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Effect of Accompanying Antiretroviral Drugs on Virologic Response to PEG-IFN and Ribavirin in HIV/HCV-Coinfected Patients

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1. BACKGROUND AND AIMS

The effect of accompanying antiretroviral therapy (ART) on the virologic response to PEG-interferon (PEG-IFN) plus ribavirin (RBV) remains uncertain.

The use of abacavir (ABC) in the context of PEG-IFN + RBV therapy has been found to negatively affect the outcome of this treatment in some studies (1-3), but not in others (4).

We evaluated the effect of ART, particularly ABC, on the response to PEG-IFN + RBV in HIV/HCV-coinfected (HIV/HCV+) patients.

1. Bani-Sadr F, et al. J Acquir Immune Defic Syndr 2007;45:123-125.
2. Vispo E, et al. Antivir Ther 2008;13:429-437.
3. Mira JA, et al. J Antimicrob Chemother 2008;62:1365-1373.
4. Laufer N, et al. Antivir Ther 2008;13:953-957.

2. METHODS

We conducted a pooled analysis of 2 cohorts of HIV/HCV+ patients initiating PEG-IFN + RBV in Spain (GESIDA 3603 and GESIDA 5006).

GESIDA 3603 is an ongoing ambispective cohort of HIV/HCV+ patients who started PEG-IFN + RBV between January 2000 and July 2007 at 20 clinical centers in Spain. The main objective is to assess long-term outcomes after anti-HCV therapy (See details in Berenguer J, et al. Hepatology 2009; 50:407-413)

GESIDA 5006 was a retrospective study of HIV/HCV+ patients who started PEG-IFN + RBV between January 2003 and June 2005 at 36 clinical centers in Spain. Its main objective was to evaluate the effectiveness and safety of PEG-IFN + RBV in HIV/HCV+ patients receiving a HAART regimen containing tenofovir (TDF) as the nucleotide backbone compared with those receiving HAART regimens based on other nucleotides (See details in González-García JJ, et al. 15th CROI, 2008)

Sustained virologic response (SVR) was defined as an undetectable HCV RNA 24 weeks after discontinuation of PEG-IFN + RBV.

Logistic regression models were used to test possible associations between nonresponse and pretreatment characteristics, including concomitant antiretroviral drugs. All analyses were performed on an ITT basis.

3. RESULTS

3.1 Patient characteristics

A total of 1701 HIV/HCV+ patients treated with PEG-IFN + RBV were included in this analysis. Baseline demographic, clinical, laboratory, and pathologic characteristics are shown in **Table 1**.

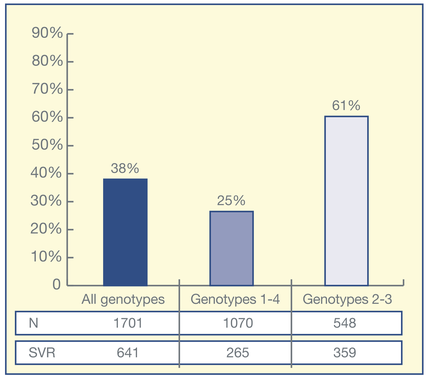
Table 1. Patient characteristics

Characteristic	Patients (N=1701)
Male sex-n (%)	1264 (75)
Age-y, median (IQR)	41 (37-44)
Weight-kg, median (IQR)	67 (60-75)
Prior injection drug use-n (%)	1382 (82)
CDC disease category-n (%)	
A	786 (49)
B	454 (28)
C	381 (23)
CD4 cells nadir/mm3, median (IQR)	204 (110-308)
CD4 cells baseline/mm3, median (IQR)	514 (390-720)
HIV RNA <50 copies/mL baseline-n (%)	1219 (74)
HCV genotype-n (%)	
1-4	1070 (63)
2-3	584 (34)
Unknown	47 (3)
HCV RNA-n (%)	
≥ 500,000 IU/mL	1117 (66)
< 500,000 IU/mL	475 (28)
Unknown	109 (6)
METAVIR fibrosis score-n (%)	
0-2	740 (44)
3-4	458 (27)
Unknown	503 (29)
Alcohol intake >50 g/day-n (%)	75 (4)
Methadone use-n (%)	190 (11)
ART during HCV treatment-n (%)	
None	199 (12)
1-2 nRTI	19 (1)
2 nRTI + 1 nnRTI	690 (41)
2 nRTI + 1 PI	461 (27)
3-4 nRTI	190 (11)
Other ART combinations	135 (8)
Unknown	7 (<1)
Anti-HCV therapy-n (%)	
Peg IFN 2b + RBV	699 (41)
Peg IFN 2a + RBV	1002 (59)
Ribavirin (mg/kg), median (IQR)	14 (13-15)

3.2 Sustained Virological Response

Overall, 641 (38%) patients achieved an SVR. The response was 25% for genotypes 1 and 4, and 61% for genotypes 2 and 3 (**Table 2**).

Table 2. Sustained virological response to PEG-IFN + RBV



3.3 Factors associated with SVR

Multiple logistic regression showed 3 variables to be independently associated with increased odds of an SVR: HCV genotype 2-3, HCV-RNA level < 500,000 IU/mL, and absence of AIDS-defining conditions (**Table 3**).

Table 3. Factors associated with SVR

Variable	Adjusted OR (95% CI)	p
Absence of ADCs	1.75 (1.31-2.33)	<.0001
HCV genotype 2-3	5.31 (4.17-6.76)	<.0001
HCV-RNA level < 500K IU/mL	1.73 (1.34-2.23)	<.0001
RBV dose (mg/kg)	1.04 (.99-1.09)	.101

0,5 1 10

3.4 Effect of accompanying antiretroviral drugs on SVR

3.4.1. Treated vs. untreated patientss

Table 4 shows the number of patients treated with or without concomitant ART at initiation of PEG-IFN + RBV and their frequency of SVR. It also shows the adjusted odds ratio (AOR) of SVR, taking the group with ART as our reference.

Table 4. SVR after PEG-IFN + RBV in patients with or without ART

ART	N	% SVR	AOR* (95% CI)	P
Any ART	1502	43.7	Reference	-
No ART	199	36.9	1.31 (.91-1.88)	.144

0% 50% 0'5 1 2

* adjusted by HCV genotype, HCV-RNA level, CDC clinical category, and RBV dose (mg/kg).

3.4.2. Effect of the nRTI backbone on SVR (all patients)

Table 5 shows the number of patients treated with the different nRTI backbones at initiation of PEG-IFN + RBV and their frequency of SVR. It also shows the AOR of SVR, taking the backbone of TDF+3TC/FTC as our reference. With the exception of regimens including AZT, the effect of other nRTI backbones had little effect on SVR. No significant differences were found between the different nRTI backbones when we repeated this analysis for patients receiving RBV < 800 mg/kg, RBV < than the median, and RBV < than the 1st quartile (data not shown).

Table 5. SVR after PEG-IFN + RBV according to the different nRTI backbones (all patients)

NRTI Backbone	N	% SVR	AOR* (95% CI)	P
TDF+3TC/FTC	380	41.8	Reference	-
3TC+D4T	264	38.6	.90 (.61-1.32)	.588
AZT+3TC global	389	35.0	.65 (.46-.93)	.017
AZT+3TC without ABC	242	36.0	.63 (.42-.94)	.023
AZT+3TC with ABC	147	33.3	.69 (.43-1.12)	.131
3TC+ABC without AZT	115	37.4	.72 (.43-1.21)	.213
DDI+D4T	47	21.3	.54 (.23-1.26)	.153
DDI+3TC/FTC	36	25.0	.59 (.23-1.52)	.273

0% 50% 0 1 2

* Adjusted for HCV genotype, HCV-RNA level, CDC clinical category, and RBV dose (mg/kg).

3.4.3 Effect of the nRTI backbone on SVR (subgroup of patients infected with HCV Genotypes 1-4 and HCV-RNA>500,000)

No significant differences were found between the different nRTI backbones when we analyzed the subgroup of patients with G1-4 and HCV-RNA>500,000 (**Table 6**). Again, no significant differences were found between the different nRTI backbones when we repeated this analysis for patients receiving RBV < 800 mg/kg, RBV < than the median, and RBV < than the 1st quartile (data not shown).

Table 6. SVR after PEG-IFN + RBV according to the different nRTI backbones including only patients with G1-4 and HCV-RNA>500,000

NRTI Backbone	N	% SVR	AOR* (95% CI)	P
TDF+3TC/FTC	172	20.9	Reference	-
3TC+D4T	104	19.2	.84 (.44-1.61)	.594
AZT+3TC global	157	18.5	.83(.46-1.50)	.542
AZT+3TC without ABC	89	18.0	.76 (.37-1.55)	.444
AZT+3TC with ABC	68	19.1	.94 (.44-2.04)	.880
3TC+ABC without AZT	54	25.9	1.20 (.53-2.70)	.660
DDI+D4T	21	9.6	.43 (.09-1.97)	.278
DDI+3TC/FTC	23	17.4	.87 (.27-2.77)	.810

0% 30% 0 1 3

* CDC clinical category, and RBV dose (mg/kg).

3.4.4. Effect of the third drug (nnRTI or PI) on SVR

Table 7 shows the number of patients treated with the different ART regimens categorized by the third drug (nnRTI or PI) at initiation of PEG-IFN + RBV and their frequencies of SVR. It also shows the AOR of SVR, taking the group with 2 nRTI + 1 nnRTI as our reference. No significant differences were found between the groups according to the third drug.

Table 7. SVR after PEG-IFN + RBV according to the third drug used in the HAART regimen (nnRTI or PI)

HAART regimens	N	% SVR	AOR* (95% CI)	P
2 nRTI + 1 nnRTI	682	39.1	Reference	-
2 nRTI + 1 non-boosted PI	172	40.7	1.09 (.72-1.64)	.684
2 nRTI + 1 boosted PI	244	30.7	.72 (.40-1.32)	.289
2nRTI + Other	37	29.7	.42 (.16-1.09)	.075
Other combinations	566	38.5	.94 (.71-1.24)	.637

0% 50% 0 1 2

* Adjusted for HCV genotype, HCV-RNA level, CDC clinical category, RBV dose (mg/kg), and use of AZT+3TC

4. CONCLUSIONS

Our results suggest that, with the exception of regimens including AZT, accompanying antiretroviral drugs have little effect on virologic response to PEG-IFN + RBV in HIV/HCV+ patients. We did not find ABC to negatively impact the outcome of PEG-IFN + RBV therapy even in difficult-to-treat patients such as those with genotypes 1 and 4 and high HCV-RNA.