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Does hepatitis B virus coinfection have any impact on treatment outcome in hepatitis C patients on hemodialysis?

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ABSTRACT

Background. HBV/HCV coinfection is a common finding among hemodialysis patients. However, there is scarce information concerning the impact of HBV coinfection on the response to treatment of HCV-infected patients on hemodialysis. **Aim.** We aimed to compare the rate of sustained virologic response (SVR) to treatment with interferon-alfa (IFN) between hemodialysis patients with HBV/HCV coinfection and those with HCV-monoinfection. **Material and methods.** HCV-infected patients on hemodialysis treated with IFN were included. Patients coinfected by HBV/HCV were compared to HCV-monoinfected patients, regarding clinical and biochemical features and rates of SVR. **Results.** One hundred and eleven patients were treated. HBV/HCV coinfection was observed in 18/111 patients (16%). Coinfected patients were younger (p = 002), had more time on dialysis (p = 0.05) and showed a tendency to present a higher prevalence of septal fibrosis (p = 0.06). The analysis by intention to treat showed SVR of 56% among coinfected patients and 18% in HCV-monoinfected patients (p = 0.004). **Conclusion.** In conclusion, end-stage renal disease patients with HBV/HCV coinfection exhibit higher rate of SVR to HCV treatment than HCV-monoinfected patients. It is possible that factors related to the host immune response and viral interaction could explain the better response observed among coinfected patients.

Key words. End-stage renal disease. Sustained virological response. Dual infection.

INTRODUCTION

Hepatitis C virus (HCV) infection is highly prevalent in patients undergoing hemodialysis[1] and the presence of concomitant infection with hepatitis B virus (HBV) is frequently found in hemodialysis patients with an estimated prevalence of 1.2-37% according to the geographical zone.[2-5]

In non-uremic patients, HBV/HCV coinfection results in a poor outcome and more severe forms of disease.[6-9] Patients with HBV/HCV coinfection may show a large spectrum of virological profiles although a dominant role of HCV suppressing HBV replication is the most common clinical pattern.[10-12] A recent meta-analysis in non-uremic patients has reported SVR achieved in HBV/HCV coinfection patients were comparable to those in HCV monoinfection patients.[13]

In uremic patients with end-stage renal disease (ESRD) our study group has demonstrated the negative impact of HBV infection in HCV-infected hemodialysis patients. In this study the fibrosis progression rate in HCV-infected ESRD-patients with HBV coinfection was higher than that observed in patients without HBV coinfection (0.25 fibrosis units/year *vs*. 0.08 fibrosis units/year, respectively).[12]

In HCV-infected hemodialysis patients the efficacy of IFN monotherapy is higher than that observed in non-uremic patients.[1] However published data regarding the treatment of chronic hepatitis C with IFN in the dialysis population have not analyzed the issue of HBV coinfection so far and the treatment response of HBV/HCV coinfection remains unknown among hemodialysis patients.

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Therefore, the aim of this study was to compare sustained virological response to IFN monotherapy between HBV/HCV coinfected and HCV-monoinfected hemodialysis patients. Data regarding tolerance and safety were also analyzed.

MATERIAL AND METHODS

Patients

Data from all patients on hemodialysis with HCV chronic infection, treated with IFN-a at the Hepatitis Unit of Federal University of São Paulo from January 1999 to December 2010 were evaluated. One hundred and eleven hemodialysis patients, candidates to renal transplantation and referred to our hospital from different hemodialysis units were included. They received IFN-α according to the following treatment criteria: serum HCV-RNA positivity and biopsy showing interface hepatitis and/or septal fibrosis, regardless serum transaminase levels.

The patients were divided into two groups: group C (HCV monoinfection); group BC (HBV/HCV coinfection). Coinfection in hemodialysis patients was defined by seropositivity for anti-HCV, HCV RNA and HBsAg for more than 6 months. HBeAg and HBV-DNA levels were assessed at baseline to adjust the therapeutic approach to HBV infection whenever both viruses were replicating.

Exclusion criteria were hepatitis delta virus (HDV) or HIV coinfection, alcohol abuse or others causes of liver disease, decompensated liver cirrhosis or previous IFN-treatment.

All patients gave a written informed consent prior to liver biopsy and IFN treatment, and accepted temporary exclusion from the transplant waiting list for at least 18 months (12 months of IFN treatment and 6 months of follow-up). This study protocol was submitted to the local Ethics Committee and followed all of the ethical premises of the Helsinki Declaration.

Demographic and epidemiological data

The following variables were analyzed: age; gender; duration of infection (estimated by the first year of hemodialysis, or first blood transfusion if occurring before 1992); and time on hemodialysis.

Biochemical tests

Serum levels of ALT and aspartate aminotransferase (AST) were analyzed by automated methods at the baseline and during treatment. The serum ALT levels were expressed as times the upper limit of normality (xULN).

Virological assays

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

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

Histological analysis

A percutaneous liver biopsy was performed during the 6 months prior to the beginning of therapy in all patients. Before the biopsy procedure, the patients were submitted to ultrasound and coagulation tests. Histological grading of the hepatic necroinflammation and staging of fibrosis were performed by the same pathologist based on the Ludwig scoring system.[14]

Treatment regimen

All patients monoinfected with HCV were scheduled to receive IFN-a at the dose of 3 MU subcutaneously, three times a week for 48 weeks at the end of each dialysis session despite of the HCV genotype.

Patients with HBV/HCV coinfection were treated according with the spectrum of virological profile at baseline: most of patients had active HCV and inactive HBV replication and they received the same treatment described above. In only four cases with evidence of significant HBV replication (HBeAg+ and/or HBV-DNA ≥ 2,000 IU/mL), the patients received IFN-α (6 MU three times a week, subcutaneously, during first 16 weeks followed by 3 MU, three times a week, until complete 48 weeks of treatment).

Visit schedule and safety evaluation

The patients were carefully followed up every 2 weeks during the first month and monthly thereaf-

ter. Blood cell counts and serum AST, ALT and liver function tests were evaluated at least every 15 days during the first month, then monthly for the duration of treatment and at 6-month post-treatment follow up. Treatment was discontinued when the neutrophil count was < 500/mm^3 or the platelet count was < 50,000/mm^3, or when symptomatic anemia or any severe adverse effect was noted.

Serum HCV-RNA was determined at baseline, at the end of treatment and after 6 months. Serum HBV-DNA levels were assessed at the same time points in co-infected patients.

Endpoints

A sustained virologic response was the primary endpoint and was defined as undetectable HCV-RNA 6 months after stopping the treatment. Patients who continued to be HCV-RNA positive by the end of treatment were classified as non-responders. Relapse was defined as HCV-RNA negativity at the end of treatment but HCV-RNA positivity at 6-month post-treatment follow-up. Secondary endpoints included the dropout rate and clinical adverse events. For patients who prematurely discontinued treatment, the ETR was assessed at the time of treatment discontinuation and patients were indicated to maintain a post-treatment follow-up to assess SVR. Patients who lacked the data at the end of follow-up to asses SVR were considered as non-responders.

Comparative analysis

Patients monoinfected with HCV were compared to HBV/HCV coinfected patients regarding epidemiologic, laboratorial and histological variables. The following epidemiological variables were considered: gender, age, duration of infection and time on hemodialysis. The serum ALT levels were evaluated before and during treatment. The level of HCV viral load pre-treatment and HCV genotype were compared between both groups. The histological variables included were the presence of interface hepatitis and septal fibrosis. Virological response and tolerance to treatment were compared between patients monoinfected with HCV and HBV/HCV coinfected.

Statistical analysis

Data were analyzed using Statistical Program for Social Sciences, version 15.0 (SPSS, Chicago, Illinois). Numerical variables were expressed as means and standard deviations (SD), and were analyzed by the Student *t*-test and Mann-Whitney test. The categorical variables were expressed as percentages of the total and were evaluated by Chi-square or Fisher's exact test. A p value < 0.05 was considered statistically significant.

RESULTS

One-hundred and eleven HCV-positive hemodialysis patients were studied (62% male with mean age of 45 ± 10 years). Mean time on dialysis was 7 ± 4 years. The patients were divided into two groups: group C-93 patients (84%) with HCV infection alone; and group BC-18 patients (16%) with HBC/HCV coinfection.

Baseline characteristics of both groups are shown in table 1. Comparison between groups revealed higher age in group C (46 ± 10 years *vs.* 38 ± 9 years, p = 0.003). On the other hand, group BC showed longer time on dialysis (9 *vs.* 6 years; p = 0.05) and a tendency to higher frequency of significant fibrosis (77 *vs.* 52%, p = 0.06). Most of HBV/HCV coinfected patients (83%) had history of blood transfusion.

Table 2 demonstrates the comparison of ALT levels during the treatment between C and BC groups. The results showed higher levels of ALT during treatment in BC group with the zenith values achieved in the third month of treatment.

In table 3 aspects related to virological response and tolerance to treatment are compared between C and BC group, showing that the treatment of BC patients had significant higher HCV SVR than hepatitis C monoinfected-patients (56 *vs.* 18%, p = 0.004). Moreover, we observed a higher rate of end of treatment response (ETR) in coinfected patients when compared with monoinfected group (72 *vs.* 36%, p = 0.023) and a lower relapse rate of relapse (15 *vs.* 53%, p = 0.019).

Overall, 62 patients (56%) of patients completed 48 weeks of treatment with the same percentage value in both groups. The reasons for IFN discontinuation were side effects in 29 patients (26%), fifteen patients (14%) were lost to follow-up and five patients (5%) which remained viremic at week 24 of treatment discontinued treatment as a stopping rule of treatment protocol. The mean time of IFN use before discontinuation in cases of severe side effects and dropout were slightly higher in monoinfected patients when compared with coinfected patients (6.0 ± 2.8 months *vs.* 5.5 ± 2.1 months).

Side effects were observed in all patients and were divided into severe and mild or moderate. Mild or

Table 1. Comparison of general baseline characteristics between groups C and BC.

	Group C (n = 93)	Group BC (n = 18)	P
Male gender	63%	56%	0.52
Age (years)	46 ± 10	38 ± 8	0.003
Duration of infection (median, years)	8	9.5	0.5
Time on hemodialysis (median, years)	6	9	0.05
Pre-treatment ALT (median x ULN)	1.5	1.7	0.12
Septal fibrosis ≥ 2	52%	72%	0.06
Moderate to severe Interface hepatitis	28%	33%	0.33
HCV Genotype (%, N)	80% (45)	100% (9)	0.33
HCV non-genotype 1 (%, N)	20% (11)	—	—
HCV viral load pre-treatment			
Detectable, not quantifiable (%, N)	31% (29)	28% (5)	—
Mean HCV-RNA level (SD), log10 IU/mL	3.6 (1.2)	3.1 (1.3)	0.95
HBeAg positivity (%)	—	22%	—
Mean HBV-DNA level (SD), log10 IU/mL	—	2.4 (2.1)	—
HBV Genotype			
Genotype A (%, N)	—	8% (1)	—
Genotype D (%, N)	—	92% (12)	—
Not available (N)	—	5	—

ALT: alanine aminotransferase. x ULN: times the upper limit of normality. SD: standard division.

Table 2. Comparison of serum ALT levels during treatment between groups C and BC.

ALT level (median x ULN)	Group C (n = 93)	Group BC (n = 18)	P
Pre-treatment	1.5	1.7	0.12
First month	0.9	1.5	0.06
Third month	0.7	1.8	0.004
Sixty month	0.8	1.5	0.06
Ninety month	0.7	1.5	0.05
End of treatment	0.7	1.3	0.05

ALT: alanine aminotransferase. x ULN: times the upper limit of normality.

Table 3. Comparison of aspects related to HCV treatment between groups C and BC.

	Overall	Group C (n = 93)	Group BC (n = 18)	P
ETR	48%	36%	72%	0.023
Relapse rate	43%	53%	15%	0.019
SVR (intention to treat)	24%	18%	56%	0.004
Interruption due to severe side effects	26%	28%	17%	0.55

ETR: end of treatment response. SVR: sustained virological response.

moderate side effects that did not require treatment discontinuation were observed in almost all patients and included flu-like symptoms in 59 patients (95%), bone-marrow depression in 54 patients (87%), diarrhea in seven (11%), depression in five (8%), infections in three (5%) and thyroid hormone dysfunction (elevated TSH) in two (3%).

A similar safety profile was observed between monoinfected and coinfected patients who interrupted the treatment due to severe side effects, observed in 28 *vs.* 17%, p = 0.55. These side effects included severe anemia (hemoglobin lower than 8.5 g/dL) that not responded to repeated escalations in doses of epoetin-alpha up to 40,000 IU per week in

33% (8 patients), pneumonia (21%), severe diarrhea (14%), cerebrovascular accident (10%), stable angina pectoris in two patients, hepatic decompensation in two non-cirrhotic patients and others causes that occurred in one patients each, what included decompensated diabetes mellitus. worsening bone pain, retinal hemorrhage and infective endocarditis.

DISCUSSION

Data regarding HBV/HCV coinfection in hemodialysis patients are very scarce in the literature. HBV and HCV infections affect the survival of dialysis patients and reduce significantly the chances of overall survival after renal transplantation.[1,15-20] Furthermore, no studies to date have evaluated the response to treatment of hepatitis C in hemodialysis patients coinfected with HBV. The present study evaluated a large cohort of HCV hemodialysis patients, comparing sustained virological response between HBV/HCV coinfected patients to HCV monoinfected, bringing new information about the response to treatment in this specific group of patients.

In the present study, the frequency HBV coinfection in HCV-infected ESRD patients indicated to treatment was 16%. Other studies evaluating treatment of hepatitis C in hemodialysis patients had not analyzed the rates of response in HBV coinfected patients.

The comparative analysis between HCV monoinfected and HBV/HCV coinfected patients revealed that HBV/HCV coinfection was associated with higher time on dialysis. This finding can be attributed to a longer exposure to environmental transmission, which increases in a cumulative manner to longer the patient remains on hemodialysis. Cross-contamination of patients via environmental surfaces, supplies, equipment, multiple dose medication vials and staff members plays the prime role in HBV transmission in hemodialysis units and investigations of dialysis associated outbreaks of HCV infection indicate that transmission most likely occurs because of inadequate infection control practices.[21]

Another interesting finding of our data was that patients with HBV/HCV coinfection were younger than monoinfected patients ($p = 0.003$). This finding is possibly explained by the fact that this is a group of patients indicated to treatment and the presence of coinfection could have lead these patients earlier to a treatment indication due to a more advanced disease.

In fact, cross-sectional studies have reported that patients with HBV/HCV coinfection had a significantly higher (two to threefold) risk of developing advanced liver disease and hepatocellular carcinoma than those with either infection alone.[22-25] Data from the Becker, *et al.*,[26] recently reported in uremic patients that the time to progression to cirrhosis was 16 years for patients in hemodialysis with HBV/HCV coinfection and 50 years for HCV monoinfected patients.

In our study, HBV replication was observed in only four patients before HCV treatment. This data are in accordance to the evidence that there is a dominant role for HCV over HBV especially among non-Asian individuals.[27,28]

Current guidelines support monotherapy with standard interferon in dialysis patients with HCV, but dual therapy including ribavirin in a well-controlled setting may be also an appropriate alternative. Low dose of ribavirin should be used very cautiously considering a higher risk for severe anemia in these patients.[29-32] The treatment of patients with ESRD with chronic HCV infection by IFN monotherapy results in SVR rates of 14-71% and approximately one-third of patients on hemodialysis with chronic hepatitis C will achieve SVR with standard IFN monotherapy.[13,33-36] Two recent randomized trials conducted in Asia by Liu, *et al.*,[37,38] involving the two largest cohort of hemodialysis patients monoinfected with HCV genotypes 1 and 2 showed higher SVR with pegylated interferon plus low-dose ribavirin than with IFN monotherapy. However, this results should be interpreted with caution in terms of extending these findings to hemodialysis patients worldwide because of the high frequency of IL-28B T/T genotype, lower mean body mass index of 22.5 kg/m^2, and lower rate of treatment discontinuation due to adverse events than in previous studies, wherefore all of these factors are associated with higher SVR rates.[39]

Despite of four coinfected patients who had dual active infection before IFN treatment had been considered to receive higher dose of IFN during first 16 weeks of treatment, all of them required very early dose reduction due to the occurrence of adverse events, specially fatigue, diarrhea and flu-like symptoms. One of them, who was not negative HCV-RNA at week 24, had treatment discontinued. Other two cases stopped treatment before six months related to dropout or adverse events and only one of them completed treatment achieving SVR. Considering these outcomes, the different

doses of IFN used to treat HBV/HCV co-replicative patients probably had not influenced the response to HCV treatment.

Two recent Asian studies showed similar SVR rate in non-uremic HCV monoinfected patients when compared to HBV/HCV coinfected[13,40] and data from Rocha, *et al.*,[41] reported HCV SVR in 24% of monoinfected hemodialysis patients without bridging fibrosis and 19% with bridging fibrosis or cirrhosis. Our data in a large group of hemodialysis patients showed a higher SVR rate among coinfected group despite of majority of patients had negative predictive factors of response, such as a high proportion of genotype 1 and higher frequency of septal fibrosis.[33,42]

Not all patients had genotype analysis at baseline due to the fact that at the time that the patients were studied, predictive factors for SVR were not well defined in hemodialysis patients and all patients were considered to treatment for 48 weeks, regardless HCV genotype and rapid or early virological response.[43]

A recent meta-analysis of Liu, *et al.*,[13] involving non-uremic patients showed that ETR and rate of relapse achieved in HBV/HCV coinfection patients were comparable to those in HCV monoinfection patients. Our study described a higher rate of ETR and a smaller rate of relapse among HBV/HCV coinfected when compared to monoinfected patients. This finding could be related to better immune response induced to IFN therapy and to an early response to IFN treatment.

Our study suggests that interferon monotherapy is at least as effective as in monoinfected patients in hemodialysis patients with HBV/HCV coinfection as in patients monoinfected with HCV. A possible explanation for this finding could be the lower baseline HCV-RNA levels in the context of HBV coinfection, as reported in some studies.[33,42] However, we didn't observe differences in HCV viral load between the two groups. The mean HCV viral load was lower in our study, compared with previously others published studies in hemodialysis patients[36,44] but similar levels were observed in both groups, making it improbable that this variable could have influenced the response to treatment.

Another possible explanation for the higher SVR observed in coinfected patients could be related to a better immune response. Comparative analysis of patients with HCV infection alone and patients with HBV/HCV coinfection showed higher levels of ALT during treatment in BC group with the zenith values achieved in the third month of treatment. This finding may reflect an enhanced host innate and adaptive immune-mediated response to the HBV and/or HCV infection providing additional evidence for the complex interactions between both virus in coinfected patient.[45,46] Regarding ALT levels, elevated levels were observed in both groups. A recent cohort published by Liu, *et al.*,[37] involving 205 hemodialysis patients with HCV-1 monoinfection also showed increased basal mean ALT levels, similar to our study. Moreover, a recent meta-analysis involving non-uremic patients found that HCV monoinfected patients achieved higher ALT normalization at the end of treatment than those with HBV/HCV coinfection.

This study has some limitations. The sample size of HBV/HCV coinfected patients is relatively small. However it must be considered that this is a very special population and the sample size of analyzed in this study is one of the largest cohorts of hemodialysis coinfected patients evaluated so far. The other limitation is related to the baseline characteristics of patients. Monoinfected and coinfected groups were not matched and were different regarding age and stage of fibrosis. Although the younger age of the coinfected group could have favored the response to therapy, this group also had a more advanced stage of fibrosis. It is well known that the fibrosis stage is one of the most important predictive factors of response and therefore the possible benefit of age in SVR of coinfected patients could have been overcome by the more advanced fibrosis observed in this group.

To the best of our knowledge there is no study evaluating the impact of HBV infection on treatment outcome in chronic HCV patients on hemodialysis. The present data showed that HBV/HCV coinfection have a positive impact on the response to interferon monotherapy in hemodialysis patients with similar safety profile.

ABREVIATIONS

- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **DNA:** deoxyribo-nucleic acid.
- **ESRD:** end-stage renal disease.
- **ETR:** end of treatment response.
- **HBV:** hepatitis B virus.
- **HCV:** hepatitis C virus.
- **IFN:** interferon.
- **RNA:** ribonucleic acid.
- **SVR:** sustained virological response.

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