

## Interferon-Free Hepatitis C Virus Treatments and the Story of HBV Reactivation

Alhaddad OM<sup>1</sup>, Elsabaawy MM<sup>1\*</sup>, Elshaarawy O<sup>1</sup>, Elsabaawy DM<sup>2</sup>, Mansour T<sup>3</sup> and Rewisha EA<sup>1</sup>

<sup>1</sup>Department of Hepatology, National Liver Institute, Menoufia University, Egypt

<sup>2</sup>Department of Clinical pharmacology, Faculty of pharmacy, Horus University, Egypt

<sup>3</sup>Internal Medicine Department, Ain Shams University, Egypt

### Abstract

In endemic areas for viral hepatitis; co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) mostly defined as co-positivity for HBs Ag and anti HCV antibodies is a quite known phenomenon. As a matter of fact; a liver cursed by dual HBV/HCV chronic infection represents a theatre for faster progression to cirrhosis and heightened cumulative HCC risk compared to mono infection status. Recently introduced interferon-free anti HCV treatments have earned extended attention. They have spacious tolerance and achieved viral suppression in more than 90% of cases. However, post-marketing safety concerns have emerged in parallel to the reports of direct-acting antiviral drugs (DAAs) relevant HBV reactivation. e years with predominance for male gender in middle age population and ranking third in place of the lipid etiology.

**Keywords:** HBV; HCV; DAAs; Reactivation

### Introduction

As HBV and HCV are mutual in their routes of transmission; co-infection, as well as superinfection, is frequent particularly in regions of viral hepatitis' endemicity and in populations prone to parenterally routed infections as intravenous drug addicts [1].

The prevalence of HCV/HBV co-infection has diverse geographical distributions and about 4 to 5 million people infected with HCV infection are having HBV coinfection [1]. A recent report from Egypt as an example of viral hepatitis endemic region; a prevalence of hepatitis B serological markers was 0.7% in a cohort of patients with chronic HCV infection [2]. In Turkey, co-infection has an intermediate prevalence of 2.6% [3]. An earlier report from India showed a prevalence of 26% for co HBV/HCV chronic liver disease [4]. In the USA, overt HBV co-infection had been found in 1.4% of HCV positive patients [5].

Indeed, testing for HBsAg alone underestimates the prevalence of this co-infection as a subset of HCV mono-infected patients have occult HBV infection with negative HBsAg and detectable HBV DNA[6]. Therefore, the true global estimates of this duplicate infection are still vague. Large-scale population-based studies are warranted to exactly define the true prevalence of co-infected patients.

HCV/HBV-related liver disease is a serious condition that unmistakably burdens the medical community and socioeconomic status. Most studies had documented the faster progression of chronic hepatitis to cirrhosis and severe disease in HCV/HBV co-infected patients in comparison to either the mono-infected alone [7]. Additionally, dual infection carries a profound risk for developing hepatocellular carcinoma with 10 years- a cumulative risk of 45% compared to 16% in HBV and 28% in HCV-mono-infected patients. Both viruses could have synergistic impact on the carcinogenic process [8].

### Co-infection, superinfection and viral interplay

Co-infection presenting as acute hepatitis had been described in few studies including a small number of patients [9]. The acute co-infection cases could culminate into the persistence of both viruses or in the most the burnout of HBV infection and the progression to HCV chronic liver disease [10]. Severe and fulminant hepatitis with the subsequent spontaneous clearance of both viruses had also been documented [11].

Super infection by HCV is quite common than by HBV in those having a chronic infection by either virus [12]. Serious complications as fulminant course and acute decompensation of cirrhosis are more evident in patients exposed to super infection compared to chronic mono-infected patients [13].

In an extended follow-up Italian study on the outcome of hepatitis C after HBV super infection; clearance of HBsAg had occurred at a higher rate than HCV clearance [14]. Also, HCV super infection in the setting of chronic hepatitis B had been reported to end by HBeAg seroconversion and in some by clearance of HBsAg along with persistent chronic hepatitis C [15]. Notably, dually infected patients had acquired both viruses as coinfection rather than superinfection on top of chronic infection [16].

Clinical studies mentioned divergent viral interaction in HBV/HCV coinfected patients, but in the most, it culminates into HCV dominance and suppression of HBV replication [17].

Stereotyping of the viremic pattern in the coinfected status is a prerequisite for proper management of dually infected patients. Raimondo et al. had described four viremic patterns; the no viral dominance as both viruses are below the predefined cut-off (HCV: 15 IU/mL and HBV 2000 IU/ml), the HBV, and both viruses dominance patterns, and in the majority; the HCV dominance pattern [18]. Nevertheless, dynamic fluctuations in HBV and HCV viremia in one-third of cases had been notified [19].

Yet, the long-term observation of HCV predominance has not been entirely justified. *In vitro* studies revealed that in HCV chronic infection in chimpanzees, the HBV replication capacity was found to be limited [20]. Also, in HBV chronically infected chimpanzees;

**\*Corresponding author:** Maha Elsabaawy, Department of Hepatology, National Liver Institute, Menoufia University, Egypt, E-mail: [maha.ahmed@liver.menofia.edu.eg](mailto:maha.ahmed@liver.menofia.edu.eg)

**Received** February 06, 2017; **Accepted** March 24, 2017; **Published** March 30, 2017

**Citation:** Alhaddad OM, Elsabaawy MM, Elshaarawy O, Elsabaawy DM, Mansour T, et al. (2017) Interferon-Free Hepatitis C Virus Treatments and the Story of HBV Reactivation. *Hepatol Pancreat Sci* 1: 107.

**Copyright:** © 2017 Alhaddad OM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

HCV super infection had reduced HBV gene expression [21]. HCV infection strongly enhances expression of type 1 interferon stimulated genes. While HCV can maintain its chronicity in face of endogenous interferons, HBV replication undergoes significant attenuation [22].

Other clinical studies had shown a predominant effect of HBV. A recent research conducted on 1049 IVDUs, found HBV/HCV co infection in 42 patients whereas single HCV infection was found in 340 and single HBV infection in 136 patients. This research showed the dominance of HBV viremia in the coinfection status and the authors concluded that HCV is acquired at a later age when most of the hepatocytes are already loaded with perinatal transmitted HBV, leaving a small number of uninfected cells for HCV [16].

To date, no comprehensive data about the interplay between HBV and HCV in co-infected individuals. Of importance, in a model cell line system; Huh-7 cell lines harbouring HBV and HCV, replication of one virus didn't impact replication and gene expression of the other one [23]. This finding argued against the long-lived theory of viral interference and suggested that suppression of one or both viruses might be indirectly related to host factors.

### The story of HBV reactivation

HBV reactivation is a flare of hepatitis initiated by viral breakthrough, reflected as biochemical relapse in a previously HBV-resolved infection or chronic carrier status [24].

Clinical outlines of HBV reactivation include spontaneous and drug-induced settings. Spontaneous HBV reactivation is the commonest and occupies an influential part of the natural history of chronic HBV monoinfected. About 20 to 30% of inactive HBV carriers can develop asymptomatic or acute hepatitis-like spontaneous reactivation. Recurrent and sustained spontaneous reactivations eventually end with advanced disease [25].

The potential risk of HBV reactivation had been long described on oncohaematological and transplant patients receiving cytotoxic and immunosuppressive agents [26]. The list of drugs which are incriminated in HBV reactivation in silent carriers is constantly expanding. They include chemotherapeutic agents and glucocorticoids, as well as biologic agents (e.g., anti-CD 20 agents, anti-TNF agents), and new classes of drugs, such as tyrosine kinase inhibitors and mechanistic target of rapamycin (mTOR)-inhibitors [26,27].

The resurgence of HBV infection had been also acknowledged in reference to HCV cure induced by interferon-based regimen in those having markers of HCV/HBV co-infection [28].

Potthoff et al. reported HBV reactivation at a rate of 37-46% during 48 weeks after interferon induced HCV eradication in HCV/HBV co-infected patients [28]. Lui et al. had reported similar results in their 4-year follow-up study as they noted significantly higher HBV reactivation rates in interferon treated patients who achieved sustained virological response (SVR) compared to those who did not [29]. Of note, severe or fulminant reactivations were uncommon and intriguingly HBsAg clearance was noted at an annual rate of 5% in coinfecting patients treated with interferon [30]. In fact, the reported HBsAg seroclearance rates induced by interferon alpha were much higher than the nucleos(t)ides [31].

The advent of all oral directly acting antiviral drugs has been colossally improved the best of care of chronic hepatitis C patients with virological response rates more than 90% [32]. Registration studies of these IFN free regimens had excluded HBV/HCV co infected patients;

viral interference had been assumed to impact the efficacy of the new drugs and might interfere with the evaluation process [33].

However, soon after the global celebration of their spectacular results; case reports and short case series of HBV reactivation in reference to prompt HCV elimination by these new antivirals have come to the fore [34-39]. Ende et al. reported the first case of DAAs related HBV reactivation. The case was HCV genotype1 only HbC IgG positive, she received sofosbuvir, simeprevir plus ribavirin and presented near the end of 12 weeks course by fulminant hepatitis, exceedingly high HBV DNA levels and negative HCV RNA. She required urgent transplantation beside treatment with tenofovir [34].

Shortly after, Takayama et al. published the second report of HBV reactivation in a 69-year-old gentleman who was viremic for both HCV and HBV but received asunaprevir and daclatasvir. The HBV-related viremia was heightened during treatment with a progressive rise in liver enzymes. Asunaprevir and daclatasvir were stopped with the initiation of entecavir followed by improved liver enzymes and reduced HBV DNA levels [35]. Concomitantly, was the report released by Collins and his colleagues; they exemplified two cases of HBV reactivation on a background of cirrhosis. HBV DNA was less than 2000 IU/ml in the first case with only HbC IgG positive in the second case [36].

The report of De Monte et al. was the premiere of HBV prompt reactivation during sofosbuvir and ledipasvir therapy for a patient with resolved HBV and HIV/HCV genotype 4 chronic liver diseases [37]. Recently, Hayashi et al. had published a different report of HBV reactivation 5 months after the end of DAAs. The patient was 83-year-old lady with baseline negative HBs Ag and received daclatasvir and asunaprevir [38].

A large Chinese observational study had examined hepatitis occurrence in an HBV-endemic area among 327 chronic HCV patients treated with different DAAs regimens. They had specified three cases of HBV reactivation among the ten patients who developed hepatitis. Baseline positive HBs antigen was substantiated to be a powerful risk factor predicting HBV reactivation [39].

The FDA Adverse Event Reporting System (FAERS) had identified 24 cases of HBV reactivation in coinfecting patients in reference to DAAs therapy during 31 months from 2013 to 2016; either published or FDA reported. Diverse clinical presentations, with no specified genotype or DAAs regimen, positive as well as negative status for HBs Ag and HBV DNA and early reactivation even during treatment were the mutual criteria [40].

Doubts have been transferred into facts as in October 2016; the FDA added black box warning to labels of the six approved DAAs considering HBV reactivation as an adverse event following DAAs therapies in HCV/HBV co-infected patients [41]. Then after, the FDA recommends testing all people for evidence of current or prior HBV before beginning HCV treatment and monitoring patients for reactivation both during treatment with DAAs and afterwards.

Likely, were the recommendations of the American association for the study of liver diseases (AASLD) and infectious diseases society of America (IDSA) for those having active HBV infection should start anti-HBV therapy before or at the same time with DAAs [41,42]. Basically, the recommended HBV screening before commencing DAAs therapy should not be limited to HBsAg, but extended to HBs Antibody along with HbC IgG [42].

In fact, liver societies believe that HBV re-expression is the payoff of the HCV' cure and not at all DAAs related toxicity. The dominance

of HCV in co HBV/HCV status would probably be mediated by host immune responses that keep HBV gene expression and replication under control leaving the upper hand for the HCV [43]. In a consequence, DAAs induced HCV elimination might disturb such immune control and permit for the resurgence of HBV expression. Another explanation might involve the decline in the circulating interferon gamma-induced protein 10 (IP-10) levels following DAAs therapy. These proteins, responsible for enhanced expression of the intrahepatic interferon stimulated genes, were found to be existing in higher levels in coinfecting cases with HCV predominance, hypothetically permitting reactivation of HBV [44]. The prospect that HCV cleared hepatocytes might give additional space for HBV replication in coinfecting liver could be faced by strong interrogations. In chronic HCV infection; not all hepatocytes are infected and the infection tend to occur in clusters with only 21% to 45% HCV RNA hepatocytes [45]. In a similar fashion, the percentage of HBV infected hepatocytes has an estimate of 21 to 27% [45]. Hence, the huge number of the hepatocytes can be a spacious seat for both HCV and HBV.

## Conclusion

In conclusion, the rates of HBV reactivation in relevance to DAAs and the actual underlying pathogenic mechanisms have not yet been defined. Therefore, a collaborative orientation and work up should be exerted by the authorities, physicians as well as patients in this prospect. In accordance with the FDA and latest international guidelines for those having no HBV viremia but a positive HBsAg and or HB c IgG antibodies; frequent monitoring during and after DAAs treatment is essential. Patient's awareness of any clinical heterogeneity during the course of DAAs therapy must be promptly assessed.

## Conflict of interest

There is no conflict of interest to any of authors.

## Financial support

No financial support to be reported.

## References

1. Kerubo G, Khamadi S, Okoth V, Madise N, Ezech A, et al. (2015) Hepatitis B, Hepatitis C and HIV-1 Coinfection in Two Informal Urban Settlements in Nairobi, Kenya. *PLoS ONE* 10: e0129247.
2. Mekky MA, Nasr AM, Saleh MA, Nasr KW, Marwa K, et al. (2013) Virologic and histologic characterization of dual hepatitis B and C co-infection in Egyptian patients. *Arab J Gastroenterol* 14: 143-147.
3. Anbazhagan G, Krishnamoorthy S, Thiyagarajan T (2010) Seroprevalence of HCV and its co-infection with HBV and HIV among liver disease patients of South Tamil Nadu. *World J Hepatol* 272: 42-48.
4. Chakravarti A, Verma V, Jain M, Kar P (2005) Characteristics of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. *Trop Gastroenterol* 26: 183-187.
5. Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, et al. (2013) Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. *Hepatology* 58: 538-545.
6. Senturk H, Tahan V, Canbakan B, Dane F, Ulger Y, et al. (2008) Clinicopathologic features of dual chronic hepatitis B and C infection: a comparison with single hepatitis B, C and delta infections. *Ann Hepatol* 7: 52-58.
7. Konstantinou D, Deutsch M (2015) The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions, and management. *Ann Gastroenterol* 28: 221-228.
8. Liu CJ, Chu YT, Shau WY, Kuo RN, Chen PJ, et al. (2014) Treatment of patients with dual hepatitis C and B by peginterferon and ribavirin reduced the risk of hepatocellular carcinoma and mortality. *Gut* 63: 506-514.
9. Wu JC, Chen CL, Hou MC, Chen TZ, Lee SD, et al. (1994) Multiple viral infections as the most common cause of fulminant and subfulminant viral hepatitis in an area endemic for hepatitis B: application and limitations of the polymerase chain reaction. *Hepatology* 19: 836-840.
10. Feray C, Gigou M, Samuel D, Reyes G, Bernuau J, et al. (1993) Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. *Gastroenterology* 104: 549-555.
11. Sato S, Fujiyama S, Tanaka M, Yamasaki K, Kuramoto I, et al. (1994) Co-infection with hepatitis C virus in patients with chronic hepatitis B infection. *J Hepatol* 21: 159-166.
12. Jardi R, Rodriguez F, Buti M, Costa X, Cotrina M, et al. (2001) Rule of hepatitis B, C and D viruses in dual and triple infection: influence of viral genotypes and hepatitis B per core and basal core promoter mutations on viral replicative interference. *Hepatology* 34: 404-10.
13. Sangelli E, Coppola N, Pisaturo M, Masiello A, Tonziello G, et al. (2009) HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. *Hepatology* 49: 1090-1097.
14. Pontisso P, Ruvoletto MG, Fattovich G, Chemello L, Gallorini A, et al. (1993) Clinical and virological profiles in patients with multiple hepatitis virus infections. *Gastroenterology* 105: 1529-1533.
15. Ohkawa K, Hayashi N, Yuki N, Hagiwara H, Kato M, et al. (1994) Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients. *J Hepatol* 21: 509-514.
16. Chen F, Zhang J, Wen B, Shan Luo, Yingbiao Lin, et al. (2016) HBV/HCV dual infection impacts viral load, antibody response, and cytokine expression differently from HBV or HCV single infection. *Sci Rep* 6: 39409.
17. Shih CM, Lo SJ, Miyamura T, S Y Chen, Y H Lee (1993) Suppression of hepatitis B virus expression and replication by hepatitis C virus core protein in Hu-H7 cells. *J Virol* 67: 5823-5832.
18. Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, et al. (2006) Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfecting patients. *Hepatology* 43: 100-107.
19. Murray JM, Stancevic O, Lütgehetmann M, Wursthorn K, Petersen J, et al. (2016) Variability in long-term hepatitis B virus dynamics under antiviral therapy. *J Theor Biol* 391: 74-80.
20. Bradley DW, Maynard JE, McCaustland KA, Murphy BL, Cook EH, et al. (1983) Non-A, non-B hepatitis in chimpanzees: interference with acute hepatitis A virus and chronic hepatitis B virus infections. *J Med Virol* 11: 207-213.
21. Wieland SF, Asabe S, Engle RE, Purcell RH, Chisari FV (2014) Limited hepatitis B virus replication space in the chronically hepatitis C virus-infected liver. *J virol* 88: 5184-5188.
22. Schuttler C, Fiedler N, Schmidt K, Repp R, Gerlich WH, et al. (2002) Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein. *J Hepatol* 37: 855-862.
23. Bellecave P, Gouttenoire J, Gajer M, Brass V, Koutsoudakis G, et al. (2009) Hepatitis B and C virus co-infection: a novel model system reveals the absence of direct viral interference. *Hepatology* 50: 46-55.
24. Kim H, Kim W (2014) Chemotherapy-related reactivation of hepatitis B infection: Updates in 2013. *World J Gastroenterol* 2820: 14581-14588.
25. Bellentani S, Dal Molin G, Miglioli L, Croce LS, Masutti F, et al. (2002) Natural history of HBV infection: a 9 years follow-up of the Dionysos cohort. *J Hepatol* 36: 228.
26. Wahlea R, Perezb R, Pereira P, Oliveira EM, Emori CT, et al. (2015) Hepatitis B virus reactivation after treatment for hepatitis C in hemodialysis patients with HBV/HCV co-infection. *Braz J Infect Dis* 19: 533-537.
27. Rossi G, Pelizzari A, Motta M, Puoti M (2001) Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HBsAg carriers with lymphoid malignancies treated with chemotherapy. *Br J Hematol* 115: 58-62.
28. Potthoff A, Berg T, Wedemeyer (2009) 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- $\alpha$ 2b and ribavirin. *Scand J Gastroenterol* 44: 1487-1490.
29. Liu CJ, Chuang WL, Lee CM, Yu ML, Lu SN, et al. (2009) An open-label, comparative, multicentre study of peginterferon alfa-2a plus ribavirin in the treatment of patients with chronic hepatitis C/hepatitis B co-infection versus those with chronic hepatitis C mono-infected. *Gastroenterology* 136: 496-504.

30. Azmi A, Tan S, Mohamed R (2014) Practical approach in hepatitis B e antigen-negative individuals to identify treatment candidates. *World J Gastroenterol* 20: 12045–12055.
31. Liaw YF (2009) HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. *Hepatol Int* 3: 425-433.
32. Adinolfi L, Guerrera B (2015) All-oral interferon-free treatments: The end of hepatitis C virus story, the dream, and the reality. *World J Hepatol* 7: 2363–2368.
33. Ording A, Cronin-Fenton D, Ehrenstein V, Lash TL, Acquavella J, et al. (2016) Challenges in translating endpoints from trials to observational cohort studies in oncology. *Clin Epidemiol* 8: 195–200.
34. Ende AR, Kim NH, Yeh MM, Harper J, Landis CS (2015) 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* 9: 164.
35. Takayama H, Sato T, Ikeda F, Fujiki S (2015) Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in a patient with HBV/HCV co-infection. *Hepatol Res* 46: 489-491.
36. Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, et al. (2015) Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis* 61: 1304-1306.
37. De Monte A, Courjon J, Anty R, Cua E, Naqvi A, et al. (2016) Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol* 78: 27-30.
38. Hayashi K, Ishigami M, Ishizu Y, Kuzuya T, Honda T, et al. (2016) 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* 9: 252-256.
39. Wang C, Ji D, Chen J, Shao Q, Li B, et al. (2016) 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* S1542-3565: 30370-30376.
40. Bersoff-Matcha S, Cao K, Jason M, Ajao A, Jones SC, et al. (2016) Hepatitis B Reactivation Associated with Direct Acting Antiviral Therapy for Hepatitis C: A Review of Spontaneous Post-Marketing Cases. *J Hepatol* LB-17: 1130A.
41. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, et al. (2016) AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 63: 261–283.
42. (2015) AASLD-IDSA recommendations for testing, managing and treating adults infected with hepatitis C virus. *Hepatology* 62: 932-954.
43. Ryan E, Hollingworth R, Grand R (2016) Activation of the DNA Damage Response by RNA Viruses. *Biomolecules* 6: 223-234.
44. Lin JC, Habersetzer F, Rodriguez-Torres M, Afdhal N, Lawitz EJ, et al. (2014) Interferon gamma-induced protein 10 kinetics in treatment-naive versus treatment-experienced patients receiving interferon-free therapy for hepatitis C virus infection: implications for the innate immune response. *J Infect Dis* 210: 1881–1885.
45. Sheahan T, Rice C (2013) Single cell analysis of HCV infected patient hepatocytes: The science is no longer science fiction. *Gastroenterology* 145: 10.

**Citation:** Alhaddad OM, Elsabaawy MM, Elshaarawy O, Elsabaawy DM, Mansour T, et al. (2017) Interferon-Free Hepatitis C Virus Treatments and the Story of HBV Reactivation. *Hepatol Pancreat Sci* 1: 107.