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Chronic hepatitis C responds poorly to combination therapy in chronic hepatitis B carriers

H. Senturk[1], V. Tahan[2*], B. Canbakan[1], S. Uraz[3], Y. Ulger[1], R. Ozaras[4], F. Tabak[4], A. Mert[4], G. Ozbay[5]

Departments of [1]Gastroenterology, [4]Infectious Diseases and [5]Pathology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, [2]Department of Gastroenterology, Marmara University School of Medicine, Altunizade, Uskudar, 34662 Istanbul, Turkey, [3]Department of Gastroenterology, Florence Nightingale Hospital, Istanbul, Turkey, [*]corresponding author: tel.: +90 216-326 70 73, e-mail: veytahan@yahoo.com

ABSTRACT

Background: The effect of conventional interferon-based therapy of hepatitis B virus (HBV) and hepatitis C virus (HCV) dual infection is controversial. Yet, no studies have been carried out into pegylated interferon treatment for chronic HBV/HCV coinfection. We aimed to evaluate the response rate and side effects of conventional or pegylated interferon combined with ribavirin on chronic HBV/HCV coinfection therapy.

Methods: The study included 36 chronic hepatitis patients (M/F: 28/8, mean age 47±12 years) who were positive for HBsAg and anti-HCV. They were tested for the presence of HBV-DNA by hybridisation assay, and the samples giving negative results were retested by polymerase chain reaction (PCR). All patients were tested for HCV-RNA using PCR, and the HCV genotype was determined.

Results: Nineteen patients were given standard interferon either alone or in combination with ribavirin, whereas 17 were given pegylated interferon and ribavirin combination therapy. None of the patients had HBV-DNA positivity; however, all had HCV-RNA detectable by PCR. All the patients had HCV genotype 1b. The mean alanine aminotransferase and aspartate aminotransferase levels were 118±65 U/l and 90±95 U/l respectively. Five patients in each group discontinued the treatment due to side effects. Only two patients (one from each group) reached sustained virological response.

Conclusion: Neither pegylated nor conventional interferon based regimes were effective for HBV/HCV coinfection, in which the dominant virus was HCV. Pegylated interferon and ribavirin therapy was not superior to conventional interferon based regimes in the treatment of HBV/HCV coinfection.

KEYWORDS

Chronic hepatitis B, chronic hepatitis C, co-infection, dual infection, pegylated interferon

INTRODUCTION

It is estimated that throughout the world 400 million people are chronically infected with hepatitis B virus (HBV), and 170 million people with hepatitis C virus (HCV).[1,2] Dual infection with HBV and HCV in the same host ranges from 1 to 15%.[3-9] It has been suggested that the actual prevalence of dual infection is much higher in regions where HBV is moderately to highly endemic. There, HBV-DNA can be detected in serum and/or liver tissue in a large proportion of patients with chronic HCV, even in those who are HBsAg negative.[10-12] The literature contains conflicting data on the prognosis of HBV/HCV dual infection. Whereas several studies report that dual infection leads to a more severe histological picture and more rapid progression to cirrhosis,[4-6,13] other studies do not support these findings.[14,15] There are also limited data regarding treatment, since dual infection is an exclusion criterion in all HBV or HCV treatment studies. A few trials indicate that the success rate of interferon monotherapy is very low.[9,16,17] On the other hand, another study in HBV-HCV dual-infected patients reported promising results with interferon-ribavirin combination therapy.[18]

Peginterferon plus ribavirin has yielded higher sustained virological response (SVR) rates compared with conventional interferon plus ribavirin for all genotypes

of chronic HCV monoinfection[19] and is now considered the gold standard of care.[20] However, a study of pegylated interferon treatment for chronic HBV/HCV dual infection is lacking. So far, there has been only one reported case in which a successful therapy response was achieved for both HBV and HCV in dual-infection chronic hepatitis.[21] To the best of our knowledge, our study is the first comprehensive study to evaluate the response rate and side effects of pegylated interferon treatment of chronic HBV/HCV dual infection.

PATIENTS AND METHODS

Patients with chronic HBV/HCV dual infection seen between January 1991 and February 2006 at the Department of Gastroenterology, Cerrahpasa Medical Faculty, University of Istanbul were considered for inclusion. Patients who had acute hepatitis, decompensated cirrhosis or hepatocellular carcinoma were excluded from the study. A total of 1950 chronic HBV or HCV patients were tested for HBsAg, HBeAg, anti-HBe, anti-HBc and anti-HCV positivity by third-generation ELISA. HBV-DNA was tested by the hybridisation technique without amplification, and the samples with negative results were retested by polymerase chain reaction (PCR) (Digene Hybrid-capture; Murex Diagnostics, Dartford, UK). All patients were also tested for HCV-RNA by RT-PCR (Roche, Amplicor, Basel, Switzerland), and the genotype was determined by the acid-guanidium-phenol-chloroform method in the patients who were HCV-RNA positive.[22] We selected 36 treatment-naive, dual-infected patients. Patients were treated according to the regimen that represented standard care at that time. The primary endpoint of the study was HCV SVR. Statistical evaluation was performed using the χ^2 test. A $p<0.05$ value was considered statistically significant.

RESULTS

We recruited 36 chronic HBV/HCV dual-infected patients (mean age 47±12 years) for the purpose of this study (*table 1*). The proportion of male patients was higher (78%; M/F: 28/8).

Five patients had compensated cirrhosis. All patients were HBsAg, anti-HBe and anti-HCV positive. PCR analyses confirmed absence of HBV-DNA, but all 36 patients carried HCV-RNA. The exclusive HCV genotype was 1b. All patients were subjected to a liver biopsy, which showed minimal hepatitis in nine patients, mild disease in 14 patients, moderate disease in eight patients and cirrhosis in five patients. Of the 36 patients, 32 had elevated serum transaminases. Mean alanine aminotransferase (ALAT) levels (118±65 U/l) and aspartate aminotransferase levels (90±95 U/l) were elevated (N: 5-37 U/l).

A total of 17 patients (M/F: 13/4, age: 46±11 year), received the combination therapy of pegylated interferon (16: pegylated interferon α2a 180 µg/week and 1: pegylated interferon α2b 120 µg/week) and ribavirin (1000 or 1200 mg/day); there were four patients with fibrosis stage 3 and two patients with fibrosis stage 4 by Knodell. Nineteen patients (M/F: 15/4, 48±12 years) received conventional interferon combination therapy; six patients had fibrosis stage 3 and three patients fibrosis stage 4 by Knodell. In 5/19 patients (26.3 %), treatment had to be stopped due to the side effects (*table 2*). Fourteen patients completed the therapy. There was no viral response by week 12, and only one patient responded in weeks 24 and 48 and finally reached SVR (*table 3*).

A total of 19 patients were given standard interferon and ribavirin combination therapy for 48 weeks. We discontinued therapy in five patients because of side effects (*table 2*). None of the patients showed an early virological response at week 12. However, we decided to continue the therapy in this special patient group and five patients (29%) were HCV negative at weeks 24 and 48, and

Table 1. *Features of the therapy groups of the chronic hepatitis B and C dual hepatitis, in which the active infection was hepatitis C*

Chronic hepatitis B and C dual hepatitis patients (n=36) (mean ± SD)	Peginterferon and ribavirin combination therapy group (n=17)	Conventional interferon and ribavirin combination therapy group (n=19)	P
Age	46±11	48±12	NS
Sex (male/female)	13/4	15/4	NS
ALAT (N:5-37) U/l	122±64	114±67	NS
ASAT (N:5-37) U/l	92±94	88±96	NS
HCV RNA IU/ml	1996,660±1871,628	2094,420 ± 1764,532	NS
HAI	10.1±3.1	12.1±4.2	NS
Fibrosis	1.8±1.4	2.0±1.6	NS

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; NS = not significant; HAI = hepatitis activity index.

Table 2. *Side effects related with the discontinuation of the therapy in chronic hepatitis B and C dual hepatitis patients, in whom the active infection was hepatitis C virus*

Patients	Combination therapy group	Side effect related with the discontinuation of the therapy
Case 1	Pegylated interferon and ribavirin	Nausea, alanine aminotransferase flare
Case 2	Pegylated interferon and ribavirin	Pruritus, severe flare up
Case 3	Pegylated interferon and ribavirin	Pneumonia
Case 4	Pegylated interferon and ribavirin	Severe weakness, low compliance
Case 5	Pegylated interferon and ribavirin	Severe weakness
Case 6	Conventional interferon and ribavirin	Severe weakness, low compliance
Case 7	Conventional interferon and ribavirin	Severe weakness
Case 8	Conventional interferon and ribavirin	Leucopenia
Case 9	Conventional interferon and ribavirin	Leucopenia
Case 10	Conventional interferon and ribavirin	Thrombocytopenia

Table 3. *The therapy responses of the chronic hepatitis B and C dual hepatitis, in which the active infection was hepatitis C*

n (male/female)	Treatment combination	Discontinuation of the therapy for side effect (n) (%)	End of therapy response (n) (%)	Sustained response (n) (%)
17 (13/4)	Peginterferon and ribavirin	5 (29%)	5 (29%)	1 (6%)
19 (15/4)	Conventional interferon and ribavirin	5 (26%)	1 (5%)	1 (5%)

one patient reached SVR (*table 3*). There was no difference between ALAT, viral load or histological severity between those who did reach SVR and those who did not.

DISCUSSION

This study presents the results of retrospective analysis of an HBV/HCV dual-infected cohort. HBV and HCV can coexist and suppress each other's replication,[5,6] indicating a mutual interference.[5,23] In general, HBV replication is most affected, suggesting that HCV plays a dominant role.[5] HCV was the dominant feature in our dual-infected patients.

Few data exist on treatment of dual infection (*table 4*). Response rates with conventional interferon monotherapy have been low. Zignego *et al.* detected HBV-DNA with PCR in the serum of 11/125 successive hepatitis C patients; no SVR was reached with interferon monotherapy.[16] This in comparison with a recent study[18] in 21 chronic HBV/HCV dual-infected patients treated with conventional interferon plus ribavirin. The dominant infection was HCV: 57% were HCV genotype 1 and 43% HCV genotype 2. HCV-RNA was undetectable at 24 weeks, at the end of the treatment, in 9/21 (43%) dual-infected patients, which was similar to the data from 30 HCV monoinfected controls (60%, p=0.63). They concluded that the treatment was as effective as in monoinfection. Hung *et al.* evaluated 36 chronic HBV/HCV dual-hepatitis patients. Adverse events led to withdrawal in three patients receiving conventional interferon. HCV clearance rate was seen in 69% at 48 weeks. Two (11%) of 18 pretreatment viraemic patients had negative serum HBV-DNA (<200 copies/ml). They concluded that conventional interferon and ribavirin combination therapy was effective in achieving sustained HCV clearance in patients with HBV/HCV dual infection[24] and that this combination was more efficient and better tolerated in patients with dual infection compared with HCV infection alone. However, in our patient group with chronic HCV, conventional interferon and ribavirin led to SVR in only 1/19 patients. Indeed, pegylation of interferon increases the half-life and improves the pharmacokinetics of the protein.[25] Although pegylated interferon has not been used in any clinical trials for dual-infected patients (*table 4*),[20] it will replace standard interferon in the treatment protocol of HBV/HCV dual infection. Rautou *et al.* report the only case, a 32-year-old man of Kampuchean origin, with genotype 1. On therapy with pegylated interferon 2a-b plus ribavirin, HCV-RNA became undetectable at weeks 17 and 48 of treatment. Two years after the end of the treatment, HCV-RNA and HBV-DNA were still undetectable. It was concluded that pegylated interferon based combination therapy is effective for both viral infections in dual infection.[21] However, in our group treated with pegylated interferon and ribavirin, only 5/17 patients showed the end of therapy response, and a mere 1/17 patients achieved SVR. In the conventional interferon and ribavirin based therapy, only 1/19 patients reached SVR. In the present study, SVR was achieved only in 2/36 patients. However, the majority of patients were male and were infected with HCV genotype 1. These factors may have an impact on the poor response

Table 4. *Summary of the therapies for chronic hepatitis B and C dual hepatitis patients*

Reference, year	HBV-DNA/ HCV-RNA	n	Treatment x duration	HBV-DNA negative	HCV-SVR
Weltman *et al.*, 1995[17]	-/+	8	IFNα 3 MU tiw x 6 months	NA	NA
Liaw *et al.*, 1997[27]	+/+	15	IFNα 9 MU tiw x 14 weeks or IFNα 4-6 MU tiw x 12 weeks	7%	0% 0%
Zignego *et al.*, 1997[16]	+/+	14	IFNα 3 MU tiw x 12 months	0%	0%
Utili *et al.*, 1999[28]	±/±	16	IFNα 5 MU tiw x 12 months	NA	44%
Guptan *et al.*, 1999[29]	+/+	7	IFNα 6 MU tiw x 6 months	86%	29%
Villa *et al.*, 2001[9]	+/+	30	IFNα 9 MU tiw x 6 months or IFN 6 MU tiw x 6 months	67%	31% 17%
Liu *et al.*, 2003[18]	+/+	21	IFNα 6 MU tiw x 3 months + 3 MU tiw x 3 months + ribavirin x 6 months	35%	43%
Marrone *et al.*, 2004[30]	+/+	8	IFNα 5 MU tiw x 12 months + lamivudine x 18 months	37.5%	50%
Chuang *et al.*, 2005[31]	+/+	42	IFNα 6 MU tiw + ribavirin x 6 months	31%	69%
Hung *et al.*, 2005[23]	+/+	36	IFNα 3-5 MU tiw +ribavirin x 6 months	11%	69%
Present study	-/+	17 19	Pegylated IFN* + ribavirin x 12 months and IFNα 3-4.5 MU tiw + ribavirin x 12 months	NA	6% 5%

HBV = hepatitis B virus; HCV = hepatitis C virus; SVR = sustained viral response; tiw = thrice weekly; IFN = interferon; thrice weekly; NA = not available; *16: peginterferon α2a 180 μg/week and 1: peginterferon α2b 120 μg/week.

rate. Successful treatment of HCV infection may induce HBV reactivation and flaring.[26] We did not observe this, probably due to the poor response rate.

REFERENCES

1. Lee W. Hepatitis B virus infection N Engl J Med 1997;337:1733-45.
2. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. Hepatology 2002:36(Suppl 1):3-20.
3. Stroffolini T, Sagnelli E, Mele A, Craxi A, Almasio P and Italian Hospitals Collaborating Group. The etiology of Chronic Hepatitis in Italy: Results from a multicentre national study. Dig Liver Dis 2004;36:829-33.
4. Zarski J-P, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998;28:27-33.
5. Jardi R, Rodriguez F, Buti M, et al. Role of hepatitis B, C, and D viruses in dual and triple infection: Influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. Hepatology 2001;34:404-10.
6. Mathurin P, Thibault V, Kadidja, et al. Replication status and histological features of patients with triple (B, C, D) and dual (B, C) hepatic infections. J Viral Hepatitis 2000;7:15-22.
7. 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 2003:39:1036-41.
8. Sagnelli E, Pasquale G, Coppola N, et al. Influence of chronic infection with hepatitis B and C virus on liver histology. Infection 2004;32:144-8.
9. Villa E, Grottola A, Buttafaco P, et al. High doses of alfa-interferon are required in chronic hepatitis due to coinfection with hepatitis B virus and hepatitis C virus: Long term results of a prospective randomized trial. Am J Gastroenterol 2001;96:2973-7.
10. Fukuda R, Ishimura N, Nigaki M, et al. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus associated chronic liver disease: Clinical and virological significance. J Med Virol 1999;58:201-7.
11. Lee DS, Huh K, Lee EH, Lee DH, Hong KS, Sung YC. HCV and HBV coexist in HBsAg-negative patients with HCV viraemia: Possibility of coinfection in these patients must be considered in HBV-high endemic area. J Gastroenterol Hepatol 1997;12:855-61.
12. Sagnelli E, Coppola N, Scolastico C, Mogavero AR, Filippini P, Piccinino F. HCV genotype and silent HBV coinfection: Two main risk factors for a more severe liver disease. J Med Virol 2001;64:350-5.
13. Kubo S, Nishiguchi S, Hirohashi K, et al. Clinical significance of prior hepatitis B virus infection in patients with hepatitis C virus-related hepatocellular carcinoma. Cancer 1999;86:793-8.
14. Ruiz J, Sangro B, Cuende JI, et al. Hepatitis B and C viral infections in patients with hepatocellular carcinoma. Hepatology 1992;16:637-41.
15. Shiratori Y, Shiina S, Zhang PY, et al. Does dual infection by hepatitis B and C viruses play an important role in the pathogenesis of hepatocellular carcinoma in Japan. Cancer 1997;80:2060-7.
16. Zignego AL, Fontana R, Puliti S, et al. Relevance of inapparent coinfection by hepatitis B virus in alpha interferon-treated patients with hepatitis C virus chronic hepatitis. J Med Virol 1997;51:313-8.
17. Weltman MD, Brotodihardjo A, Crewe EB, et al. Coinfection with hepatitis B and C or B, C and delta viruses results in severe chronic liver disease and responds poorly to interferon-alpha treatment. J Viral Hepat 1995;2:39-45.
18. 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;37:568-76.
19. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-65.
20. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147-71.
21. Rautou PE, Asselah T, Saadoun D, Martinot M, Valla D, Marcellin P. Hepatitis C virus eradication followed by HBeAg to anti-HBe seroconversion after pegylated interferon-a2b plus ribavirin treatment in a patient with hepatitis B and C coinfection. Eur J Gastroenterol Hepatol 2006,18:1019-22.
22. Chomcynski P, Sacci N. Single step method of RNA isolation by acid-guanidium thiocyanate-phenol-chloroform axtraction. Anal Biochem 1984;162:156-9.
23. Shih CM, Lo SJ, Miyamura T, Chen SY, Lee YH. Suppression of hepatitis B virus expression and replication by hepatitis C virus core protein in HuH-7 cells. J Virol 1993;67:5823-32.
24. Hung CH, Lee CM, Lu SN, Wang JH, Tung HD, Chen CH, Changchien CS. 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.

25. Foster GR. Review article: pegylated interferons: chemical and clinical differences. Aliment Pharmacol Ther 2004;20:825-30.

26. Yalcin K, Degertekin H, Yildiz F, Kilinc N. A severe hepatitis flare in an HBV-HCV coinfected patient during combination therapy with alpha-interferon and ribavirin. J Gastroenterol 2003;38:796-800.

27. Liaw YF, Chien RN, Lin SM, et al. Response of patients with dual hepatitis B virus and C virus infection to interferon therapy. J Interferon Cytokine Res 1997;17:449-52.

28. Utili R, Zampino R, Bellopede P, et al. Dual or single hepatitis B and C virus infections in childhood cancer survivors: long-term follow-up and effect of interferon treatment. Blood 1999,94:4046-52.

29. Guptan RC, Thakur V, Raina V, Sarin SK. Alpha-interferon therapy in chronic hepatitis due to active dual infection with hepatitis B and C viruses. J Gastroenterol Hepatol 1999;14:893-8.

30. Marrone A, Zampino R, D'Onofrio M, Ricciotti R, Ruggiero G, Utili R. Combined interferon plus lamivudine treatment in young patients with dual HBV (HBeAg positive) and HCV chronic infection. J Hepatol 2004;41:1064-5.

31. Chuang WL, Dai CY, Chang WY, et al. Viral interaction and responses in chronic hepatitis C and B coinfected patients with interferon-alpha plus ribavirin combination therapy. Antivir Ther 2005;10:125-33.