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Journal of Antimicrobial Chemotherapy (2008) **62**, 1365–1373
doi:10.1093/jac/dkn420
Advance Access publication 13 October 2008

Efficacy of pegylated interferon plus ribavirin treatment in HIV/hepatitis C virus co-infected patients receiving abacavir plus lamivudine or tenofovir plus either lamivudine or emtricitabine as nucleoside analogue backbone

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Received 15 March 2008; returned 23 April 2008; revised 7 September 2008; accepted 14 September 2008

***Objectives*: To compare the response to hepatitis C virus (HCV) therapy among human immunodeficiency virus (HIV)/HCV co-infected patients receiving a nucleos(t)ide reverse transcriptase inhibitor [N(t)RTI] backbone consisting of abacavir plus lamivudine with that observed in subjects who receive tenofovir plus lamivudine or emtricitabine.**

***Methods*: A total of 256 subjects, enrolled in a cohort of 948 HIV-infected patients who received pegylated interferon and ribavirin from October 2001 to January 2006, were included in this study. All patients were taking one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor and abacavir plus lamivudine or tenofovir plus lamivudine or emtricitabine as N(t)RTI backbone during HCV therapy. Sustained virological response (SVR) rates in both backbone groups were compared.**

***Results*: In an intention-to-treat analysis, 20 out of 70 (29%) individuals under abacavir and 83 out of 186 (45%) under tenofovir showed SVR ($P = 0.02$). N(t)RTI backbone containing tenofovir was an independent predictor of SVR in the multivariate analysis [adjusted odds ratio (95% CI), 2.6 (1.05–6.9); $P = 0.03$]. The association between abacavir use and lower SVR was chiefly seen in patients with plasma HCV-RNA load higher than 600 000 IU/mL and genotype 1 or 4. Among patients treated with**

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ribavirin dose <13.2 mg/kg/day, 3 (20%) of those under abacavir versus 22 (52%) under tenofovir reached SVR ($P = 0.03$), whereas the rates were 31% and 38% ($P = 0.4$), respectively, in those receiving ≥13.2 mg/kg/day.

***Conclusions*: HIV-infected patients who receive abacavir plus lamivudine respond worse to pegylated interferon plus ribavirin than those who are given tenofovir plus lamivudine or emtricitabine as N(t)RTI backbone, especially in those receiving lower ribavirin doses.**

Keywords: antiretroviral therapy, sustained virological response, HCV genotype

Introduction

The combination of pegylated interferon plus ribavirin is currently the treatment of choice for hepatitis C virus (HCV) infection in patients with human immunodeficiency virus (HIV) infection. Data from clinical trials and cohort studies have shown that such therapy eradicates HCV only in 27% to 44% of co-infected individuals.[1–5] These proportions are lower than the rates reported in HCV mono-infected patients.[6–8] The simultaneous use of some antiretroviral drugs with pegylated interferon and ribavirin may play a relevant role in these differences. Indeed, some nucleoside reverse transcriptase inhibitors (NRTIs), such as didanosine, can interact with ribavirin, leading to enhanced drug toxicity.[9–11] Similarly, some side effects of antiretroviral drugs and anti-HCV therapy may be additive, such as blood cytopenias or psychiatric adverse effects.[11] All of these factors may contribute to lower the efficacy of pegylated interferon plus ribavirin treatment in HIV/HCV co-infected patients.

Recent studies have provided data suggesting that the administration of abacavir along with pegylated interferon and ribavirin is associated with higher rates of non-response to HCV therapy. Thus, in a substudy of the Ribavic clinical trial, the virological response at week 12 of therapy was lower among patients taking abacavir simultaneously.[12] On the other hand, a study carried out in a cohort of co-infected individuals treated with pegylated interferon and ribavirin suggested that combinations of tenofovir plus lamivudine could be associated with higher rates of sustained virological response (SVR) than abacavir plus lamivudine, both as nucleos(t)ide reverse transcriptase inhibitor [N(t)RTI] backbone.[13] However, this difference in the SVR did not reach statistical significance, probably due to lack of statistical power.[13] Finally, it has been recently reported that abacavir could reduce the efficacy of therapy against HCV, particularly in individuals with low plasma levels of ribavirin.[14] However, in most of the former studies, abacavir was given along with zidovudine in a substantial proportion of patients. As the latter antiretroviral may enhance the haematological toxicity of ribavirin,[11–15] it could have been a confounder in these studies. In addition, the most commonly used N(t)RTI backbones in developed countries are currently abacavir plus lamivudine and tenofovir plus emtricitabine. Because of these reasons, it is critical to clarify whether the combination of abacavir plus lamivudine as N(t)RTI backbone is associated with lower SVR rates to pegylated interferon and ribavirin treatment.

The objective of the present study was to compare the efficacy of a pegylated interferon plus ribavirin combination among HIV/HCV co-infected patients taking an N(t)RTI backbone consisting of abacavir plus lamivudine with that observed in subjects who receive tenofovir plus lamivudine or emtricitabine.

Patients and methods

Patients and follow-up

From October 2001 to January 2006, a cohort of 5940 HIV/HCV co-infected patients was followed at 15 hospitals in Spain. Of these, a total of 948 started therapy with pegylated interferon plus ribavirin during this period (Figure 1). All individuals were followed at least every 4 weeks during the first 24 weeks of therapy, and every 8–12 weeks thereafter. After discontinuing therapy, subjects were followed for at least 24 weeks in order to assess SVR. Clinical, biochemical and haematological assessments were performed at every visit. All patients belonging to the former group, who fulfilled the following criteria, were selected for the present retrospective study: (i) had received a three-drug antiretroviral regimen including one protease inhibitor (PI) or one non-NRTI (NNRTI) along with abacavir plus lamivudine or tenofovir plus lamivudine or emtricitabine as N(t)RTI backbone during HCV therapy; (ii) older than 16 years; and (iii) previously naive for therapy against HCV infection. The sample size was determined *a priori* according to data from a recent work.[13] Thus, our study was designed to have a statistical power of 80% (with a two-sided α value of 0.05) to detect a difference in the rate of SVR between both groups of 20%, assuming that the percentage of subjects treated with abacavir plus lamivudine was 35% of the study population. The minimum sample size thus calculated was 69 patients for the abacavir group and 170 individuals for the tenofovir group.

Treatment regimens

All individuals were treated with the combination of subcutaneous peginterferon alfa-2a at a dose of 180 μg given once weekly or peginterferon alfa-2b at a dose of 1.5 μg/kg given once weekly along with oral ribavirin at a daily dose of 600 to 1500 mg. The length of the therapy was 48 weeks in all HCV genotype 1 or 4 carriers. Subjects harbouring HCV genotype 2 or 3 received HCV therapy for 24 or 48 weeks, according to the decision of the caring physician. At weeks 12 and 24, HCV therapy was prematurely discontinued in non-responders (see below). Dose adjustments for pegylated interferon and ribavirin were made according to the criteria of the physician attending the patient. The use of granulocyte colony-stimulating factor and erythropoietin was available for all participating hospitals. Both growth factors were used according to the criteria of the physician who was in charge of the patient.

Antiretroviral therapy, including the N(t)RTI backbone, was prescribed according to the availability of drugs and the recommendations of international guidelines at the time of prescription. Namely, the guidelines of the Department of Health and Human Services of the USA (http://AIDSinfo.nih.gov) and of the Grupo Español para el Estudio del SIDA (GESIDA) (www.gesida.seimc.org) were followed. The physician responsible for the patient selected the specific drugs included in the combinations.

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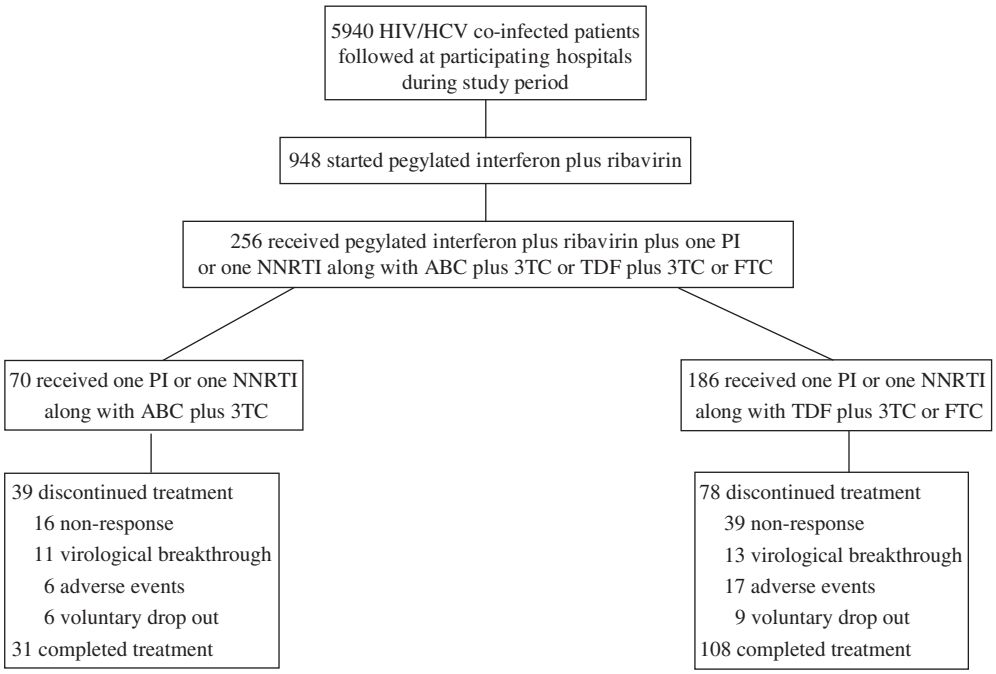

Figure 1. Patient flow diagram. TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir.

Assessment of efficacy

The main outcome variable was SVR, defined as undetectable serum HCV-RNA 24 weeks after completion of pegylated interferon plus ribavirin treatment. Decreases in plasma HCV-RNA concentration of at least 2 $\log_{10}$ or below the level of detection at week 12 were considered as early virological response. End of treatment response (ETR) was defined as undetectable serum HCV-RNA at the end of therapy. Non-response was defined as a failure to reach a decline of at least 2 $\log_{10}$ in HCV-RNA levels at week 12 of treatment or undetectable serum HCV-RNA 24 weeks after initiating therapy. Virological breakthrough was defined as detectable serum HCV-RNA after 24 weeks of therapy in patients with undetectable HCV load before. Relapses were defined as detectable serum HCV-RNA after having reached ETR. Two sensitivity analyses were carried out for estimating the efficacy. The first one was done according the principle of intention to treat, considering all missing values as failures. The second one was per-protocol analysis. In the latter, both patients in whom the N(t)RTI analysed in this study were withdrawn and those in whom the HCV course of therapy or the subsequent 24 weeks of follow-up was not completed due to causes other than non-response or virological breakthrough were not included.

Laboratory methods

Plasma HCV-RNA load was measured using a quantitative PCR assay (Cobas Amplicor HCV Monitor; Roche Diagnostic Systems Inc., Branchburg, NJ, USA: detection limit of $<$600 IU/mL; Cobas AmpliPrep-Cobas TaqMan; Roche Diagnostic Systems Inc., Meylan, France: detection limit of $<$50 IU/mL; Cobas TaqMan; Roche Diagnostic Systems Inc., Pleasanton, CA, USA: detection limit of $<$10 IU/mL, according to the available technique at each participating centre). Measurements of plasma HCV-RNA load were performed at baseline and at least 12, 24 and 48 weeks after starting therapy and, in all cases, 6 months after stopping therapy. HCV genotype was determined by line-probe assay (INNOLiPA HCV, Innogenetics, Ghent, Belgium).

Statistical analysis

The association between SVR and the type of N(t)RTI backbone administered during the course of HCV therapy was analysed. Likewise, we appraised the relationship between SVR and the following potential predictors: age; sex; body weight; risk factor for HCV transmission; HCV genotype; baseline plasma HCV-RNA load; baseline serum level of alanine aminotransferase and low-density lipoprotein (LDL) cholesterol; CDC clinical category; CD4+ cell count and HIV-RNA at baseline; liver fibrosis stage according to the Scheuer's scoring system;[16] type of pegylated interferon; daily dose of ribavirin by weight; participating centre; calendar year of starting pegylated interferon plus ribavirin treatment; use of hematopoietic growth factors; self-reported compliance with HCV therapy; third drug included in antiretroviral regimen; use of PI at any time before HCV therapy; and length of HCV infection. In this study, the duration of HCV infection was estimated in injecting users who had shared needles. The year of infection was estimated as the first year sharing needles.

Continuous variables are expressed as median (Q1–Q3) and the categorical variables as numbers (percentage). Student's *t*-test was used for comparisons between continuous variables if a normal distribution was followed and the Mann–Whitney *U*-test otherwise. Frequencies were compared with the χ^2 test or the Fisher's test when appropriate. The variables that showed a relationship with SVR in the univariate analysis with a $P < 0.2$ were entered in a multivariate stepwise logistic regression model. The adjusted odds ratio (AOR) and the respective 95% CIs were calculated. The goodness of fit of the models was assessed by the Hosmer–Lemeshow test. Associations with $P < 0.05$ were considered significant. Data were analysed using the SPSS statistical software package release 14.0 (SPSS Inc., Chicago, IL, USA).

Ethical aspects

The study was designed and performed according to the Helsinki Declaration and was approved by the Ethics Committee of the Hospital Universitario de Valme.

Results

Features of the study population

Two hundred and fifty-six patients met the inclusion criteria (Figure 1). Seventy (27%) patients were treated with abacavir plus lamivudine and 186 (73%) individuals with tenofovir plus lamivudine or emtricitabine (156 with lamivudine and 30 with emtricitabine). Fifty-two (74%) individuals who were given abacavir harboured HCV genotype 1 or 4 versus 121 (65%) out of those who received combinations of tenofovir ($P = 0.2$). The remaining baseline characteristics of both groups are summarized in Table 1. The antiretroviral drugs prescribed as third agent in combination with the studied N(t)RTI backbones are shown in Table 2. In two subjects, abacavir had to be replaced during the HCV therapy course with other N(t)RTI, specifically tenofovir and stavudine, due to suspected drug toxicity. Tenofovir was not discontinued in any patient during the follow-up.

Virological response

In an intention-to-treat analysis, 103 (40%) subjects achieved SVR: 20 (29%) in the abacavir group and 83 (45%) in the tenofovir group ($P = 0.02$). Among those individuals receiving an N(t)RTI backbone containing tenofovir, 72 (46%) patients treated with lamivudine showed SVR compared with 11 (37%) of those who received emtricitabine ($P = 0.4$). When we analysed the response to HCV therapy excluding those patients who received emtricitabine, the rates of SVR were 29% in the abacavir group and 46% among tenofovir recipients ($P = 0.013$). In the group of subjects with HCV genotype 1 or 4, 9 (17%) of those treated with abacavir plus lamivudine versus 37 (31%) who received tenofovir plus lamivudine or emtricitabine reached SVR ($P = 0.07$). For genotype 2 or 3, 11 (61%) patients in the abacavir group and 46 (71%) in the tenofovir group showed SVR ($P = 0.4$). The virological response at different time points and discontinuations of pegylated interferon plus ribavirin treatment in both groups are depicted in Figures 1 and 2. The frequency of pegylated interferon or ribavirin dose reductions was similar in both treatment groups (Table 1).

As patients in the abacavir group showed significantly higher levels of baseline plasma HCV-RNA load, we analysed SVR stratifying the population according to this parameter. In patients with baseline plasma HCV viral load lower than 600 000 IU/mL,

Table 1. Main characteristics of both treatment groups

Parameter	TDF-3TC/FTC group $n = 186$	ABC-3TC group $n = 70$	P
Age (years)[a]	42 (38–45)	41 (39–44)	0.6
Male gender, *n* (%)	149 (80)	50 (71)	0.2
Baseline body weight (kg)[a]	69 (61–76)	68 (60–76)	0.5
Former IDU, *n* (%)	150 (81)	59 (84)	0.6
Duration of HCV infection (years)[a,b]	15 (10.7–19.7)	12.1 (11.08–17.4)	0.1
Baseline HCV-RNA load (log IU/mL)[a]	5.8 (5.4–6.5)	6 (5.6–6.7)	0.02
Liver fibrosis stage ≥F3, *n* (%)[c]	56 (46)	28 (49)	0.7
Baseline serum ALT (IU/L)[a]	81 (59–108)	87 (56–124)	0.8
HCV genotype, *n* (%)			0.1
1	95 (51)	46 (66)	
2	6 (3)	0 (0)	
3	59 (32)	18 (26)	
4	26 (14)	6 (9)	
Use of PEG-IFN alfa-2a, *n* (%)	170 (91)	64 (91)	0.9
RBV dose/weight (mg/kg/day)[a,d]	14.7 (13.1–16.1)	14.7 (13.3–16.3)	0.8
RBV dose >10.6 mg/kg/day, *n* (%)[d]	162 (97)	66 (96)	0.9
Baseline CD4 cell counts/mm^3[a]	479 (351–699)	458 (301–600)	0.3
Baseline undetectable HIV viral load, *n* (%)	159 (85)	63 (90)	0.4
Baseline LDL cholesterol (mg/dL)[a]	91 (66–112)	89 (65–115)	0.7
Compliance with HCV therapy ≥80%, *n* (%)	180 (97)	64 (91)	0.1
PI use at any time before HCV therapy, *n* (%)	151 (81)	62 (89)	0.3
Use of growth factors, *n* (%)	13 (7)	6 (9)	0.6
PEG-IFN dose reduction, *n* (%)	22 (12)	7 (10)	0.8
RBV dose reduction, *n* (%)	19 (10)	8 (11)	0.8

TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir; IDU, intravenous drug user; ALT, alanine aminotransferase; PEG-IFN, pegylated interferon; RBV, ribavirin; LDL, low-density lipoprotein; PI, protease inhibitor.

[a]Median (Q1–Q3).

[b]Available in 112 subjects in the tenofovir group and in 31 patients in the abacavir group.

[c]Liver biopsy was available in 123 individuals in the tenofovir group and in 57 subjects in the abacavir group.

[d]Available in 167 patients in the tenofovir group and in 69 individuals in the abacavir group.

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Table 2. Third drugs used along with the two N(t)RTI backbones during the course of pegylated interferon plus ribavirin treatment

Antiretroviral drug	TDF-3TC/FTC group, *n* (%)	ABC-3TC group, *n* (%)	*P*
NNRTIs	107 (58)	34 (49)	0.2
efavirenz	84 (45)	24 (34)	0.1
nevirapine	23 (12)	10 (14)	0.8
Protease inhibitors	79 (42)	36 (51)	0.2
nelfinavir	8 (4)	2 (3)	0.8
lopinavir/ritonavir	37 (20)	11 (16)	0.5
atazanavir/ritonavir	16 (9)	7 (10)	0.9
fosamprenavir/ritonavir	5 (3)	2 (3)	0.9
saquinavir/ritonavir	13 (7)	14 (20)	0.005

TDF, tenofovir; 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; NNRTIs, non-nucleoside reverse transcriptase inhibitors.

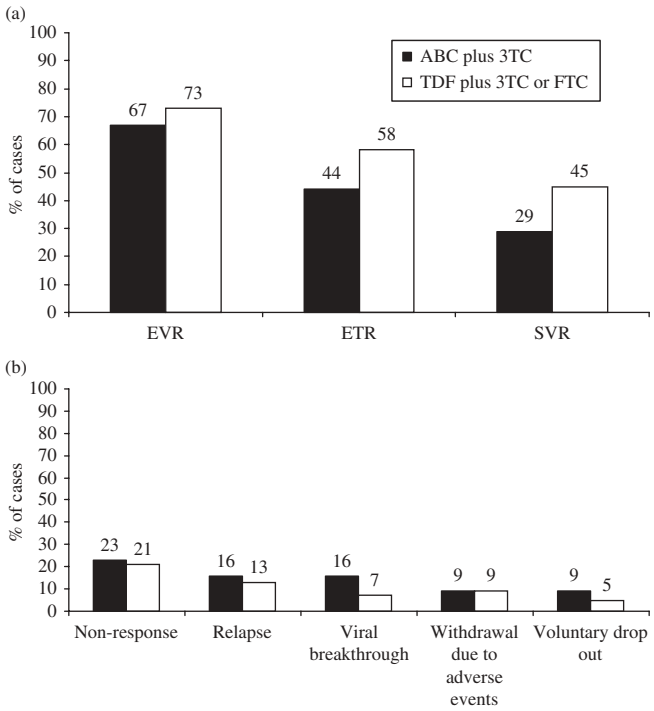

Figure 2. (a) Response to pegylated interferon plus ribavirin in patients included in the two N(t)RTI backbone groups (intention-to-treat analysis). *P* values for EVR, ETR and SVR were 0.3, 0.049 and 0.02, respectively. (b) Causes of lack of SVR in both arms. All *P* values were >0.05, except for viral breakthrough ($P = 0.05$). EVR, early virological response; ETR, end of treatment response; SVR, sustained virological response; TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir.

41 (51%) individuals on tenofovir and 10 (47%) on abacavir reached SVR ($P = 0.8$). In the subpopulation with baseline levels of plasma HCV viral load equal or higher than 600 000 IU/mL, 42 (40%) patients in the tenofovir group and 10 (20%) subjects in the abacavir group achieved SVR ($P = 0.02$).

In the per-protocol analysis, 19 (33%) individuals who were given abacavir showed SVR compared with 83 (52%) patients treated with combinations of tenofovir ($P = 0.01$). Among the subpopulation of patients harbouring HCV genotype 1 or 4, the rates of SVR in the abacavir and tenofovir group were 20% and 37%, respectively ($P = 0.07$). The rates of SVR were 77% in the abacavir group and 78% among tenofovir recipients harbouring HCV genotype 2 or 3 ($P = 0.9$).

Predictors of SVR

Besides N(t)RTI backbone containing tenofovir plus lamivudine or emtricitabine, HCV genotype 2 or 3, lower baseline plasma HCV-RNA load, baseline LDL cholesterol levels equal or higher than 100 mg/dL and undetectable HIV viral load at baseline predicted SVR in the univariate analysis (Table 3). All of the above-mentioned factors were independent predictors of SVR in the multivariate analysis (Table 3). The participant hospital was not associated with SVR (data not shown).

Influence of abacavir on response to HCV therapy according to the ribavirin dose

The negative impact of abacavir on SVR depended on the daily dose of ribavirin adjusted by weight. In more detail, SVR was lower among patients in the abacavir group who received doses below 13.2 mg/kg/day, the first quartile of weight-adjusted ribavirin dose. Namely, 3 (20%) of 15 patients in the abacavir group and 22 (52%) of 42 subjects in the tenofovir group who were prescribed <13.2 mg/kg/day achieved SVR ($P = 0.03$) (Table 4). Among the subpopulation of patients harbouring HCV genotype 1 or 4 who received ribavirin doses lower than 13.2 mg/kg/day, the rates of SVR in the abacavir and tenofovir group were 0% and 38%, respectively ($P = 0.06$). For patients harbouring HCV genotype 2 or 3 who were treated with doses below 13.2 mg/kg/day, the rates of SVR were 50% in the abacavir group and 66% among tenofovir recipients ($P = 0.6$).

Discussion

In this study, we found that HIV/HCV co-infected patients who receive a three-drug regimen including one PI or one NNRTI and abacavir plus lamivudine respond worse to pegylated interferon plus ribavirin treatment than those who take tenofovir plus lamivudine or emtricitabine as N(t)RTI backbone. The negative impact of abacavir on SVR is particularly remarkable among individuals receiving lower ribavirin doses per body weight and in patients who need to be treated with higher doses of ribavirin, as carriers of elevated baseline HCV-RNA levels and of HCV genotype 1 or 4. Altogether, these data could suggest an interference of abacavir in the metabolism of ribavirin.

In this study, the negative influence of treatment with abacavir plus lamivudine on SVR was independent of other known predictors of poorer response to HCV therapy, such as HCV genotype, HCV-RNA load and baseline LDL cholesterol levels. In two unpublished works, there was not significant association between the use of this NRTI and lower SVR rates.[17,18] In contrast, some studies had shown a significant association between abacavir use and poorer early virological response or an association with worse SVR restricted to patients with lower plasma levels of ribavirin.[12,14] However, potential confounders, such as concomitant

Table 3. SVR according to different variables

Parameter	SVR, *n* (%)	*P* univariate	AOR (95% CI)	*P* multivariate
Age (years)				
<41	53 (39)			
≥41	50 (42)	0.7	—	—
Gender				
male	78 (39)			
female	25 (44)	0.6	—	—
Baseline ALT (IU/L)				
≤84	48 (41)			
>84	55 (40)	0.9	—	—
Injecting drug user				
yes	86 (41)			
no	17 (36)	0.6	—	—
Liver fibrosis				
≤2	38 (40)			
≥3	28 (33)	0.4	—	—
HCV genotype				
1–4	46 (27)			
2–3	57 (69)	<0.001	8.9 (4–20)	<0.001
Duration of HCV infection (years)[a]				
<14.4	28 (41)			
≥14.4	33 (45)	0.6		
Baseline HCV-RNA load (log IU/mL)[b]	—	—	1.85[c] (1.1–3.1)	0.016
Daily dose of RBV (mg/kg)				
<13.2	25 (44)			
≥13.2	65 (36)	0.3	—	—
Type of PEG-IFN				
alfa-2a	94 (40)			
alfa-2b	9 (41)	0.9	—	—
Initiation of PEG-IFN therapy				
2001–04	47 (45)			
2005–06	56 (39)	0.3	—	—
Exposure to HCV therapy				
<80%	3 (25)			
≥80%	100 (41)	0.3	—	—
Baseline undetectable plasma HIV-RNA				
yes	96 (43)		3.5 (1.01–12.5)	
no	7 (21)	0.02		0.03
Baseline CD4 cell count/mm^3				
≥200	99 (40)			
<200	4 (44)	0.8	—	—
Baseline LDL-cholesterol (mg/L)				
≥100	34 (56)		3.06 (1.4–6.7)	
<100	35 (31)	0.003		0.004

Continued

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Table 3. *Continued*

Parameter	SVR, *n* (%)	*P* univariate	AOR (95% CI)	*P* multivariate
PIs use at any time before HCV therapy				
yes	85 (40)			
no	18 (42)	0.8		
N(t)RTI backbone				
ABC plus 3TC	20 (29)			
TDF plus 3TC or FTC	83 (45)	0.02	2.6 (1.05–6.9)	0.03
Third drug in ART combination				
PIs	40 (35)			
NNRTIs	63 (45)	0.1	—	—
Use of nevirapine				
yes	16 (48)			
no	87 (39)	0.4	—	—
Use of efavirenz				
yes	47 (43)			
no	56 (38)	0.4	—	—
Use of lopinavir/ritonavir				
yes	17 (35)			
no	86 (41)	0.5	—	—
Use of atazanavir/ritonavir				
yes	8 (35)			
no	95 (41)	0.7	—	—
Use of saquinavir/ritonavir				
yes	9 (33)			
no	94 (41)	0.6	—	—

ALT, alanine aminotransferase; RBV, ribavirin; PEG-IFN, pegylated interferon; LDL, low-density lipoprotein; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine; ART, antiretroviral therapy; PIs, protease inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors.
[a]Categorized by median.
[b]Median (Q1–Q3) HCV-RNA levels in patients with and without SVR were 5.8 log IU/mL (5.2–6.1) and 6 log IU/mL (5.6–6.7), respectively ($P = 0.02$).
[c]Increase in AOR per 1 log HCV-RNA decrease.

Table 4. SVR in both treatment groups according to the daily dose of ribavirin per body weight ($n = 236$)

Ribavirin dose (mg/kg)	TDF-3TC/FTC group SVR/no. (%)	ABC-3TC group SVR/no. (%)	*P*
<13.2	22/42 (52)	3/15 (20)	0.03
≥13.2	48/125 (38)	17/54 (31)	0.4

TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir.

zidovudine use along with abacavir, may have been involved in the findings observed in all of these previous studies.[12,14,17,18] Administration of zidovudine along with ribavirin increases the risk of anaemia and the likelihood of ribavirin dose reductions.[11,15] It is well known that lower doses of ribavirin are associated with poorer SVR rates, particularly among hard-to-treat patients.[10,19] For this reason, only individuals who received lamivudine or emtricitabine plus tenofovir or lamivudine plus abacavir were included in our study, in order to avoid potential confounders. Due to this design, this study provides the strongest support for a negative impact of abacavir on SVR among the data reported so far on this issue. In addition, this study supplies information about the differential impact on SVR of the currently most commonly used combinations of N(t)RTI.

Abacavir has been found to reduce the response to pegylated interferon plus ribavirin in HIV/HCV co-infected patients with plasma ribavirin levels lower than 2.3 μg/mL in a recent report.[14] This could suggest an interaction between abacavir and ribavirin. This finding agrees with the results observed in our study concerning the relationship between abacavir and a poorer SVR in patients with low ribavirin doses per body weight and in patients who need higher doses of ribavirin. In this regard, given that both drugs are guanosine analogues and share some metabolic pathways,[20,21] an inhibitory competition in the phosphorylation could

occur between ribavirin and abacavir. The differential impact of abacavir and tenofovir containing combinations on the response to pegylated interferon plus ribavirin was seen from the first weeks of anti-HCV therapy. Also, HCV viral breakthroughs were more common among abacavir-treated patients. These findings suggest that the antiviral potency of pegylated interferon plus ribavirin is reduced when abacavir is given concomitantly, which is also consistent with an interaction. *In vitro* studies are needed in order to confirm this possible interaction between abacavir and ribavirin.

This study provides valuable information regarding the selection of the best N(t)RTI backbone in HIV/HCV co-infected patients when treatment with pegylated interferon plus ribavirin is planned to be started in the short term. According to previous studies and the latest international guidelines for the care of HIV/HCV co-infected patients,[9–11] the use of didanosine along with ribavirin is not recommended in this population due to an increased risk of lactic acidosis, hyperlactataemia and pancreatitis. Likewise, the use of zidovudine is associated with an increased frequency of severe anaemia and ribavirin dose reduction.[15] When possible, zidovudine should be changed by another NRTI prior to starting therapy against HCV, in order to avoid the need for ribavirin dose reductions.[10,15] On the other hand, stavudine has been shown to be associated with similar rates of SVR to HCV therapy as tenofovir in a recent study,[13] but its poor safety profile prevents the use of this drug as the first choice. Due to these reasons and the results of our study, tenofovir plus lamivudine or emtricitabine seems to be the preferred N(t)RTI backbone during pegylated interferon and ribavirin treatment in HIV/HCV co-infected patients who require simultaneous antiretroviral therapy. Abacavir plus lamivudine could be an alternative, provided that the daily dose of ribavirin is high enough and, especially, in patients with genotype 2 or 3 and in those with lower plasma HCV-RNA. The combination of abacavir plus lamivudine along with high doses of ribavirin should be analysed in properly designed randomized clinical trials.

Other predictors of SVR found in this study, particularly HCV genotype 2 or 3 and lower plasma HCV-RNA load, have been previously reported in most clinical trials and cohort studies performed in HIV/HCV co-infected patients.[1–4,13,22] Likewise, higher serum LDL cholesterol levels have been shown to be associated with SVR to pegylated interferon plus ribavirin, both in HCV mono-infected individuals and in the HIV-infected population.[23–25] On the other hand, our study has shown a relationship between undetectable HIV viral load at baseline and better response to therapy against HCV, which has not been reported as a predictor of SVR in other works.[1–4,13] Nevertheless, this finding was also found in a recent substudy conducted in subjects with genotype non-1 infection enrolled in the APRICOT trial.[22] The authors of this study proposed an improvement in HCV-specific immune responses associated with well-controlled HIV replication as a possible explanation.[22] An alternative and, perhaps, more likely explanation is that undetectable HIV-RNA load is a surrogate marker of good adherence to treatments, even better than the self-reported compliance.

Our study has some limitations. On the one hand, biases related to the observational design might have impacted the results. Thus, baseline predictors of response could have not been equally frequent in subjects belonging to both treatment groups. In fact, in this study, the median HCV-RNA level at baseline was higher among patients who were treated with abacavir than in those who received tenofovir, which might have been involved in the differences in the SVR. However, the differences between the two N(t)RTI backbones remained after stratifying by baseline HCV-RNA levels in the univariate analysis, and patients with higher baseline HCV-RNA load who received abacavir-based regimens showed significantly poorer SVR. Moreover, multivariate analysis adjusted for baseline HCV-RNA concentration showed that the association of abacavir with SVR was independent of HCV-RNA levels. Finally, the difference in the median baseline HCV-RNA load between the abacavir and tenofovir groups was 0.2 logs. This difference is not biologically significant. Whatever the assay, differences or changes of <0.5 logs should be considered irrelevant, as they may be due to intrinsic or between-patient variability.[26] On the other hand, we considered emtricitabine and lamivudine as equivalent, when they are given along with tenofovir, and both drugs are not identical. Nevertheless, we did not find significant differences in SVR between both NRTIs, which suggest that they are comparable with regard to this issue.

In summary, based on the results of this study, the N(t)RTI backbone tenofovir plus lamivudine or emtricitabine for HIV/HCV co-infected seems to be the preferred choice in patients on treatment for HCV infection. An N(t)RTI backbone including abacavir could be an alternative, particularly in patients with HCV genotype 2 or 3 and low levels of HCV-RNA load, but ribavirin doses higher than 13.2 mg/kg/day should be used. An interference of abacavir with the activity of ribavirin against HCV could explain the lower efficacy of pegylated interferon plus ribavirin in individuals receiving this NRTI. Controlled clinical trials are warranted in order to determine the best antiretroviral combination during therapy against HCV in the HIV-infected population.

Funding

This study has been partly supported by grants from Consejería de Salud of the Junta de Andalucía (reference: 0017/07) and the ISCIII-RETIC RD06/006.

Transparency declarations

J. A. M. has received a research grant from GlaxoSmithKline. C. T. reports having received consulting fees from Abbot, Roche Pharma and GlaxoSmithKline. D. M. reports having participated as an investigator in a clinical trial supported by GlaxoSmithKline. She has received consulting fees from Roche, Abbot and Bristol-Myers Squibb. A. R. reports having received consulting fees from Bristol-Myers Squibb, Abbot, Gilead, Roche Pharma and Boehringer Ingelheim Pharmaceuticals. M. G.-S. reports having participated as an investigator in clinical trials supported by Roche and GlaxoSmith-Kline. She has received lecture fees from Boehringer Ingelheim. J. M. has been an investigator in clinical trials supported by Roche, Bristol-Myers Squibb and Abbot Pharmaceuticals. He has received lectures fees from Roche and consulting fees from Boehringer Ingelheim. J. A. P. reports having received consulting fees from GlaxoSmithKline, Bristol-Myers Squibb, Abbot, Gilead and Boehringer Ingelheim Pharmaceuticals. He has received research support from GlaxoSmithKline, Roche, Bristol-Myers Squibb, Schering-Plough, Abbot and Boehringer Ingelheim Pharmaceuticals and has received lecture fees from GlaxoSmithKline, Roche, Abbot, Bristol-Myers Squibb, Boehringer Ingelheim and Schering-Plough Pharmaceuticals. The remaining authors have no conflicts of interest.

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