Tratamiento e historia natural de la hepatitis crónica C en pacientes coinfectados por VIH-1

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Tesis Doctoral

TRATAMIENTO E HISTORIA NATURAL DE LA HEPATITIS CRÓNICA C EN PACIENTES COINFECTADOS POR VIH-1

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ANEXO 1:PUBLICACIONES

Short communication

Abacavir does not influence the rate of virological response in HIV–HCV-coinfected patients treated with pegylated interferon and weight-adjusted ribavirin

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Background: The combination of pegylated interferon (PEG-IFN) plus ribavirin (RBV) is the standard of care for hepatitis C virus (HCV) treatment in HIV-coinfected individuals. In 2007, abacavir (ABC)-based antiretroviral therapy was, for the first time, reported to be associated with early virological failure during HCV treatment. The aim of our study was to evaluate the effect of ABC on the response rate to HCV therapy.

Methods: A retrospective analysis of HIV–HCV-coinfected patients treated with PEG-IFN and weight-adjusted RBV in four hospitals in Spain was performed. An analysis of baseline descriptive variables was conducted. Logistic regression models were used to test possible associations between non-response and pretreatment characteristics, including antiretroviral drugs.

Results: A total of 244 HIV–HCV-coinfected patients treated with PEG-IFN and RBV were included. Overall, 85% of patients were on highly active antiretroviral therapy; of these patients, 24% received ABC-based regimens. The most frequent genotypes were 1 and 3. RBV dosing was ≥13.2 mg/kg/day in 97% of the patients. In the global intent-to-treat analyses, 46.3% of patients reached a sustained virological response (SVR; 46.2% in ABC group versus 46.7% in non-ABC group, $P=1$). The only two factors in the multivariate analysis that were statistically associated with an increased risk of failure to achieve SVR were HCV genotypes 1 or 4 and older age. The use of ABC was not associated with failure to achieve SVR at any of the other time points evaluated.

Conclusions: Our data suggest that the use of ABC-based regimens in the context of HCV therapy does not negatively affect the outcome of this treatment.

Introduction

Combined treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) has become the standard of care for hepatitis C virus (HCV) treatment in HIV-coinfected patients since 2004, with a rate of sustained virological response (SVR; defined as negative HCV RNA 6 months after the end of treatment) of 40–44% [1–4]. Baseline serum HCV RNA and HCV genotype are the main predictors of SVR [5,6]. However, several other factors influence the outcome of this therapy, including age, ethnicity, body mass index, insulin resistance, grade of hepatic fibrosis [7], $CD4^+$ T-cell count and HIV viral load [8].

Certain antiretroviral drugs might present synergistic or antagonistic effects when combined with anti-HCV therapy. RBV is a purine nucleoside analogue that extensively distributes into red blood cells after oral administration and competes *in vitro* for thymidine and cytosine analogues, such as zidovudine and stavudine [9,10]. The concomitant use of RBV with zidovudine should be avoided whenever possible because of the increased risk of anaemia [11] and with stavudine because of the risk of lactic acidosis. The phosphorylation of didanosine is increased by RBV; the use of this drug in patients receiving RBV is contraindicated because of the risk of

life-threatening complications, such as lactic acidosis, decompensated cirrhosis and pancreatitis [12].

Until last year, there had been no reports of decreased rate of response to HCV therapy because of the antiretroviral regimen prescribed. In May 2007, the French group RIBAVIC reported for the first time that abacavir (ABC)-based antiretroviral therapy (ART) was associated with an early virological failure during HCV treatment. Since then, several reports have shown discordant results; Vispo *et al.* [13] and Mira *et al.* [14] demonstrated a negative effect of ABC on SVR. By contrast, Moreno *et al.* [15] and Pineda *et al.* [16] did not find any differences in SRV rates when comparing patients receiving ABC with patients on other nucleoside or nucleotide reverse transcriptase inhibitors.

The aim of our study was to evaluate the effect of ABC on the rate of response to HCV therapy in HIV–HCV-coinfected patients.

Methods

Patients

This was a retrospective cohort study of HIV–HCV-coinfected patients from four hospitals (Hospital Clinic, Barcelona, Spain; Hospital Son Llàtzer, Palma de Mallorca, Spain; Hospital Son Dureta, Palma de Mallorca, Spain; and Hospital Joan XXIII, Tarragona, Spain) who were treated, between 2002 and 2006, with PEG-IFN and RBV. Patients were included in the analysis if they were not previously treated for chronic hepatitis C with PEG-IFN and RBV, had positive HCV RNA in plasma, had alanine aminotransferase (ALT)>1.5-fold the upper normal limit, had control of the HIV infection with $CD4^+$ T-cell count >250 cells/mm^3 and an HIV viral load <50,000 copies/ml and were in response to a stable ART or without ART if not required. Exclusion criteria were the presence of other causes of hepatopathy, decompensated cirrhosis, pregnancy and potential contraindications for IFN or for RBV therapy such as haemoglobinopathies, cardiopathy, autoimmune diseases, major depression or other severe psychiatric pathologies and active illicit drug consumption within the last 12 months.

Treatment was planned for 48 weeks in all patients. Overall, 60% of patients received PEG-IFN-α2b (Peg-Intron-A; Schering Corp., Kenilworth, NJ, USA) subcutaneously each week (80–150 μg, body weight-adjusted dosing) plus oral RBV (Rebetol; Schering Corp., Kenilworth, NJ, USA) every day and 40% of patients received PEG-IFN-α2a (Pegasys; Roche Corp., Hertfordshire, UK) subcutaneously each week (180 μg) plus daily oral RBV (Copegus; Roche Corp.). RBV dosing was body weight-adjusted in all cases to 800 mg when the body weight was <60 kg, 1,000 mg when it was between 60–75 kg and 1,200 mg when body weight was >75 kg. When a ≥2 log reduction in HCV RNA at week 12 was obtained, patients continued treatment and were re-evaluated at week 24; if HCV RNA was negative they continued treatment until week 48.

Monitoring

Patients were evaluated before treatment, 2 weeks after starting therapy and every 4 weeks until the cessation of therapy. Also, SVR was evaluated 24 weeks after treatment was ended. Blood analysis, including a haemogram and a complete biochemistry with lactate, was carried out at every medical visit in addition to a medical interview to establish possible secondary effects of the treatment. At week 4, and every 12 weeks thereafter, thyroid function, HIV viral load and $CD4^+$ T-cell count were determined. Serum HCV RNA was measured by quantitative PCR assay at baseline and 12 weeks after starting therapy (Branched DNA; Siemens, Tarrytown, NY, USA). During treatment at weeks 4, 24, 36 and 48, and at 24 weeks after cessation of therapy, HCV RNA was measured by qualitative PCR assay (Transcription Mediated Amplification, Siemens; sensitivity was 30 UI/ml). Genotyping was done as previously described [17].

Statistical analyses

A descriptive analysis of baseline variables was conducted, looking at the central tendency and dispersion. These values were compared with the aim of ensuring that the demographic, epidemiological, clinical, biochemical and histopathological characteristics were similar among patients in both groups of therapy. Fisher's exact test was used to analyse qualitative variables and Mann–Whitney U test was used to analyse quantitative variables. Logistic regression models were used to test possible associations between non-response (outcome variable) and pretreatment characteristics. Characteristics with P-value <0.1 in univariate analysis were included in a multivariate logistic model based on the backward elimination procedure. All statistical tests were two-tailed, with a type I error of 5%. Data were analysed in the Epidemiology and Statistics Unit, UASP, Hospital Clinic, Barcelona, Spain.

Results

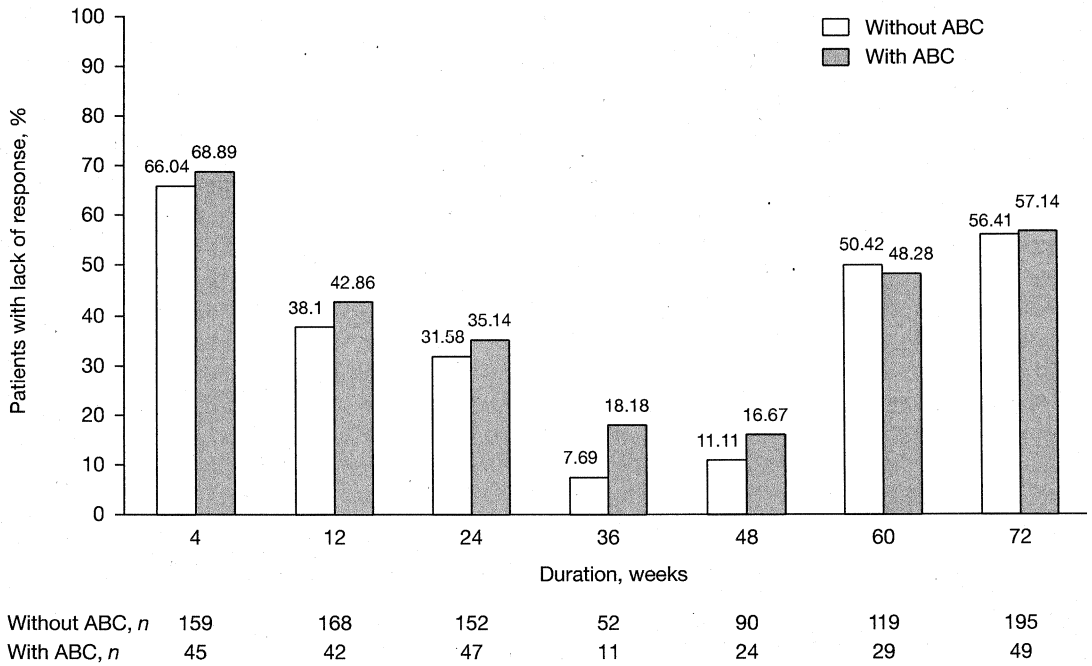
A total of 244 HIV–HCV-coinfected patients treated with PEG-IFN and RBV were included in this retrospective analysis. Overall, 85% of patients were on highly active antiretroviral therapy (HAART) and among these patients 49 (24%) received ABC-based regimens. Baseline characteristics were similar between the group of patients on ABC-based regimens and those who were not (Table 1) and they only differed in the mean time of known chronic hepatitis

Table 1. Baseline characteristics

Characteristic	ABC-based ART regimen		All (*n*=244)	*P*-value
	No* (*n*=195)	Yes (*n*=49)		
Male gender, *n* (%)	134 (68.7)	39 (79.6)	173 (70.9)	0.16
Mean age, years (±SD)	40.7 (5.2)	40.2 (5.4)	40.5 (5.2)	0.83
Mean age at time of HCV infection, years (±SD)	22.4 (6.2)	24.8 (8.1)	22,9 (6.7)	0.19
Mean baseline weight, kg (±SD)	67.4 (11.8)	67.6 (11.6)	67.5 (11.7)	0.69
Mean duration with HCV infection, years (±SD)	18.3 (5.9)	15.4 (5.6)	17.7 (6.1)	0.02
HCV genotype 1 or 4, *n* (%)	112 (59.8)	35 (72.9)	147 (62.5)	0.13
Baseline HCV RNA>800,000 IU/ml, *n* (%)	102 (53.1)	26 (56.5)	128 (53.8)	0.74
Fibrosis METAVIR score 3–4, *n* (%)	57 (32.5)	18 (40.9)	75 (34.2)	0.37
Baseline ALT≥60 IU/ml, *n* (%)	142 (73)	41 (83.6)	183 (75.3)	0.14
HIV risk group (IDU), *n* (%)	149 (76.4)	35 (72.9)	184 (75.7)	0.56
Mean baseline $CD4^+$ T-cell count, cells/ml (±SD)	597.5 (260.7)	551.1 (294.6)	588.1 (267.8)	0.15
HIV viral load <200 copies/ml, *n* (%)	137 (70.6)	40 (81.6)	177 (72.8)	0.40

*Patients who were not receiving antiretroviral therapy (ART) were included in the non-abacavir (ABC)-based ART regimen group. ALT, alanine aminotransferase; HCV, hepatitis C virus; IDU; intravenous drug user.

Figure 1. Effect of abacavir use on virological response to pegylated interferon plus ribavirin in HIV–HCV-coinfected patients



ABC, abacavir; HCV, hepatitis C virus.

C infection (15.4 versus 18.3 years, *P*=0.02). The majority of the patients were male (71%) with a mean age of 41 years, a mean weight of 67.5 kg and a mean height of 170 cm. A history of illicit intravenous drug consumption was found in 76% of patients. The more frequent genotypes in our study were 1 and 3 (48% and 34%, respectively). RBV dose was ≥13.2 mg/kg/day in 97% of patients. Regarding HCV RNA, 60% of the patients had a viral load >600,000 UI/ml and 75% were >400,000 UI/ml.

Response rates are summarized in Figure 1. In the global intent-to-treat analysis, 46.3% of patients reached SVR (46.2% in the ABC group versus 46.7% in the non-ABC group, *P*=1).

To examine the influence of potentially important prognostic factors on SVR, the univariate and multivariate analyses were used to assess HCV genotype, baseline HCV RNA, degree of fibrosis before starting therapy, presence of steatosis, age, gender, baseline CD4+ T-cell count, baseline HIV viral load, years with HCV infection, use or not of HAART, baseline body weight, type of PEG-IFN and the necessity or not to modify the dose of HCV therapy, baseline ALT level, therapy containing ABC and therapy with tenofovir.

The factors included in the multivariate analysis were age, genotype, ALT level, baseline HCV RNA and CD4+ T-cell count. The only two factors that remained statistically associated with an increased risk of failure to achieve SVR were HCV genotype 1 or 4 and older age (>40 years). Specifically, the use of ABC was not associated with higher rates of failure to achieve virological response at any of the time points evaluated (weeks 4, 12, 24, 48 and 72).

Discussion

Since the first report on the negative effect of ABC-based therapy in the response to HCV treatment in HIV-coinfected patients, an inhibitory competition between ABC and RBV (both guanosine analogues) has been suggested [13,14]. The same authors describe that this negative effect might be overcome by high RBV exposure. However, a low-level of antagonism between RBV and both tenofovir and ABC has been reported *in vitro*, whereas a much higher level of antagonism with zidovudine, stavudine, emtricitabine and lamivudine was observed [18].

In our study the rate of SVR was not affected by the use of ABC-based regimens, in concordance with the data presented by Moreno *et al.* and Pineda *et al.* [15,16]. One of the main reasons for this might be that all patients included in this study were receiving high doses of RBV.

After multivariate analyses, only HCV genotype 1 or 4 and older age, two already well known prognostic factors, were independently associated with the failure to achieve SVR. Even though patients without ABC had a statistically significant longer duration of known HCV infection than patients in the ABC group, no difference in the grade of fibrosis was found between the two groups. For this reason it could be assumed that the longer time of HCV infection found in the non-ABC group did not negatively affect the outcome of HCV therapy.

Our data suggest that the use of ABC-based regimens in HIV-infected patients in the context of HCV therapy does not negatively affect the outcome of this treatment.

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Table 2. Univariate and multivariate analyses of predictors of sustained virological response

Effect	Univariate analysis crude OR (95% CI)	*P*-value	Multivariate analysis adjusted OR (95% CI)	*P*-value
Age ≤40 versus >40 years	0.567 (0.340–0.946)	0.0299	0.581 (0.334–1.008)	0.0536
Genotype 2 and 3 versus 1 and 4	0.252 (0.144–0.441)	<0.0001	0.247 (0.141–0.435)	<0.0001
PEG-IFN-α2b versus PEG-IFN-α2a	1.060 (0.630–1.785)	0.8250	–	–
ART change, yes versus no	0.791 (0.424–1.474)	0.4599	–	–
Steatosis, yes versus no	0.896 (0.322–2.497)	0.8339	–	–
Male versus female	0.934 (0.534–1.633)	0.8107	–	–
HIV viral load ≤200 versus >200 copies/ml	0.788 (0.443–1.402)	0.4176	–	–
ALT <60 versus ≥60 IU/ml	1.955 (1.056–3.622)	0.0330	–	–
Weight >75 versus ≤75 kg	1.585 (0.850–2.954)	0.1474	–	–
EVR, yes versus no	<0.001 (<0.001–>999.9)	0.9326	–	–
RVR, yes versus no	0.080 (0.039–0.166)	<0.0001	–	–
HCV RNA >400,000 versus ≤400,000 UI/ml	1.761 (0.973–3.187)	0.0613	–	–
CD4+ T-cell count >300 versus ≤300 cells/ml	2.258 (0.980–5.204)	0.0559	–	–
Fibrosis score 2–4 versus 0–1	1.393 (0.766–2.533)	0.2775	–	–
ABC, yes versus no	1.030 (0.547–1.940)	0.9264	–	–
TDF, yes versus no	1.301 (0.678–2.496)	0.4292	–	–
HAART, yes versus no	1.281 (0.635–2.583)	0.4886	–	–
HCV RNA >600,000 versus ≤600,000 UI/ml	1.596 (0.947–2.691)	0.0794	–	–

For multivariate analysis, only statistically significant values were included in the table. ABC, abacavir; ALT, alanine aminotransferase; ART, antiretroviral therapy; CI, confidence interval; EVR, early virological response; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; OR, odds ratio; PEG-IFN, pegylated interferon; RVR, rapid virological response; TDF, tenofovir.

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Disclosure statement

The authors declare no competing interests.

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