



The Brazilian Journal of INFECTIOUS DISEASES

www.elsevier.com/locate/bjid



Brief communication

Hepatitis B virus reactivation after treatment for hepatitis C in hemodialysis patients with HBV/HCV coinfection



Raul Carlos Wahle^{a,*}, Renata Mello Perez^b, Patrícia Fucuta Pereira^a,
Elze Maria Gomes Oliveira^a, Christini Takemi Emori^a,
Silvia Naomi de Oliveira Uehara^a, Ivonete Sandra de Souza Silva^a,
Antônio Eduardo Benedito Silva^a, Maria Lucia Gomes Ferraz^a

^a Discipline of Gastroenterology, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil

^b Department of Internal Medicine, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:

Received 23 December 2014

Accepted 17 April 2015

Available online 18 May 2015

Keywords:

Coinfection HBV/HCV

Reactivation HBV

Hemodialysis

ABSTRACT

In coinfecting HBV/HCV patients, HBV replication is usually suppressed by HCV over the time. No study to date has evaluated the HBV viremia in long-term follow-up after HCV treatment in hemodialysis patients with HBV/HCV coinfection. This study aimed to assess the evolution of HBV viremia after HCV treatment in this special population. Ten hemodialysis patients with HBV/HCV coinfection with dominant HCV infection (HBV lower than 2000 IU/mL) and significant fibrosis were treated with interferon-alpha 3 MU 3×/week for 12 months and could be followed for at least 36 months after HCV treatment. Six cases of HBV reactivation (60%) during follow-up were observed and 5/6 had been successfully treated for HCV. Patients with HBV reactivation received anti-HBV therapy. Our preliminary findings indicate that treatment of hepatitis C in HBV/HCV coinfecting hemodialysis patients may favor HBV reactivation. Thus, continued monitoring of HBV viremia must be recommended and prompt anti-HBV therapy should be implemented.

© 2015 Elsevier Editora Ltda. All rights reserved.

Hepatitis C virus (HCV) coinfection occurs in 7–15% of patients with chronic HBV infection. It is more frequent in intravenous drug users, in endemic areas of HBV, and in hemodialysis patients.¹ Although chronic HBV infection in patients on dialysis is usually asymptomatic and indolent, HBsAg positivity is an independent risk factor for renal graft failure after kidney transplantation.^{2,3} Moreover, most studies show higher

mortality in renal transplant recipients infected with HBV, compared with renal transplant recipients without hepatitis B virus (HBV) infection.

In HBV/HCV coinfecting patients, HBV replication is usually suppressed by HCV. Nevertheless, in many cases, a dynamic viral interference between HBV and HCV does exist and viral levels of both viruses may vary during follow-up.⁴ In patients

* Corresponding author at: Rua Martiniano de Carvalho, 905, 013210-000 São Paulo, SP, Brazil.

E-mail address: wahle@uol.com.br (R.C. Wahle).

<http://dx.doi.org/10.1016/j.bjid.2015.04.003>

1413-8670/© 2015 Elsevier Editora Ltda. All rights reserved.

Table 1 – Demographic, clinical and laboratory characteristics of patients at baseline and during follow-up.

	Total (n = 10)	HBV reactivation (n = 6)	No HBV reactivation (n = 4)
Age, years, mean ± SD	40 ± 10	44 ± 9	37 ± 9
Mean time of follow-up, months	40	43	38
Mean time of HBV reactivation, months, mean ± SD	–	22 ± 9	–
Male gender, n/%	6/60%	4/67%	2/50%
Advanced fibrosis (F ≥ 3)	2/20%	0	2/50%
Anti-HBe (+) at HCV EOT, n/%	8/80%	5/83%	3/75%
Loss of HBsAg, n/%	0	0	0
Undetectable HBV-DNA at HCV EOT, n/%	10/100%	6/100%	4/100%
SVR HCV, n/%	7/70%	5/83%	2/50%

Abbreviation: SD, standard deviation; SVR, sustained virologic response; EOT, end of treatment.

with undetectable HBV-DNA, treatment for hepatitis C may cause reactivation of HBV replication, as has been reported in several patients, reaching 61.8% in the latest study with pegylated-IFN and ribavirin in non-uremic patients.⁵ To the best of our knowledge, there is no data regarding long-term follow-up after treatment for HCV in hemodialysis patients with HBV/HCV coinfection. Therefore, this study aimed to assess the evolution of HBV viremia after treatment of hepatitis C in hemodialysis patients with HBV/HCV coinfection.

A retrospective analysis of HBV viremia was performed in a cohort of patients on hemodialysis with HBV/HCV coinfection treated for hepatitis C. We included HBV/HCV coinfecting patients with dominant HCV infection (HBV lower than 2000 IU/mL) that had been treated with interferon-alpha 3 MU 3×/week for 12 months at the Hepatitis Unit of Federal University of São Paulo from January 1999 to December 2010.

At the end of HCV treatment the patients with no significant HBV viremia could be followed for at least three years

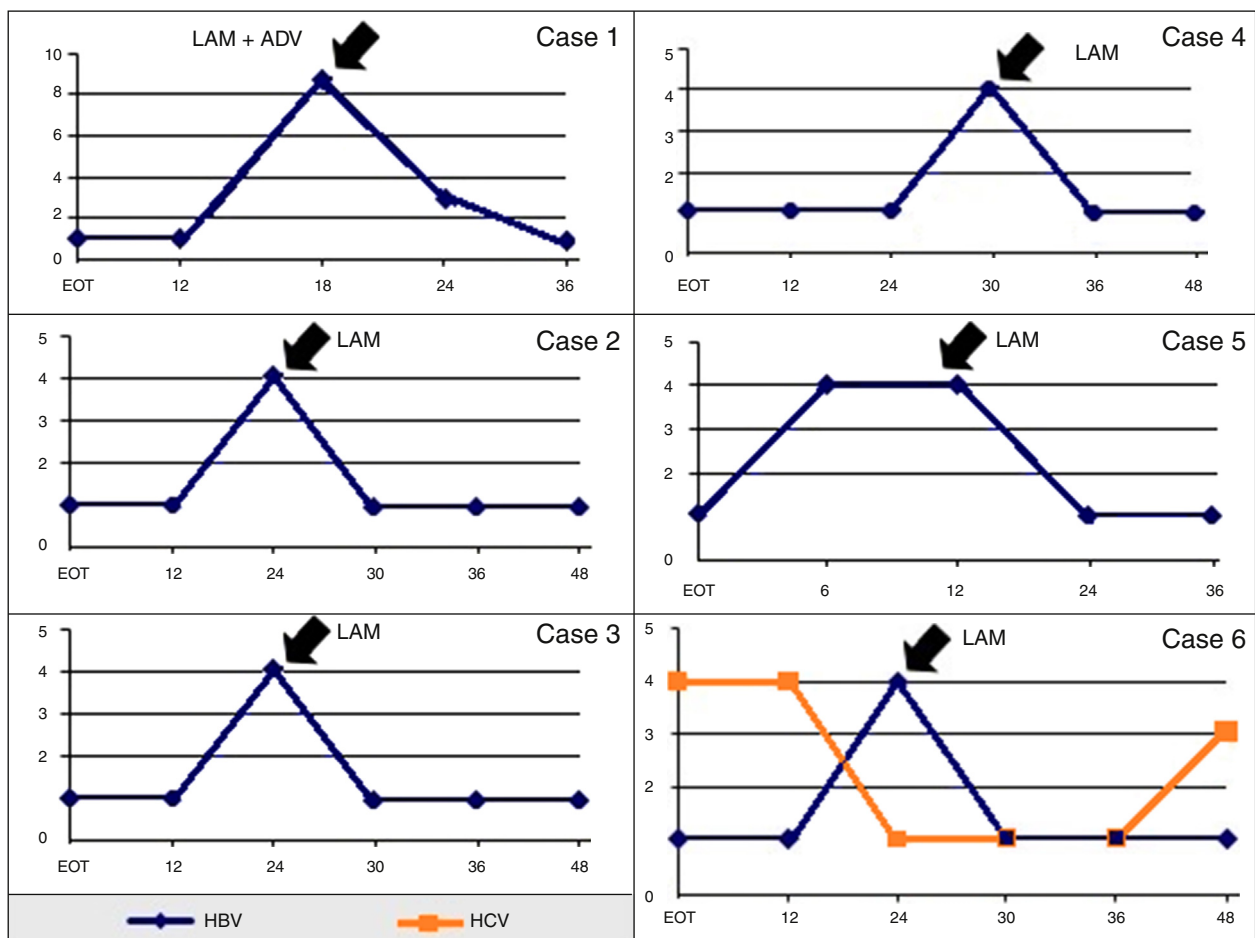


Fig. 1 – Profiles of serum HCV-RNA and HBV-DNA in six patients with HBV reactivation during follow-up after HCV treatment in months. HCV-RNA and HBV-DNA levels are expressed as log₁₀ IU/mL and lower limit of detection of both tests are 50 IU/mL. Abbreviation: EOT, end of hepatitis C treatment; LAM, lamivudine; ADV, adefovir.

Table 2 – Virological characteristics before HCV treatment, follow-up at month 6 and most recent follow-up.

No.	Before HCV treatment					Follow-up month 6				Most recent follow-up			HBV treatment
	HBeAg status	HBV-DNA (IU/mL)	HBV-GT	HCV-DNA (IU/mL)	HCV-GT	HBeAg Status	HBV-DNA (IU/mL)	HCV-DNA (IU/mL)	Follow-up (months)	HBeAg Status	HBV-DNA (IU/mL)	HCV-DNA (IU/mL)	
1	–	1771	D	+	1A	–	Neg.	Neg.	48	–	Neg.	Neg.	LAM
2	–	Neg.	–	255	1A	–	Neg.	+	48	–	Neg.	+	LAM
3	–	250	D	+	1A	–	Neg.	+	36	–	Neg.	+	–
4	–	Neg.	A2	+	–	–	2061	Neg.	36	–	Neg.	Neg.	LAM
5	–	1409	D	134	–	–	Neg.	Neg.	40	–	Neg.	Neg.	LAM + ADV
6	–	Neg.	–	+	–	–	Neg.	+	44	–	Neg.	+	–
7	–	1306	D	36,672	1A	–	964	Neg.	36	–	Neg.	Neg.	–
8	–	167	D	+	–	–	Neg.	Neg.	48	–	Neg.	Neg.	LAM
9	–	Neg.	–	+	–	–	Neg.	Neg.	36	–	Neg.	Neg.	–
10	–	Neg.	–	+	1A	–	Neg.	Neg.	36	–	Neg.	Neg.	LAM

Abbreviation: GT, genotype; LAM, lamivudine; ADV, adefovir.

in order to assess HBV reactivation. Patients with significant HBV viremia at the end of HCV treatment or with early HBV reactivation during HCV treatment were excluded from further follow-up.

Serum markers HBsAg, HBeAg and anti-HCV were assayed using commercially available enzyme immunoassay kits (Abbott Laboratories, USA).

HBV viral load were performed every three months during follow-up. Serum HCV-RNA was determined at the end of treatment and six months after stopping therapy to evaluate sustained virologic response (SVR) to HCV therapy and determined annually thereafter.

Serum HBV-DNA was quantified by real-time PCR with a lower detection limit of 50 IU/mL and HBV genotypes were determined using a line probe assay (INNo-LiPA HBV Genotyping, Innogenetics NV, Belgium). Serum HCV-RNA was detected with an HCV RNA qualitative assay (Cobas Amplicor 2.0, Roche Diagnostics, Basel, Switzerland) with a lower detection limit of 50 IU/mL. HCV Genotyping was performed using a line probe assay (INNo-LiPA HCV II, Innogenetics NV, Belgium).

All patients gave a written informed consent prior to liver biopsy and/or IFN treatment. This study protocol was submitted to local Ethics Committees and followed all of the ethical premises of the Helsinki Declaration.

Herein we report long-term follow-up data of 10 HBV/HCV coinfecting patients on hemodialysis that could be followed for at least three years after HCV therapy. Baseline clinical and laboratorial characteristics are shown in Table 1. During the follow-up period, 6/10 patients showed HBV reactivation (60%) 22 ± 9 months after the end of HCV treatment and only one case of early reactivation (within the first six months of follow-up) was observed (Table 2). Characteristics of HBV viremia over time in the six cases of HBV reactivation are shown in Fig. 1. In the only case of HBV reactivation without SVR for HCV therapy, a dynamic viral interaction was observed during follow-up (case #6). At first, there was active HCV infection and HBV-DNA was undetectable at the end on HCV treatment; 24 months later, occurred reactivation of HBV infection and HCV-RNA became negative. After introduction of lamivudine for HBV treatment there was a sustained suppression of HBV viral load and reappearance of HCV-RNA.

No case of HBsAg loss was observed during the follow-up period. In our series, all six cases with significant elevation of HBV viremia were treated promptly regardless of ALT elevation considering that all patients had significant fibrosis at baseline and most of them were already listed for kidney transplantation. In five patients treatment was initiated with lamivudine 10 mg/day since at that time entecavir or tenofovir were not available yet. One patient with very high viral load used lamivudine 10 mg/day plus adefovir 10 mg/week, to reduce the chance of virologic breakthrough. There were no fatal cases due to HBV reactivation and the six patients were released for renal transplantation with undetectable HBV viremia while maintaining continued use of oral antiviral treatment.

This is the first report of HBV reactivation after HCV treatment in coinfecting HBV/HCV hemodialysis patients. Our study showed a similar rate of HBV reactivation as recently reported by Yu et al., in a cohort of 76 non-uremic coinfecting patients, with pretreatment undetectable HBV-DNA.⁵ In that study,

reappearance of HBV-DNA was found in 47 (61.8%) patients that occurred either during the course of treatment (38.3%) or during post-treatment follow-up (61.7%). Other studies in non-uremic patients also reported a frequent rate of HBV reactivation after HCV treatment, with rates varying from 15.4% to 100%.⁶⁻¹¹

In our study, we also observed that HBV reactivation occurred more frequently in patients who had been successfully treated for HCV. Two Asian studies also observed that HBV reactivation rate was significantly higher among those who achieved HCV SVR (44.8 and 33.3%) compared to those without HCV SVR (8.7 and 8.3%).^{7,11} According to a recent meta-analysis by Liu et al. the risk of reappearance of HBV-DNA in coinfecting HBV/HCV patients was three times higher in those who achieved HCV SVR ($p = 0.009$).¹²

Despite of reappearance of HBV after HCV treatment, it has not resulted in clinically evident hepatitis. Other studies in non-uremic patients also observed the same finding and spontaneous resolution of HBV viremia seems to be frequent.^{13,14} In the Asian cohort of 76 patients, this phenomenon was transient in 44.7%, intermittent in 25.5% and sustained in 29.8%.⁵ The impact of the HBV reactivation in the setting of end-stage renal disease may have an unfavorable outcome, considering that these patients have an impaired immune system, affecting both acquired as well as innate immunity.^{15,16} Thus, reactivation of HBV in this population may lead to greater chance of developing chronic liver disease before renal transplant, and hepatic decompensation after renal transplantation with the use of immunosuppressive therapy.¹⁷

Due to the scarcity of data so far, the significance of HBV reappearance after effective treatment of HCV in patients with chronic HBV/HCV coinfection in uremic patients requires further analysis. Up to now, treatment with oral nucleosides/nucleotides in patients under hemodialysis should be started in cases of HBV-DNA >2000 IU/mL, regardless of ALT activity especially if they have significant fibrosis on liver biopsy or estimated by a non-invasive marker.¹⁸

In conclusion, our data showed that in HBV/HCV coinfecting hemodialysis patients reactivation of HBV infection is a frequent phenomenon after treatment of hepatitis C. Continued monitoring of HBV viremia must be recommended for these patients in order to establish early antiviral treatment, especially in patients who are candidates for renal transplantation. Based on this evidence, transplant physicians should be aware of the risk of HBV reactivation in coinfecting patients especially when HCV has been eradicated before renal transplantation.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Rapti IN, Hadziyannis SJ. Treatment of special populations with chronic hepatitis B infection. *Expert Rev Gastroenterol Hepatol.* 2011;5:323-39.

2. Fabrizi F, Messa P, Basile C, et al. Hepatic disorders in chronic kidney disease. *Nat Rev Nephrol.* 2010;6:395-403.
3. Fabrizi F, Martin P, Dixit VF, et al. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant.* 2005;5:2913-21.
4. Raimondo G, Brunetto MR, Pontisso P, et al. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus co-infected patients. *Hepatology.* 2006;43:100-7.
5. Yu ML, Lee CM, Chen CL, et al. Sustained HCV clearance and increased HBsAg seroclearance in patients with dual chronic hepatitis C and B during post-treatment follow-up. *Hepatology.* 2013;57:2135-42.
6. Liu CJ, Chen PJ, Lai MY, et al. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. *Hepatology.* 2003;37:568-76.
7. Chuang WL, Dai CY, Chang WY, et al. Viral interaction and responses in chronic hepatitis C and B coinfecting patients with interferon-alpha plus ribavirin combination therapy. *Antivir Ther.* 2005;10:125-33.
8. Hung CH, Lee CM, Lu SN, et al. Combination therapy with interferon-alpha and ribavirin in patients with dual hepatitis B and hepatitis C virus infection. *J Gastroenterol Hepatol.* 2005;20:727-32.
9. Kim YJ, Lee JW, Kim YS, et al. Clinical features and treatment efficacy of peginterferon alfa plus ribavirin in chronic hepatitis C patients coinfecting with hepatitis B virus. *Korean J Hepatol.* 2011;17:199-205.
10. 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.
11. Yu JW, Sun LJ, Zhao YH, et al. Analysis of the efficacy of treatment with peginterferon alpha-2a and ribavirin in patients coinfecting with hepatitis B virus and hepatitis C virus. *Liver Int.* 2009;29:1485-93.
12. Liu JY, Sheng YJ, Hu HD, et al. The influence of hepatitis B virus on antiviral treatment with interferon and ribavirin in Asian patients with hepatitis C virus/hepatitis B virus coinfection: a meta-analysis. *Virology.* 2012;9:186.
13. Potthoff A, Berg T, Wedemeyer H. 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;44:1487-90.
14. Gordon SC, Sherman KE. Treatment of HBV/HCV coinfection: releasing the enemy within. *Gastroenterology.* 2009;136:393-6.
15. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol.* 2008;3:1526-33.
16. Vaziri ND, Pahl MV, Crum A, et al. Effect of uremia on structure and function of immune system. *J Ren Nutr.* 2012;22:149-56.
17. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57:167-85.
18. Pipili C, Cholongitas E, Papatheodoridis G. Review article: nucleos(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease. *Aliment Pharmacol Ther.* 2014;39:35-46.