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Plasma Ribavirin Trough Concentrations at Week 4 Predict Hepatitis C Virus (HCV) Relapse in HIV-HCV-Coinfected Patients Treated for Chronic Hepatitis C▽

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The influence of ribavirin trough concentrations (RBV C_{trough}) on the risk of hepatitis C virus (HCV) relapse was retrospectively analyzed in 99 HIV-HCV-coinfected patients who achieved end-of-treatment response with pegylated alpha interferon plus weight-based RBV. The independent predictors (odds ratio [OR] [95% confidence interval (CI)]) of HCV relapse were RBV plasma C_{trough} of <2.5 μg/ml (4.5 [1.3 to 15.5]), baseline serum HCV RNA (2.5 [1.2 to 5.1]), and HCV genotype 1 or 4 (13.3 [2.6 to 66.7]). Monitoring of RBV C_{trough} may permit early adjustment of RBV dosage to avoid HCV relapse.

The standard treatment for chronic hepatitis C virus (HCV) infection is the combination of pegylated alpha interferon (pegIFN) and ribavirin (RBV), which allows cure of HCV in around 50 to 60% of HCV-monoinfected patients (8, 12) and 30 to 40% of HIV-HCV-coinfected individuals (4, 21). Although new drugs for treating HCV infection, such as HCV protease inhibitors, are currently being developed, preliminary evidence (9, 10) suggests that the use of RBV seems unavoidable for maximizing the chances of sustained virological response (SVR).

RBV is a synthetic guanosine analogue. Several mechanisms of action have been proposed to explain its anti-HCV effect, including direct inhibition of the viral RNA polymerase, IMP dehydrogenase inhibition, hypermutagenesis, and immunomodulation (7). Pharmacokinetic-pharmacodynamic studies conducted in HCV-monoinfected and HIV-HCV-coinfected patients have found an association between RBV concentrations and achievement of early and sustained virological responses (reviewed in references 5 and 15 and a recent paper [3]), indirectly supporting a role for therapeutic drug monitoring of RBV concentrations to tailor RBV dosage early in treatment and in this way to try to enhance the chances of SVR.

In addition to a lower initial response to hepatitis C therapy, a higher rate of HCV relapse (range, 15% to 37%) (4, 6, 16, 20, 21, 23) could contribute to the lower rate of SVR seen in HIV-HCV-coinfected patients than in HCV-monoinfected patients. Several factors such as high baseline HCV RNA and lack of rapid virological response (RVR) have been associated with HCV relapse (16). However, the impact of RBV concentrations on the risk of HCV relapse is unknown. If a significant association exists, adjustment of RBV dosages based on early RBV concentrations could be very useful to minimize the risk of HCV relapse.

A retrospective study was performed in HIV-HCV-coinfected patients who achieved end-of-treatment (EOT) response with pegIFN-α 2a or 2b (180 μg/week or 1.5 μg/kg of body weight/week) plus weight-based RBV (1,000 or 1,200 mg/day for patients weighting <75 or >75 kg, respectively) since 2004 at our clinic. The duration of treatment was based on HCV genotype and the achievement of undetectable HCV RNA at week 4 (RVR), ranging from 6 to 18 months (11, 17).

Demographics and other clinical characteristics were recorded in a case report form specially designed for this study. Serum HCV RNA was measured at baseline, every 4 to 12 weeks of therapy, and 24 weeks after completion of treatment by TaqMan (Roche), with a limit of detection of 10 IU/ml. HCV genotyping was examined using a hybridization assay (InnoLipa-HCV; Bayer). RBV plasma trough concentrations (RBV C_{trough}) were measured before the intake of the first daily dose of RBV at week 4 of therapy by high-performance liquid chromatography with ultraviolet detector (HPLC-UV) (14).

EOT response was defined as undetectable HCV RNA at the end of therapy. HCV relapse was defined as detectable HCV RNA within the next 24 weeks after achieving EOT response.

Statistical analyses were performed using the SPSS v13.0 program (SPSS Inc., Chicago, IL). Quantitative and qualitative variables were compared using the Mann-Whitney U and the chi-square tests, respectively. Logistic regression analyses were performed to assess which factors could influence the risk of HCV relapse. Receiving operating characteristic curves were performed to calculate the sensitivity and specificity values for RBV C_{trough} at which HCV relapse was more likely to occur.

A total of 99 patients with EOT response were analyzed. The main baseline characteristics of these individuals were as follows: median (interquartile range) age was 42 (39 to 46) years, 68% were male, all but one were Caucasians, median HCV RNA was 6.03 (5.43 to 6.53) log IU/ml, 60% were in-

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TABLE 1. Predictors of HCV relapse[a]

Variable	Bivariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.97 (0.9–1.1)	0.56		
Male gender	1.1 (0.5–2.8)	0.76		
Caucasian ethnicity	0.9 (0.9–1)	1		
Advanced liver fibrosis (Metavir F3F4)	0.44 (0.1–1.8)	0.26		
Ribavirin dose	0.99 (0.9–1)	0.62		
RBV C_{trough} of <2.5 μg/ml	**2.89 (1.1–7.3)**	**0.025**	**4.5 (1.3–15.5)**	**0.018**
HCV genotype 1 or 4	**5.9 (2.0–17.2)**	**0.001**	**13.3 (2.6–66.7)**	**0.002**
High baseline HCV RNA (IU/ml)	**2.1 (1.1–3.9)**	**0.022**	**2.5 (1.19–5.15)**	**0.015**
Prior HCV treatment	2.2 (0.4–11.6)	0.35		
Antiretroviral therapy	2.8 (0.7–10.4)	0.128	0.87 (4.8–0.16)	0.87
Abacavir use	**2.5 (1.0–6.1)**	**0.047**	**3.3 (0.91–11.9)**	**0.07**

[a] Values in bold are significantly associated with HCV relapse. OR, odds ratio; CI, confidence interval.

fected by HCV genotype 1 or 4, and advanced liver fibrosis (F3F4 Metavir estimates) was recognized in 16% of patients. Overall, 82% of patients were on antiretroviral therapy and 30% were taking abacavir.

Overall, 67 (68%) patients with EOT response attained SVR while 32 (32%) relapsed. Median RBV C_{trough} at week 4 was higher in patients who achieved SVR than in those who experienced HCV relapse (2.73 [1.98 to 3.21] versus 2.12 [1.1 to 2.78] μg/ml, $P = 0.006$). The best RBV C_{trough} threshold discriminating SVR and HCV relapse was 2.5 μg/ml (66% sensitivity and 60% specificity, $P = 0.007$).

The independent predictors of HCV relapse in the multivariate analysis were HCV genotype 1 or 4, RBV C_{trough} at week 4 of <2.5 μg/ml, and high baseline HCV RNA (Table 1). When considering these three independent predictors of HCV relapse (HCV RNA of >6 log IU/ml, HCV genotype 1 or 4, and RBV C_{trough} at week 4 of <2.5 μg/ml), the positive predictive value of HCV relapse was 86% ($P = 0.032$).

In contrast with other studies (2, 13, 22), concomitant abacavir use during HCV therapy was a predictor of HCV relapse in the bivariate analysis but significance vanished in the multivariate analysis. However, 47% of patients treated with abacavir compared to only 26% of the rest experienced HCV relapse ($P = 0.044$). Interestingly, median RBV C_{trough} was significantly lower in patients on abacavir who relapsed than in those who did not (2.05 [1.13 to 2.78] versus 2.99 [2.66 to 3.78], respectively; $P = 0.002$) (Fig. 1). These results agree with the previous observation of a lower SVR in patients treated with abacavir who had low RBV C_{trough} (22). A possible mechanism might be competition between these two guanosine analogues for the intracellular enzymes involved in their phosphorylation. Therefore, abacavir might lead to a diminished phosphorylation of RBV, reducing its anti-HCV inhibitory activity. This effect, however, could be counterbalanced in the presence of high RBV exposure.

In summary, high baseline HCV RNA, HCV genotype 1 or 4, and C_{trough} of <2.5 μg/ml RBV were found to be indepen-

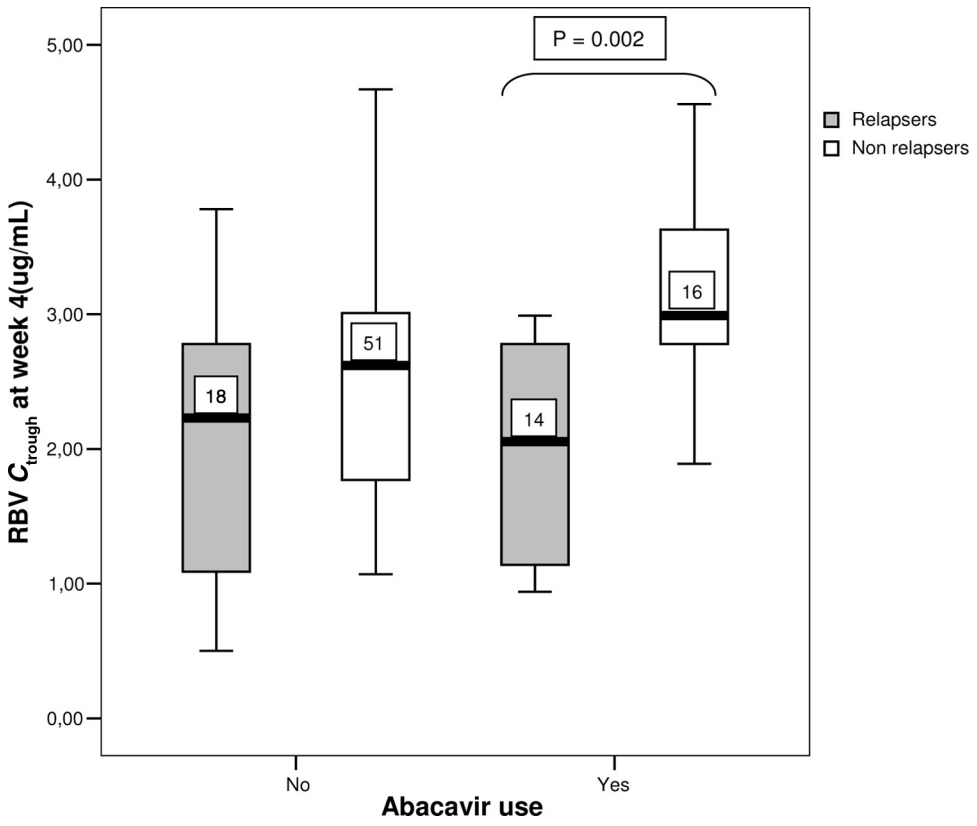

FIG. 1. RBV C_{trough} at week 4 and HCV relapse in HIV-HCV-coinfected patients according to abacavir use during hepatitis C therapy. Numbers in boxes indicate numbers of patients.

dent predictors of HCV relapse in HIV-HCV-coinfected patients. Lower cutoff values of RBV C_{trough} have been found to predict SVR in HIV-HCV-coinfected patients (1, 3). These differences may be explained by distinct characteristics of patients that may affect ribavirin pharmacokinetics (age, gender, renal function, body weight, race, and drug and food interactions) and technical aspects regarding the quantification of RBV C_{trough} (day after therapy initiation at which RBV C_{trough} was quantified, time between blood extraction and plasma separation, and methodology for RBV C_{trough} quantification).

To our knowledge this is the first study to examine the impact of RBV C_{trough} on the risk of HCV relapse. The association between RBV C_{trough} and relapse supports the essential role of RBV exposure in the clearance of HCV and highlights the idea that besides influencing the early decay of HCV clearance (18, 19), it may influence as well the risk of HCV relapse independently of any effect on RVR, as recently shown in trials testing HCV protease inhibitors (9, 10). This observation is important since monitoring of RBV C_{trough} at week 4 might allow adaptation strategies to maximize the chances of cure with standard HCV therapy. Patients with RBV C_{trough} of <2.5 μg/ml at week 4 of therapy might benefit from extending the length of therapy and/or from increasing RBV dosing.

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