2):230-5. DOI: 10.1016/0016-5085(84)90406-2
5. Fattovich G, Brollo L, Alberti A, Realdi G, Pontisso P, Giustina G, et al. Spontaneous reactivation of hepatitis B virus infection in patients with chronic type B hepatitis. Liver. 1990 Jun;10(3):141-6. DOI: 10.1111/j.1600-0676.1990.tb00449.x
6. Puri P. Acute Exacerbation of Chronic Hepatitis B: The Dilemma of Differentiation from Acute Viral Hepatitis B. J Clin Exp Hepatol. 2013 Dec;3(4):301-12. DOI: 10.1016/j.jceh.2013.08.014
7. Kazemi-Shirazi L, Petermann D, Müller C. Hepatitis B virus DNA in sera and liver tissue of HBsAg negative patients with chronic hepatitis C. J Hepatol. 2000 Nov;33(5):785-90. DOI: 10.1016/S0168-8278(00)80311-6
8. Yuen MF, Lee C, Wong D, Fung J, Hung I, Hsu A, et al. Prevalence of occult hepatitis B infection in a highly endemic area for chronic hepatitis B: a study of a large blood donor population. Gut. 2010 Oct 1;59:1389-93. DOI: 10.1136/gut.2010.209148
9. Raimondo G, Locarnini S, Pollicino T, Levrero M, Zoulim F, Lok AS, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J Hepatol. 2019 Aug;71(2):397-408. DOI: 10.1016/j.jhep.2019.03.034
10. Makvandi M. Update on occult hepatitis B virus infection. World J Gastroenterol. 2016 Oct 21;22(39):8720-34. DOI: 10.3748/wjg.v22.i39.8720
11. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies and future directions. Gastroenterology. 2017 May;152(6):1297-309. DOI: 10.1053/j.gastro.2017.02.009
12. Villadolid J, Laplant KD, Markham MJ, Nelson DR, George TJ. Hepatitis B reactivation and rituximab in the oncology practice. The Oncologist. 2010;15(10):1113-21. DOI: 10.1634/theoncologist.2010-0106
13. Muraishi J, Shibata M, Honma Y, Hiura M, Abe S, Harada M. Reactivation of Occult Hepatitis B Virus Infection 27 Months after the End of Chemotherapy Including Rituximab for Malignant Lymphoma. Intern Med Tokyo Jpn. 2017;56(15):1967-71. DOI: 10.2169/internalmedicine.56.8233
14. Tsutsumi Y, Yamamoto Y, Ito S, Ohigashi H, Shiratori S, Naruse H, et al. Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol. 2015 Sep 28;7(21):2344-51. DOI: 10.4254/wjh.v7.i21.2344
15. Sagnelli C, Pisaturo M, Calò F, Martini S, Sagnelli E, Coppola N. Reactivation of hepatitis B virus infection in patients with hemo-lymphoproliferative diseases, and its prevention. World J Gastroenterol. 2019 Jul 14;25(26):3299-312. DOI: 10.3748/wjg.v25.i26.3299
16. Kim GA, Lim YS, An J, Lee D, Shim JH, Kim KM, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut. 2014 Aug;63(8):1325-32. DOI: 10.1136/gutjnl-2013-305517
17. Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. Hepatology. 2008;48(4):1062-9. DOI: 10.1002/hep.22462
18. Ueda Y, Marusawa H, Ichinohe T, Kadowaki N, Uchiyama T, Chiba T. Effective treatment for de novo hepatitis B with nucleotide analogue in patients with hematological malignancies. Am J Hematol. 2009 May;84(5):315-6. DOI: 10.1002/ajh.21388
19. Sanchez MJ, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. J Hepatol. 2009 Dec 1;51(6):1091-6. DOI: 10.1016/j.jhep.2009.07.012
20. Brost S, Schnitzler P, Stremmel W, Eisenbach C. Entecavir as treatment for reactivation of hepatitis B in immunosuppressed patients. World J Gastroenterol WJG. 2010 Nov 21;16(43):5447-51. DOI: 10.3748/wjg.v16.i43.5447
21. Nagaoka S, Abiru S, Komori A, Sasaki R, Bekki S, Hashimoto S, et al. Hepatic flares promote rapid decline of serum hepatitis B surface antigen (HBsAg) in patients with HBsAg seroclearance: A long-term follow-up study. Hepatol Res. 2016;46(3):E89-99. DOI: 10.1111/hepr.12533

22. Buti M, Riveiro-Barciela M, Esteban R. Long-term safety and efficacy of nucleo(t)side analogue therapy in hepatitis B. Liver Int. 2018;38(S1):84-9. DOI: 10.1111/liv.13641
23. Popescu C, Lobodan A, Rădulescu M, Negru A, Molagic V, Hristea A, et al. Treatment of chronic HBV hepatitis - between immune control and virological control. BMC Infect Dis. 2014 Oct 15;14(7):O10. DOI: 10.1186/1471-2334-14-S7-O10
24. Aydemir S, Yildirmak MT, Sayan M, Atak S, Kucuk M. A chronic hepatitis B patient infected with HBsAg diagnostic-escape strain in the presence of anti-HBs positivity. Rev Romana Med Lab. 2019;27(4):421-6. DOI:10.2478/rrlm-2019-0038