Ribavirin and abacavir drug interaction in HIV–HCV coinfected patients: fact or fiction?

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Objective(s): To examine the impact of ribavirin and abacavir coadministration on hepatitis C virus (HCV) virological response and trough ribavirin plasma concentration (Cmin) in HIV–HCV coinfected patients.

Design: Pharmacokinetic substudy on patients from the ANRS CO-13 HEPAVIH cohort.

Methods: Patients receiving ribavirin–pegylated interferon for whom a ribavirin steady state Cmin was prospectively determined were included. Rapid virological response (RVR), early virological response (EVR) and sustained virological response (SVR) as well as HCV-RNA decline were evaluated.

Results: Overall, 124 HIV–HCV coinfected patients (95% on antiretroviral therapy) were enrolled. Of these patients, 22% received abacavir. The overall median (interquartile range) ribavirin Cmin was 1.6 mg/l (1.2–2.2) with no statistical difference between abacavir users and nonusers [1.5 mg/l (0.99–2.1) and 1.7 (1.2–2.3), $P = 0.15$]. RVR and EVR were 52 and 72%, respectively. There was no difference observed in the proportion of abacavir users vs. nonusers achieving RVR (respectively 59 vs. 50%, $P = 0.40$) or EVR (72 vs. 73%, $P = 0.94$), or in the HCV-RNA decline at week 4 [−2.24 $\log_{10}$ IU/ml, (−3.58; −0.81) and −1.27 (−2.8; −0.47) $P = 0.28$] or at week 12 [−1.76 $\log_{10}$ IU/ml (−3.67; −0.35) and −1.85 (−3.13; −1.13) ($P = 0.58$)]. The SVR rate was 45% for abacavir users and 24% for abacavir nonusers, but the difference was not statistically significant ($P = 0.059$).

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Conclusion: In our study, there was no evidence that abacavir affected HCV treatment outcomes and the ribavirin Cmin was similar in abacavir users and nonusers, confirming the absence of pharmacokinetic interaction between abacavir and ribavirin. An abacavir-containing regimen is, therefore, a well tolerated treatment alternative for coinfected patients starting HCV treatment.

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Introduction

The combination of ribavirin and pegylated interferon (Peg-IFN) is still the standard of treatment for HIV–HCV coinfected patients, although new drugs, such as anti-HCV protease inhibitors, are becoming available for patients infected with HCV genotype 1. In France, almost one-third of HIV patients are chronically HCV coinfected and liver disease constitutes one of the leading causes of morbidity and mortality in this population [1]. Several factors have been associated with sustained virological response to anti-HCV treatment such as HCV genotype, baseline HCV-RNA or trough ribavirin plasma concentration [2–4]. Scientific evidence suggests that trough ribavirin plasma concentrations above 2 mg/l at week 4 are the best predictive factor of sustained virological responses (SVRs) [5–7].

Ribavirin is a purine nucleoside analogue that may interfere with the intracellular metabolism of other anti-HIV nucleoside analogues (such as didanosine, zidovudine or stavudine), thereby increasing the risk of toxicity [8]. Previous observational studies conducted on HIV–HCV coinfected patients receiving ribavirin–Peg-IFN and an abacavir-containing regimen have reported contradictory HCV response results (Table 1).

However, not all guidelines agree on the use of abacavir to manage HIV–HCV coinfection. Some of them recommend its use exclusively in the absence of alternative treatment and only if ribavirin plasma concentrations are monitored, whereas others consider data scarce [9,10].

In the context of the ANRS CO-13 HEPAVIH cohort, we conducted a substudy to examine the impact of ribavirin and abacavir coadministration on HCV virological response and ribavirin plasma concentration. Because tenofovir was the most frequently used nucleos(t)ide reverse transcriptase inhibitors (NRTI), we also compared ribavirin plasma concentration and HCV virological response between abacavir-containing and tenofovir-containing regimens.

Methods

HEPAVIH cohort and study design

A pharmacokinetic substudy was performed on patients who had initiated ribavirin–Peg-IFN therapy for 48 weeks and whose ribavirin concentrations were measured prospectively and before any dose adjustment.

The ANRS CO-13 HEPAVIH is a French multicenter cohort that follows 1175 HIV-1/HCV chronically coinfected patients or patients having cleared HCV after a successful anti-HCV treatment [11]. Patients are followed-up as recommended by the European consensus conference on hepatitis C, that is, every year for noncirrhotic patients and every 6 months for cirrhotic patients [12]. Five specific additional visits are scheduled when ribavirin–Peg-IFN is initiated (baseline, week 4, week 12, end of treatment and six months after completion of treatment).

Data collection

Demographic and therapeutic data (age, sex, BMI, HIV and HCV risk factors, HCV genotype, fibrosis score (according to the METAVIR histological scoring system), ribavirin dosage, HIV treatment) and biological parameters (CD4 cell count, plasma HIV-RNA and serum HCV-RNA) were extracted from the standardized medical questionnaire. Serum HCV-RNA was recorded at baseline, after 4 and 12 weeks of therapy and 24 weeks after treatment completion. Steady-state trough ribavirin plasma concentrations (Cmin, 12 ± 2-h interval between last drug intake and sampling) prospectively determined during follow-up were retrospectively analyzed.

The virological outcomes evaluated were rapid virological responses (RVRs), early virological responses (EVRs) and SVRs. RVR and EVR were defined as a decrease in serum HCV-RNA $2\log_{10}$ IU/ml or more and/or an undetectable serum HCV-RNA at weeks 4 and 12, respectively. SVR was defined as an undetectable serum HVC-RNA 24 weeks after the end of treatment. Secondary outcomes were serum HCV-RNA decline between baseline and both weeks 4 and 12.

Table 1. Summary of study characteristics of ribavirin and abacavir interaction.

Methodology	Endpoint, statistical analysis	Results	Impact of ABC on viral response
HC02-RIBAVIC substudy; $N=154$ naive patients (22 with ABC) Peg-INFα2b + RBV 800 mg per day for 48 weeks	EVR = <50 IU/ml or decrease >2log$_{10}$ Multivariate analysis for predictive factors	EVR = 63% Negative impact of ABC on EVR OR = 4.92 (95% CI: 1.5–16.06); $P=0.0083$	Yes [13]
Retrospective, multicenter $N=256$ naive patients receiving PI or NNRTI + either ABC/3TC ($n=70$) or TDF/XTC ($n=186$) Peg IFN α2b/a + RBV 600–1200 mg per day for 48 weeks (HCV genotypes 1/4) and for 24 or 48 weeks (HCV genotypes 2/3)	% SVR in both groups Multivariate analysis for predictive factors	SVR = 40%; 29 (ABC) vs. 45% (TDF); $P=0.02$ Lower SVR rate in ABC group associated with baseline HCV-RNA >600 000 IU/ml ($P=0.02$), HCV genotype 1/4 ($P=0.07$) and daily dose of RBV <13.2 mg/kg per day ($P=0.03$) TDF predictive of SVR: OR = 2.6 (95%: 1.05–6.9); $P=0.03$	Yes [14]
Retrospective, multicenter $N=493$ naive patients, receiving 2 N(t)RTIs + either PI or NNRTI or third N(t)RTI (115 with ABC) Peg IFN α2b/a + RBV 1000/1200 mg per day	SVR W4 plasma RBV Cmin Multivariate analysis for predictive factors	SVR = 38% Predictors of absence of SVR were higher for baseline HCV-RNA ($P=0.003$), HCV genotype 1/4 ($P<0.001$) and lower RBV Cmin ($P=0.005$). ABC associated with absence of SVR only in patients with RBV Cmin <2.3 μg/ml [OR = 7.63 (95%: 1.39–41.6); $P=0.02$]	Yes [15]
Retrospective, multicenter $N=258$ naive patients under HAART (68 with ABC) Peg IFN α2b/a + RBV 500–1500 mg per day for 48 weeks (HCV genotype 1/4) and for 24 or 48 weeks (HCV genotype 2/3)	SVR Multivariate analysis for predictive factors	SVR = 37% Predictors of SVR were baseline HCV-RNA <600 000 IU/ml ($P=0.003$), HCV genotype 2/3 ($P<0.001$), exposure to HCV therapy >80% ($P=0.005$) and baseline CD4 >300/mm^3 ($P=0.02$). 44% SVR with use of TDF or D4t + 3tc + 1 PI or NNRTI vs. 29% with other ART strategies ($P=0.014$)	No [16]
Retrospective, multicenter $N=244$ naive patients (49 with ABC), HAART in 85% Peg IFN α2b/a + RBV 800/1000/1200 mg per day for 48 weeks	SVR Multivariate analysis for predictive factors	SVR: 46.2 (ABC users) vs. 46.7% (ABC nonusers), $P=1$ ABC not associated with virological failure at any of the time frames evaluated (W4, 12, 24, 48, 72) Predictors of absence of SVR were HCV genotype 1/4 ($P<0.0001$) and age >40 years ($P=0.053$)	No [17]
Retrospective, multicenter $N=212$ patients under HAART (74 with ABC) Peg IFN α2b/a + RBV 800/1000/1200 mg per day for 48 weeks	EVR (decrease >2log$_{10}$ IU/ml at W12) and SVR Multivariable logistic regression analysis to evaluate the association between ABC use and EVR or SVR	EVR = 45% (ABC users) vs. 50% (ABC nonusers); adjusted OR = 0.99 (95% CI: 0.53–1.84) SVR = 15% (ABC users) vs. 16% (ABC nonusers); adjusted OR = 1.11 (95%CI: 0.48–2.59) No difference according to HCV genotype	No [18]

ABC, abacavir; CI, confidence interval; Cmin, trough plasma concentration; EVR, early virological response; HCV, hepatitis C virus; OR, odds ratio; RBV, ribavirin; SVR, sustained virological response.

Statistical analysis

Results are expressed as a median value [interquartile range (IQR)] or *n* (%). Ribavirin Cmin and virological outcomes were compared between abacavir users and nonusers and between abacavir users and tenofovir users. Characteristics between groups were compared using the Wilcoxon rank-sum or χ^2 test as appropriate. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

One hundred and twenty-four HIV–HCV coinfected patients receiving ribavirin–Peg-IFN (95% on antiretroviral therapy) were enrolled. The baseline patient characteristics are presented in Table 2 and were similar for abacavir users and nonusers. The median (range) ribavirin dose at baseline was 1000 mg/day (400–1600). At least one ribavirin dose adjustment (usually a 200 mg daily dose increase) following the first Cmin result was made in 39% (48/124) of patients. The main antiretroviral regimens prescribed were one or two NRTIs along with a protease inhibitor in 77% of patients. Atazanavir was the third agent most frequently used in abacavir users (44%) and nonusers (35%). Overall, 27 patients (22%) received abacavir and another NRTI and in most patients either a protease inhibitor or NNRTI. Of the 97 patients not on an abacavir-containing regimen, the most frequent regimen prescribed was tenofovir–emtricitabine (75%).

Impact of abacavir on ribavirin Cmin

The overall median (IQR) ribavirin Cmin was 1.6 mg/l (1.2–2.2) with no statistical difference between abacavir users and nonusers [1.5 (0.99–2.1) and 1.7 (1.2–2.3), $P = 0.15$]. Regardless of the ribavirin Cmin cutoff (2.0 or 2.3 mg/l as proposed by Vispo *et al.* [15]), the proportion of suboptimal concentrations was similar for both groups (70 vs. 64%, $P = 0.53$ and 89 vs. 74% $P = 0.10$). There was no difference in the frequency of ribavirin dose adjustments between abacavir users and nonusers (48 vs. 36%, $P = 0.25$). When comparing patients receiving abacavir ($n = 23$) to those receiving tenofovir ($n = 78$), there was no significant difference in the ribavirin Cmin [respectively 1.5 mg/l (1.0–2.1) vs. 1.7 mg/l (1.2–2.3), $P = 0.18$] or the proportion of suboptimal Cmin,

Table 2. Baseline characteristics of the population.

Characteristic	All patients ($N = 124$)		Abacavir nonusers ($N = 97$)		Abacavir users ($N = 27$)		
	$n_{available}$	Median (IQR) or *n* (%)	$n_{available}$	Median (IQR) or *n* (%)	$n_{available}$	Median (IQR) or *n* (%)	*P**
Age (years)	124	45 (42–48)	97	45 (43–48)	27	44 (41–50)	0.93
Male	124	90 (73)	97	75 (77)	27	15 (56)	0.025
BMI (kg/m^2)	124	21.9 (20.0–24.1)	97	22.1 (19.8–24.5)	27	21.2 (20.3–23.9)	0.69
CD4 cell count (cells/μl)	114	445 (337–600)	89	455 (337–600)	25	438 (274–599)	0.66
CD4 cell count <200 cells/μl	114	6 (5)	89	5 (6)	25	1 (4)	1.00
Plasma HIV RNA <50 c/ml	114	97 (85)	89	76 (85)	25	21 (84)	1.00
HCV genotype	124		97		27		0.73
1 or 4		86 (69)		68 (70)		18 (67)	
2 or 3		38 (31)		29 (30)		9 (33)	
Serum HCV viral load, $\log_{10}$ IU/ml	124	6.17 (5.65–6.52)	97	6.17 (5.64–6.56)	27	6.20 (5.69–6.34)	0.85
Serum HCV viral load >800 000 IU/ml	124	76 (61)	97	58 (60)	27	18 (67)	0.52
METAVIR score F >3	123	57 (46)	97	41 (42)	26	16 (62)	0.08
Peg-IFN	124		97		27		0.24
α-2a		104 (84)		79 (81)		25 (93)	
α-2b		20 (16)		18 (19)		2 (7)	
Baseline ribavirin dose/body weight (mg/kg per day)	124	16.2 (13.8–18.9)	97	16.2 (13.8–18.7)		16.0 (13.4–19.0)	0.84
PI use	124	96 (77)	97	76 (78)	27	20 (74)	0.64
Atazanavir/r, atazanavir		46 (37)		34 (35)		12 (44)	0.37
Lopinavir/r		22 (18)		17 (18)		5 (19)	1.00
Fosamprenavir/r		15 (12)		13 (13)		2 (7)	0.52
Darunavir/r		6 (5)		5 (5)		1 (4)	1.00
NNRTI use	124	20 (16)	97	15 (15)	27	5 (19)	0.77
Efavirenz		12 (10)		8 (8)		4 (15)	0.29
Nevirapine		6 (5)		5 (5)		1 (4)	1.00
Raltegravir use	124	10 (8)	97	9 (9)	27	1 (4)	0.69
NRTI use	124	112 (90)	97	85 (88)	27	27 (100)	0.07
Tenofovir		82 (66)		78 (80)		4 (15)	<10–4
Lamivudine		31 (25)		8 (8)		23 (85)	<10–4
Emtricitabine		77 (62)		75 (77)		2 (7)	<10–4
Zidovudine		3 (2)		2 (2)		1 (4)	0.52

Cmin, trough ribavirin plasma concentration; HCV, hepatitis C virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.
*Wilcoxon rank-sum test or χ^2 test

regardless of the cutoff value examined [2.0 mg/l (74 vs. 63%, $P=0.32$) or 2.3 mg/l (87 vs. 73%, $P=0.17$)].

Impact of abacavir on virological outcomes

Overall, response rates were 52% (63/121) for RVR and 72% (82/113) for EVR. At week 4, there was no difference observed between the proportions of abacavir users vs. nonusers achieving RVR (59 vs. 50%, $P=0.40$). Also, there was no difference observed between these two groups in HCV-RNA decline between baseline and week 4 [-2.24 $\log_{10}$ IU/ml, (-3.58; -0.81) and -1.27 log10 IU/ml (-2.8; -0.47) $P=0.28$]. Comparable results were obtained at week 12 with similar EVR rates for abacavir users and nonusers (72 vs. 73%, $P=0.94$). The serum HCV-RNA decline was -1.76 $\log_{10}$ IU/ml (-3.67; -0.35) for abacavir users and -1.85 $\log_{10}$ IU/ml (-3.13; -1.13) for abacavir nonusers ($P=0.58$). Only 88 out of 124 patients were evaluable 6 months after anti-HCV treatment completion, and 26 (29.5%) out of the 88 achieved SVR. The SVR rate for abacavir users was higher than for nonusers (45 vs. 24%), although the difference was not statistically significant ($P=0.059$).

Finally, similar results were observed when comparing virological outcomes for abacavir-containing vs. tenofovir-containing regimens. The same proportion of patients in both groups achieved RVR (56 vs. 53%, $P=0.74$) and EVR (74 vs. 72%, $P=0.84$). The HCV-RNA decline was also not significantly different for abacavir users vs. tenofovir users at week 4 [respectively -1.19 $\log_{10}$ IU/ml (-2.96; -0.50) vs. -1.45 $\log_{10}$ IU/ml (-2.86; -0.54), $P=0.87$] and at week 12 [-2.06 log10 IU/ml (-3.78; -0.56) vs. -1.84 log10 IU/ml (-2.93; -1.13), $P=0.79$]. Of the 49 evaluable patients, 47% (9/19) achieved SVR in the abacavir group vs. 24% (12/51) in the tenofovir group ($P=0.053$). Although this result was almost statistically significant, the number of patients examined was limited.

Discussion

In our study, there was no evidence that abacavir affected the ribavirin Cmin or HCV treatment outcomes. The median ribavirin Cmin was similar for abacavir users and nonusers, confirming the absence of pharmacokinetic interaction between abacavir and ribavirin. Moreover, the proportion of patients with an inadequate ribavirin Cmin was similar in both groups. In terms of virological outcomes, there were no differences in the proportion of patients achieving RVR, EVR or SVR, even when abacavir-containing and tenofovir-containing regimens were compared. It is important to note that the two groups were comparable in terms of HCV genotype distribution, serum HCV-RNA and proportion of patients with a F at least 3 METAVIR score.

Previous studies conducted on HIV–HCV coinfected patients receiving Peg-IFN–ribavirin and on an abacavir-containing regimen reported contradictory results for HCV response. The first report from the RIBAVIC study showed that abacavir-based antiretroviral therapy is associated with a lower EVR rate [13]. Because both drugs are guanosine analogues, the authors hypothesized that abacavir and ribavirin compete for intracellular phosphorylation. Thereafter, two studies reported abacavir's negative impact on SVR [14,15], whereas three other studies did not find any significant relationship between abacavir-based therapy and the SVR rate [16–18]. Surprisingly, Vispo *et al.* [15], who reported abacavir's negative impact on SVR, showed no difference between abacavir users and nonusers regarding the ribavirin plasma concentrations or the rate of Cmin reaching the 2.3 mg/l cutoff. Moreover, abacavir was associated with an absence of SVR in the multivariate analysis when it was restricted to patients with lower ribavirin plasma concentrations (<2.3 mg/l). Two concomitant Spanish multicenter studies involving similar patient numbers and SVR rates reported discordant results for abacavir's impact on SVR [14,16]. In the study showing abacavir's negative effect on SVR, the association was only found in patients with a high baseline serum HCV viral load, HCV genotype 1 or 4 and a ribavirin dose below 13.2 mg/kg per day [14]. Unfortunately, no pharmacokinetic data were presented in any of the studies reporting no association between abacavir and SVR, except for the one reported by Vispo *et al.* More recently, three other studies also demonstrated the absence of a relationship between abacavir and a lower SVR rate [19–21]. In-vitro studies show a similar, low-level anti-HIV antagonistic effect when ribavirin was combined with either abacavir or tenofovir [22]. Recently, Van den Eynde *et al.* [23] showed that ribavirin's suppression of an HCV replicon system *in vitro* is not modified by abacavir, tenofovir or lamivudine. The authors concluded that the current recommendation to avoid abacavir is no longer justified.

The absence of abacavir's negative effect on virological responses of ribavirin–Peg-IFN therapy in HIV–HCV-coinfected patients found in our study confirmed other recently published data and is supported by the absence of a difference in ribavirin exposure between abacavir users and nonusers. Although our study presents some limits, that is it is retrospective and was conducted on a limited number of abacavir-treated patients, the experimental conditions were similar to other studies. The discordant results observed may be due to differences in the ribavirin doses used between studies. In fact, in the RIBAVIC study, patients received only 800 mg per day (12.2 mg/kg per day) of ribavirin [13] and the lower SVR rate reported in other studies was observed only in patients with either lower ribavirin exposure [15] or a lower ribavirin dose [14]. Therefore, it seems that suboptimal exposure to ribavirin rather than an abacavir and ribavirin interaction

may explain the poor virological response reported in those studies.

In our study, the median ribavirin Cmin was consistent with the ribavirin daily dose and only 39% of patients had a dose adjustment following initial therapeutic ribavirin monitoring. However, the relatively low within-patient variability of ribavirin Cmin (approximately 22%) might reinforce the level of ribavirin dose adjustment evidence based on therapeutic ribavirin drug monitoring.

In summary, our results confirmed that an abacavir-containing regimen is a well tolerated treatment alternative for coinfected patients starting HCV treatment.

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Conflicts of interest

There are no conflicts of interest.

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