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Hepatitis B and C coinfection in a real-life setting: viral interactions and treatment issues

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Abstract

Background Only limited data concerning hepatitis B (HBV) and C viruses (HCV) coinfection are available. Direct-acting antivirals (DAAs) may be more effective for HCV clearance than interferon (IFN)-based regimens with a risk of HBV reactivation.

Methods We retrospectively enrolled 40 HBV/HCV-coinfected patients to evaluate their clinical profile and treatment outcomes.

Results Chronic dual infection was present in 25/40 (62.5%) patients, acute HCV superinfection in 5/40 (12.5%) patients and acute HBV superinfection in 10/40 (25%). Twenty-five patients (62.5%) were treated: 16/25 (64%) with IFN, 4/25 (16%) with nucleot(s)ide analogs (NUCs) and 5/25 (20%) with DAAs. Of the 16 patients treated with IFN-based therapy, 6 (37.5%) achieved both sustained virological response (SVR) and HBsAg clearance. Of the 4 patients treated with NUCs, one (25%) achieved both SVR and HBsAg clearance. All five patients treated with DAAs (100%) achieved SVR, while one case of HBV reactivation was recorded. Fifteen of the 40 patients (37.5%) did not receive any treatment. Eight of them (53.5%) presented with acute HBV superinfection: spontaneous HCV clearance was recorded in 5/8 (62.5%), while HBsAg clearance occurred in 6/8 (75%). Three of them (20%) presented with acute HCV superinfection; spontaneous HCV clearance was recorded in one of the three (33.5%). The other four patients (26.5%) presented with dual HBV/HCV infection.

Conclusions A significant proportion of patients presented with active HBV replication. Treatment with DAAs seems to be efficacious for HCV eradication. However, clinicians should be aware of HBV reactivation. HBV superinfection may lead to both HBsAg and HCV clearance.

Keywords Hepatitis B, hepatitis C, direct-acting antivirals, interferon

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Introduction

The exact prevalence of hepatitis B (HBV) and C viruses (HCV) coinfection is actually unknown. It is estimated to be between 0.7% and 16%, a percentage that ranges over a wide interval among several studies in the literature, mainly depending on the geographical region and the study population [1-3]. However, in regions where HBV is endemic the probability of coinfection increases, especially in groups of patients with well-known risk factors for HCV infection, such as persons who inject drugs (PWID) or had blood transfusions before 1990-91.

On the other hand, HBV/HCV-coinfected patients represent a group with significant heterogeneity regarding clinical features, impact on the severity of liver disease and therapeutic options. While liver disease activity and progression are generally more severe in the presence of

double infection, the host's immune response plays an important role in coordinating each single viral replication and the viral interference, usually leading to a predominance of one of the two viruses [1-2, 4-5]. Thus, several clinical scenarios have been described in the natural course of this dual infection [6]. HCV superinfection is more frequent, while HBV superinfection is rare [7-8]. In addition, acute HBV/HCV coinfection is more prevalent in PWID [9]. Most HBV/HCV-coinfected patients have HCV RNA levels similar to those in patients with HCV mono-infection, but relatively lower levels of serum HBV DNA compared to patients with chronic HBV mono-infection [10].

Treatment may result in complete disruption of the delicate co-existence of HBV/HCV viruses. Thus, the treatment-induced eradication of each virus could lead to reactivation of the other [6].

In this retrospective study, we aimed to evaluate a series of HBV/HCV-coinfected patients followed in our units, emphasizing their initial clinical profile, treatment efficacy and outcomes.

Patients and methods

We reviewed the records of all anti-HCV and HBsAg-positive patients who visited two tertiary liver centers in Athens between 1990 and 2016. Patients who were coinfected with human immunodeficiency virus were excluded. The database included patients' demographic and epidemiological characteristics, medical history data, clinical and laboratory data, and treatment history. The study was performed according to the World Medical Association Declaration of Helsinki and was approved by the hospital's ethics committee.

Management profile and treatment decisions were individualized for each patient according to their compliance and the practice of the treating physicians. Contraindications for interferon (IFN)-based therapies included current uncontrolled depression, psychosis, or epilepsy, uncontrolled autoimmune diseases, pregnancy or unwillingness to use adequate contraception, alcohol use, decompensated cirrhosis, severe heart failure, and chronic obstructive pulmonary disease.

Definitions

Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) dual infection was defined as anti-HCV-positive with detectable HCV RNA accompanying by positive HBsAg/anti-HBc with HBV DNA levels either >2000 IU/mL or <2000 IU/mL (inactive HBV carriers). Acute HCV superinfection was defined as documented anti-HCV detection in patients with known CHB. Acute HBV superinfection was defined as documented HBsAg/anti-HBc detection in patients with known CHC.

Hepatitis C sustained virological response (SVR) was defined as serum HCV RNA undetectability by qualitative polymerase chain reaction (PCR) at 6 months (SVR24) after stopping treatment with interferon and ribavirin, or at 3 months after (SVR12) stopping treatment with direct-acting antivirals (DAAs). Patients with undetectable serum HCV RNA at the end and detectable HCV RNA after the end of treatment were considered as relapse responders and patients with detectable serum HCV RNA at the end of treatment as non-responders. Treatment response in HBV infection was defined as HBsAg clearance. HBV reactivation after DAA treatment was defined as a >1 log increase in HBV DNA accompanying by a ≥3-fold increase in baseline levels of alanine aminotransferase (ALT). Increases >1 log in HBV DNA levels that did not led to clinical acute hepatitis (≥3-fold increase in ALT) were considered as HBV DNA flares of no clinical significance.

Laboratory methods

Hematological and biochemical parameters were determined using commercially available assays. The upper limit of normal for both ALT and aspartate aminotransferase was 40 IU/L. Commercially available enzyme immunoassays were used for detection of anti-HCV, while quantitative determination of HCV RNA and HBV DNA were performed using quantitative real-time PCR (Quantiplex HCV RNA, Chiron Co and COBAS Taqman HBV Test; Roche Diagnostics). HCV genotype was also determined by a commercially available assay (InnoLipa; Innogenetics).

Statistical analysis

All statistical analyses were carried out using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA). General descriptive methods, including frequencies and mean values ± standard deviation, were used to express percentages and continuous variables.

Results

We included 40 patients with HBV/HCV coinfection. Their mean age was 47±15 years and 65% of them were male. The majority (87.5%) were Greeks. About half of the patients (52.5%) had a history of parenteral drug use, while 11 patients (27.5%) were cirrhotics. The mean follow-up time was 50.5±7 months. HBeAg was positive in 13/40 (32.5%) patients (7 patients with acute HBV superinfection, 5 patients with CHB/CHC dual infection and one patient with acute HCV superinfection). Mean ALT levels were 171±336 IU/L, mean HCV RNA levels were $1\times10^6\pm2\times10^6$ IU/mL and mean HBV DNA levels were $1\times10^8\pm36\times10^7$ IU/mL (Table 1).

Baseline data in subgroups

CHB/CHC dual infection was present in 25/40 (62.5%) patients, of whom 14 (56%) had long-term normal aminotransferases and low or undetectable HBV DNA (inactive HBV carriers). Acute HCV superinfection was found in 5/40 (12.5%) patients and acute HBV superinfection in 10/40 (25%) patients (Table 1).

Treatment decision and outcome

Of the 40 patients, 25 (62.5%) were treated for HCV and/or HBV. According to each treating physician's decision, 16 (64%) of the 25 patients received treatment with (peg)IFN ± ribavirin (IFN-based), 4 (16%) patients were treated with nucleot(s)ide analogs (NUCs) and 5 (20%) patients were treated with DAAs.

CHB/CHC patients

Twenty-one (84%) of this subgroup of 25 patients were treated: 13/21 (62%) with IFN-based treatment, resulting in both HBsAg clearance and HCV eradication in 4 patients (31%); 3/21 (14%) with NUCs and no HBsAg clearance or HCV eradication; and 5/21 (24%) with DAAs, resulting in HCV eradication in 3 patients (60%) with no HBsAg clearance.

Acute HCV superinfection

Only 2/25 (8%) patients of this subgroup were treated: 2/2 (100%) with IFN-based treatment, resulting in both HBsAg clearance and HCV eradication in both patients (100%).

Acute HBV superinfection

Only 2/25 (8%) patients of this subgroup were treated: 1 patient (50%) with IFN-based treatment, with no HBsAg clearance or HCV eradication, and 1 patient (50%) with NUC, resulting in both HBsAg clearance and HCV eradication.

Clearance

Among 16 patients treated with IFN based therapy, 6 (37.5%) achieved both SVR and HBsAg clearance. Of the 4 patients treated with NUCs, 1 patient (25%) who presented with acute HBV superinfection achieved both SVR and HBsAg clearance. Among 5 patients treated with DAAs, all cases (100%) achieved SVR12. One case of HBV reactivation was recorded among these 5 patients who achieved SVR with DAAs. He was a cirrhotic 55-year-old Caucasian male with genotype 1b CHC/inactive HBV carrier (baseline HBV DNA levels: 215 IU/mL), initially treated with ledipasvir/sofosbuvir and ribavirin. He achieved SVR12, but one month later he experienced HBV reactivation, with HBV DNA levels of 460,000 IU/mL, accompanied by clinical hepatitis (ALT levels of 352 IU/L). Antiviral therapy with tenofovir disoproxil fumarate (TDF, 300 mg once daily) was initiated. Six months later, ALT levels were within normal range and serum HBV DNA was undetectable. We also recorded a case of HBV DNA flare. She was a 57-year-old Caucasian female with genotype 1a CHC/CHB (HBeAg-positive with baseline HBV DNA levels 1,000,000 IU/mL), treated with peg-IFN plus ribavirin for 48 weeks. She achieved SVR24 accompanying by <1 log increase in HBV DNA levels (3,070,000 IU/mL) without clinical or laboratory findings of acute hepatitis. The patient did not receive treatment for

Table 1 Baseline demographic and clinical characteristics

Characteristics	All N=40	CHB/CHC N=25	Acute HCV superinfection N=5	Acute HBV superinfection N=10	P-value
Age (mean±SD), years	47±15	52.5±14	42±6.5	38±15	0.034
Sex: Male, n/N (%)	26/40 (65)	13/25 (52)	4/5 (80)	9/10 (90)	0.064
Descent: Greek, n/N (%)	35/40 (87.5)	22/25 (88)	5/5 (100)	8/10 (80)	0.891
PWID, n/N (%)	21/40 (52.5)	10/25 (40)	3/5 (60)	8/10 (80)	0.138
Cirrhosis, n/N (%)	11/40 (27.5)	9/25 (36)	0/5 (0)	2/10 (20)	0.085
HBeAg-positive, n/N (%)	13/40 (32.5)	5/25 (20)	1/5 (20)	7/10 (70)	0.239
HBV DNA (mean±SD), IU/mL	$1\times10^8\pm36\times10^7$	$63\times10^6\pm25\times10^7$	$6\times10^3\pm76\times10^2$	$3\times10^9\pm7\times10^8$	0.622
HCV RNA (mean±SD), IU/mL	$1\times10^6\pm2\times10^6$	$1.5\times10^6\pm2\times10^6$	$6\times10^5\pm4.6\times10^5$	$13\times10^2\pm2\times10^3$	0.269
ALT (mean±SD), U/L	171±336	77±86	431±803	279±253	0.020
Treatment, n/N (%)	25/40 (62.5)	21/25 (84)	2/5 (40)	2/10 (20)	0.039
Follow up (mean±SD), months	50.5±7	66±79	26±19	19±3	0.162

CHB/CHC, chronic hepatitis B/C; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; PWID, persons who inject drugs

HBV and is still HBeAg-positive without any increases in ALT levels (Table 2).

Non-treated patients

A significant proportion of this cohort, 15/40 patients (37.5%), did not receive any treatment, mainly because of the physician's decision or a contraindication (12/15; 80%). Eight of these patients (53.5%) presented with acute HBV superinfection: spontaneous HCV clearance was recorded in 5/8 (62.5%), while HBsAg clearance occurred in 6/8 (75%). Three of them (20%) presented with acute HCV superinfection: spontaneous HCV clearance was recorded in one of them (33.5%). four patients (26.5%) presented with dual HBV/HCV infection: two of them (50%) did not receive any treatment due to contraindication, one patient (25%) did not wish to receive treatment and one patient (25%) was lost during the follow up (Table 3).

Discussion

The worldwide prevalence of HBV/HCV coinfection is unknown and may be underestimated, while the disease outcomes, including cirrhosis, are more severe than in patients with mono-infection [11]. HBV/HCV coinfection is frequently found in several high-risk populations, such as PWID [12]. Unfortunately, HBV/HCV-coinfected patients have very heterogeneous clinical manifestations. There is either HCV predominance, with high HCV RNA levels and low HBV DNA levels, or HBV predominance, with high HBV DNA levels and low HCV RNA levels. It seems that the time of acquisition of each infection is crucial for the prevalence of one virus over the other. In areas with a high prevalence of HBV infection, such as Asia-Pacific countries, patients may have acquired HBV infection at birth, with HCV occurring later as a superinfection, while most patients from Europe and the USA present HBV superinfection on CHC [13]. However, most cases are characterized by an inhibition of HBV replication. In accordance with these reports, most of our HBV/HCV-

Table 2 Outcomes according to initial clinical features among treated patients (N=25)

Clinical features, n/N (%)	Treatment regimen, n (%)	HBsAg clearance, n (%)	HCV eradication, n (%)
CHB/CHC, 21/25 (84)	IFN-based, 13 (62)	4 (31)	4 (31)
	NUC, 3 (14)	0 (0)	0 (0)
	DAAs, 5 (24)	0	5 (100)
Acute HCV superinfection, 2/25 (8)	IFN-based, 2 (100)	2 (100)	2 (100)
Acute HBV superinfection, 2/25 (8)	IFN-based, 1 (50)	0 (0)	0 (0)
	NUC, 1 (50)	1 (100)	1 (100)
Overall, n/N (%)	IFN-based, 16/25 (64)	6/16 (37.5)	6/16 (37.5)
	NUC-based, 4/25 (16)	1/4 (25)	1/4 (25)
	DAAs, 5/25 (20)	0/5 (0)*	5/5 (100)

*HBV reactivation in one patient

CHB/CHC, chronic hepatitis B/C; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN interferon; NUC, nucleot (s) ide analogs

Table 3 Outcomes according to initial clinical features among non-treated patients (N=15)

Clinical features, n/N (%)	Reason of no treatment, n (%)	HBsAg clearance, n (%)	HCV eradication, n (%)
CHB/CHC, 4/15 (26.5)	Contraindication or physician's choice, 2 (50)	0 (0)	0 (0)
	Patient's choice, 1 (25)	0 (0)	0 (0)
	Lost, 1 (25)	Unknown	Unknown
Acute HCV superinfection, 3/15 (20)	Contraindication or physician's choice, 3 (100)	0 (0)	1 (33.5)
Acute HBV superinfection, 8/15 (53.5)	Contraindication, 7 (87.5)	6 (75)	5 (62.5)
	Lost, 1 (12.5)	Unknown	Unknown
Overall, n/N (%)	Contraindication or physician's choice, 12/15 (80)	6/12 (50)	6/12 (50)
	Patient's choice, 1/15 (6.5)	0/1 (0)	0/1 (0)
	Lost, 2/15 (13.5)	Unknown	Unknown

CHB/CHC, chronic hepatitis B/C; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus;

coinfected patients (14/25; 56%) presented with HCV predominance as HBV replication was suppressed. However, a significant proportion of our patients presented either with dually active HBV/HCV infection (11/25; 44%) or with acute HBV superinfection (10/40; 25%), indicating a significant role for HBV in our cohort. This finding can be explained by the fact that, while Greece has been associated with intermediate endemicity for HBV infection, a significant number of HBsAg/HBeAg-positive immigrants have registered in our country during the last two decades, changing the epidemiology of HBV infection [14]. In Greece, as in most countries with intermediate endemicity for HBV infection, most of these infections occurred through horizontal transmission during infancy or early childhood; thus, patients had HBV infection for many years before being infected by HCV. As proposed by Chen *et al*, patients who acquired HCV infection later than HBV infection have a minority of hepatocytes uninfected by HBV and thus "available" for HCV superinfection; this unequal distribution of the coinfection leads to HBV dominance [15].

Detailed serological and virological evaluations are required for coinfected patients before the initiation of antiviral therapy. It has been demonstrated that IFN-based therapies are safe and can achieve SVR rates comparable to those expected with HCV mono-infection, leading to a reduction in liver-related complications [16-18]. Our cohort included 25 treated patients. The majority (64%) were treated with IFN-based therapies. Both HBsAg clearance and HCV eradication were documented in 37.5% of them. We also observed both HBsAg clearance and HCV eradication in a patient treated with NUC. However, this patient presented with acute HBV superinfection. Sagnelli *et al* conducted a long-term follow-up study in Italy of HBV superinfection in CHC patients. In that study, more than 90% of patients cleared HBsAg, while all patients had undetectable HCV RNA during acute hepatitis B [19]. Several case reports suggested the dominant role of HBV leading to HCV clearance after HBV superinfection [8]. There is a hypothesis that HCV eradication in HBV superinfection is favorable because the T-cell response targets HBV [20]. Thus, the role of NUC treatment in this patient's HBV/HCV clearance is unclear. Furthermore, our data indicate the favorable role of acute HBV superinfection in HBsAg and HCV clearance; we recorded 75% HBsAg clearance and 50% HCV spontaneous eradication in eight untreated patients with HBV superinfection.

Recently, several cases of HBV reactivation have been reported in HBV/HCV-coinfected patients receiving DAAs, raising potential safety concerns [21-24]. HBV reactivation according to various definitions may occur in >50% of HBsAg-positive patients who receive treatment with DAAs for CHC, but is very rare in patients with resolved HBV hepatitis (HBsAg-negative/antiHBc-positive) [23]. On the other hand, recently published data showed frequent HBV reactivations in CHB/CHC patients, but no signs of clinical flares, while none of the patients required antiviral treatment for HBV [25]. HBV reactivation in HBV/HCV dually infected patients was initially described with IFN-based treatment several years ago [26]. It seems that HBV reactivation may occur much earlier after treatment with DAAs compared to IFN-based treatment [23]. As a result, the US Food and Drug Administration issued a warning about the risk of HBV reactivation and suggests screening and monitoring for HBV in all patients receiving DDA treatment [27-28]. Recently published recommendations from the European Association for the Study of the Liver (EASL) regarding the treatment of hepatitis C indicate that patients with HBV/HCV coinfection should be treated with the same regimens, following the same rules as HCV mono-infected patients,and if active CHB or "occult" HBV infection is detected, concurrent NUC therapy is indicated [29]. However, more recently published EASL recommendations for the treatment of hepatitis B indicate that HBsAg-negative/anti-HBc-positive patients undergoing DAA treatment should be monitored and tested for HBV reactivation only in case of ALT elevation [30]. Consistently with these reports, one of our patients experienced HBV reactivation after DAA treatment. As described above, he was treated with TDF for HBV reactivation without any signs of

Summary Box

What is already known:

- Liver disease activity and progression are generally more severe in hepatitis B (HBV) and C (HCV)-coinfected patients
- Viral interference usually leads to a predominance of one of the two viruses, which in most cases is HCV
- Treatment-induced eradication of each virus could lead to reactivation of the other; several cases of HBV reactivation have been reported in HBV/HCV-coinfected patients receiving direct-acting antivirals (DAAs)

What the new findings are:

- As Greece has been associated with intermediate endemicity for HBV infection, a significant proportion of our patients presented either with dually-active HBV/HCV infection or with acute HBV superinfection, indicating a significant role for HBV in our cohort
- A significant proportion of this cohort (37.5%) did not receive any treatment
- Our data indicate the favorable role of acute HBV superinfection in HBsAg and HCV clearance; we recorded 75% HBsAg clearance and 50% HCV spontaneous eradication in eight untreated patients with HBV superinfection
- Treatment with DAAs seems to be efficacious in HCV eradication; however, one of our five treated patients with DAAs experienced HBV reactivation and he was successfully treated with tenofovir disoproxil fumarate

liver function deterioration, despite the fact he was cirrhotic. Six months later he achieved complete viral suppression with normal liver function tests and undetectable HBV DNA. In fact, according to the EASL published guidelines, HBsAg-positive cirrhotic patients with detectable HBV DNA levels at baseline require antiviral treatment with NUC even before DAA treatment, regardless of ALT levels [30].

Because of the retrospective design of our study, we unfortunately did not have frequent follow-up data regarding concurrent measurements of HBV DNA and HCV RNA during follow up, which could have been helpful for a better understanding of the viral interactions without or during antiviral treatment. However, prospective studies are not easy to perform, because of the small number of cases and the high heterogeneity of the clinical presentations.

In conclusion, although HCV dominance was documented, a significant proportion of our patients presented with active HBV replication, either as dually active HBV/HCV infection or as acute HBV superinfection over CHC. Treatment with DAAs seems to be efficacious in HCV eradication. However, clinicians should be alert for HBV reactivation after DAA therapy and all patients with HCV/HBV coinfection should be closely monitored. Finally, acute HBV superinfection may lead to both HBsAg and HCV clearance.

References

1. Chakravarti A, Verma V, Jain M, Kar P. Characteristics of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. *Trop Gastroenterol* 2005;**26**:183-187.
2. Mekky MA, Nasr AM, Saleh MA, et al. Virologic and histologic characterisation of dual hepatitis B and C co-infection in Egyptian patients. *Arab J Gastroenterol* 2013;**14**:143-147.
3. Gaeta GB, Stornaiuolo G, Precone DF, et al. Epidemiological and clinical burden of chronic hepatitis B virus/hepatitis C virus infection. A multicenter Italian study. *J Hepatol* 2003;**39**:1036-1041.
4. Alberti A, Pontisso P, Chemello L, et al. The interaction between hepatitis B virus and hepatitis C virus in acute and chronic liver disease. *J Hepatol* 1995;**22**:38-41.
5. Senturk H, Tahan V, Canbakan B, et al. Clinicopathologic features of dual chronic hepatitis B and C infection: a comparison with single hepatitis B, C and delta infections. *Ann Hepatol* 2008;**7**:52-58.
6. Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management. *Ann Gastroenterol* 2015;**28**:221-228.
7. Liaw YF. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *J Gastroenterol* 2002;**37** Suppl 13:65-68.
8. Liaw YF, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. *Am J Gastroenterol* 2000;**95**:2978-2980.
9. Yan BM, Lee SS. Acute coinfection with hepatitis B and hepatitis C viruses. *Can J Gastroenterol* 2005;**19**:729-730.
10. Liu CJ, Chen PJ, Chen DS. Dual chronic hepatitis B virus and hepatitis C virus infection. *Hepatol Int* 2009;**3**:517-525.
11. Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. *J Formos Med Assoc* 2005;**104**:783-791.
12. Pallás JR, Fariñas-Alvarez C, Prieto D, Delgado-Rodríguez M. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. *Eur J Epidemiol* 1999;**15**:699-704.
13. Nguyen LH, Ko S, Wong SS, et al. Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. *Hepatology* 2011;**53**:1839-1845.
14. Raptopoulou M, Papatheodoridis G, Antoniou A, et al. Epidemiology, course and disease burden of chronic hepatitis B virus infection. HEPNET study for chronic hepatitis B: a multicentre Greek study. *J Viral Hepat* 2009;**16**:195-202.
15. Chen F, Zhang J, Wen B, et al. HBV/HCV dual infection impacts viral load, antibody response, and cytokine expression differently from HBV or HCV single infection. *Sci Rep* 2016;**6**:39409.
16. Liu CJ, Chu YT, Shau WY, Kuo RN, Chen PJ, Lai MS. Treatment of patients with dual hepatitis C and B by peginterferon α and ribavirin reduced risk of hepatocellular carcinoma and mortality. *Gut* 2014;**63**:506-514.
17. Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. *Hepatology* 2003;**37**:568-576.
18. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009;**136**:496-504.
19. Sagnelli E, Coppola N, Pisaturo M, et al. HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. *Hepatology* 2009;**49**:1090-1097.
20. Gruener NH, Jung MC, Ulsenheimer A, et al. Hepatitis C virus eradication associated with hepatitis B virus superinfection and development of a hepatitis B virus specific T cell response. *J Hepatol* 2002;**37**:866-869.
21. Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis* 2015;**61**:1304-1306.
22. Belperio PS, Shahoumian TA, Mole LA, Backus LI. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. *Hepatology* 2017;**66**:27-36.
23. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. *Hepatology* 2017;**66**:13-26.
24. Mücke VT, Mücke MM, Peiffer KH, et al. No evidence of hepatitis B virus reactivation in patients with resolved infection treated with direct-acting antivirals for hepatitis C in a large real-world cohort. *Aliment Pharmacol Ther* 2017;**46**:432-439.
25. Londoño MC, Lens S, Mariño Z, et al. Hepatitis B reactivation in patients with chronic hepatitis C undergoing anti-viral therapy with an interferon-free regimen. *Aliment Pharmacol Ther* 2017;**45**:1156-1161.
26. Potthoff A, Berg T, Wedemeyer H; HEP-NET B/C Coinfection Study Group. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon-a2b and ribavirin. *Scand J Gastroenterol* 2009;**44**:1487-1490.
27. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf [Accessed March 5, 2018].
28. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. food and drug administration adverse event reporting system. *Ann Intern Med* 2017;**166**:792-798.
29. European Association for the Study of the Liver. EASL Recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017;**66**:153-194.
30. 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**:370-398.