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Effect of accompanying antiretroviral drugs on virological response to pegylated interferon and ribavirin in patients co-infected with HIV and hepatitis C virus

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Objectives: The effects of antiretroviral drugs on the response to pegylated interferon plus ribavirin remain uncertain. We evaluated whether antiretroviral drugs affected the response to pegylated interferon plus ribavirin in patients co-infected with HIV and hepatitis C virus (HCV).

Methods: We conducted a retrospective analysis of two cohorts of HIV/HCV-co-infected patients treated with pegylated interferon plus ribavirin between 2001 and 2007 in Spain. The outcome measure was sustained virological response (SVR). Logistic regression models were used to test possible associations between non-response and pre-treatment characteristics, including accompanying antiretroviral drugs.

Results: The study sample comprised 1701 patients: 63% were infected with HCV genotype (G) 1 or 4 and 88% were taking highly active antiretroviral therapy (HAART). Factors independently associated with increased odds of SVR were G2 or 3, HVC RNA <500 000 IU/mL and CDC clinical category A or B. When we adjusted for these prognostic factors and dose of ribavirin/kg, the adjusted odds ratio (AOR) of SVR for patients without HAART was 1.31 [95% confidence interval (CI) 0.91–1.88; $P=0.144$]. Taking the backbone of tenofovir and lamivudine/emtricitabine as a reference, we found that, with the exception of regimens including zidovudine, the effect of other nucleoside reverse transcriptase inhibitor backbones had little effect on SVR. The AOR of SVR for zidovudine and lamivudine was 0.65 (95% CI 0.46–0.93, $P=0.017$). We carried out several sensitivity analyses, the results of which were consistent with the findings of the primary analysis.

Conclusions: Our results suggest that, with the exception of regimens including zidovudine, accompanying antiretroviral drugs have little effect on the virological response to pegylated interferon plus ribavirin in HIV/HCV-co-infected patients.

Keywords: HIV infection, HCV, ribavirin antiviral agents, drug interactions

Introduction

Treatment of hepatitis C virus (HCV) infection aims to achieve a sustained virological response (SVR), defined as HCV RNA being undetectable using a sensitive PCR assay 24 weeks after the end of treatment. Available evidence suggests that SVR is associated with reductions in long-term HCV-related morbidity and mortality in both HCV-mono-infected[1,2] and HIV/HCV-co-infected patients.[3] SVR rates with the current standard therapy (pegylated interferon plus ribavirin) remain unsatisfactory:

~55% in HCV-mono-infected patients[4–6] and ~33% in HIV/HCV-co-infected patients.[7]

The most important baseline predictors of SVR after therapy with interferon plus ribavirin in both mono-infected and co-infected patients are virus-related factors, namely HCV genotype and HCV RNA.[8,9] The response to treatment can also be affected by demographic factors (age, gender, weight and race), histological parameters (stage of fibrosis and steatosis) and treatment-related factors (dosage of ribavirin).[4,6,9,10] The presence of insulin resistance has also been associated with a reduced response to interferon plus ribavirin in HCV-mono-infected patients[11,12] and in HIV/HCV-co-infected patients.[13] Recently, a single-nucleotide polymorphism near the *IL28B* gene encoding interferon-λ-3 has been shown to predict treatment response in both HCV-mono-infected and HIV/HCV-co-infected patients carrying genotype 1 or 4.[14–16] Once treatment has been initiated, adherence and the fall in HCV RNA are important predictors of SVR. In particular, a rapid virological response, defined as undetectable HCV RNA at week 4 of therapy, has been recognized as one of the most powerful predictors of SVR in both HCV-mono-infected[17–19] and HIV/HCV-co-infected patients.[20–23]

An important issue among HIV/HCV-co-infected patients is the selection of antiretroviral therapy (ART) during treatment with pegylated interferon plus ribavirin, because some antiretroviral drugs, namely nucleoside reverse transcriptase inhibitors (NRTIs), can increase the risk of side effects as a result of overlapping toxicities such as anaemia and/or neutropenia with zidovudine,[24,25] enhanced mitochondrial damage with didanosine and stavudine,[26–28] and pancreatitis, lactic acidosis and decompensated cirrhosis with didanosine.[26,27,29,30] A second potential mechanism by which NRTIs might affect HCV therapy is interference with the activity of ribavirin against HCV. In this setting, abacavir with pegylated interferon plus ribavirin has been found to affect the outcome of this treatment negatively in some studies[31–33] but not in others.[34,35] We assessed the effect of ART, particularly abacavir, on the response to pegylated interferon plus ribavirin in HIV/HCV-co-infected patients.

Patients and methods

Study population

The study population comprised patients from GESIDA 3603 and GESIDA 5006, two cohorts of HIV/HCV-co-infected patients initiating pegylated interferon plus ribavirin in Spain at hospitals affiliated to the Grupo de Estudio del SIDA (AIDS Study Group, GESIDA) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (Spanish Society of Infectious Diseases and Clinical Microbiology, SEIMC). GESIDA 3603 is an ongoing ambispective cohort of HIV/HCV-co-infected patients who started pegylated interferon plus ribavirin between January 2000 and July 2007 at 19 clinical centres in Spain. The main objective is to assess long-term outcomes after anti-HCV therapy; for details see Berenguer *et al*.[3] GESIDA 5006 was a retrospective study of HIV/HCV-co-infected patients who started pegylated interferon plus ribavirin between January 2003 and June 2005 at 36 clinical centres in Spain. Its main objective was to evaluate the effectiveness and safety of pegylated interferon plus ribavirin in HIV/HCV-co-infected patients receiving a highly active antiretroviral therapy (HAART) regimen containing tenofovir as the NRTI backbone compared with those receiving HAART regimens based on other NRTIs.[36] The local ethics committees of all centres approved the analysis of anonymous routine clinical data of patients included in GESIDA 3603 and GESIDA 5006 without written informed consent with a view to scientific publication.

Anti-HCV therapy in Spain is provided by hospital pharmacies and is covered by the national health system. The decision to administer anti-HCV therapy to co-infected patients was taken by infectious diseases physicians at each institution according to national and international guidelines. The eligibility criteria for anti-HCV therapy included absence of prior hepatic decompensation, CD4+ cell count >200 cells/mm^3, stable ART or no need for ART, absence of active opportunistic infections and no active drug addiction. Patients were counselled against the use of alcohol. Anti-HCV therapy was stopped in all patients with detectable HCV RNA at week 24 of treatment. Since 2002, some institutions have been applying the so-called 2-log stopping rule, i.e. discontinuation of therapy in patients with detectable HCV RNA at week 12 of treatment with a reduction of <2 log IU/mL in HCV RNA.

Clinical and laboratory assessment

The information obtained from the databases of the GESIDA 3603 and GESIDA 5006 cohorts was as follows: age, sex, height and weight at the initiation of therapy with interferon plus ribavirin; HIV transmission category; prior AIDS-defining conditions; baseline and nadir CD4+ cell counts; baseline HIV viral load; and methadone use. We also recorded information about HAART, including type, date of initiation and whether or not it was maintained or changed during therapy. Information related to HCV infection included genotype, HCV RNA levels and estimated year of HCV infection, which, for injection drug users, was taken to be the first year needles were unsafely shared. Duration of HCV infection was considered to be unknown for patients infected through sexual contact. In both GESIDA 3603 and GESIDA 5006, patients were asked about their alcohol intake. We considered the consumption of >50 g of alcohol per day for at least 12 months as a high intake. Local pathologists, who all had extensive experience in scoring samples from patients with viral hepatitis, scored liver biopsy samples following the criteria established by the METAVIR Cooperative Study Group,[37] as follows: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis or rare portal–portal septa; F3, fibrous septa with architectural distortion and no obvious cirrhosis (bridging fibrosis); and F4, definite cirrhosis.

Assessment of response to pegylated interferon plus ribavirin

For each patient, we assessed the SVR, defined as an undetectable serum HCV RNA level 24 weeks after discontinuation of pegylated interferon plus ribavirin therapy. Patients not fulfilling SVR criteria, including those who relapsed after achieving an end-of-treatment response, were classified as non-SVR.

Statistics

Comparisons between groups were made using the Mann–Whitney test or the *t*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Multivariate logistic regression models were constructed to identify factors that were associated with the achievement of SVR. First, we created a multivariate model to assess pre-treatment patient characteristics (not including ART) independently associated with SVR. To assess the effect of accompanying ART drugs on SVR we developed several multivariate models adjusting for variables found to be independently associated with SVR in the first model. All analyses were performed on an intention-to-treat basis and included adjustment for the daily ribavirin dose (mg/kg). All tests were two-tailed and *P* values <0.05 were considered significant. Statistical analysis was performed using SPSS 15.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The study sample comprised 1701 HIV/HCV+ patients treated with pegylated interferon plus ribavirin. Baseline demographic, clinical, laboratory and pathological characteristics are shown in Table 1.

SVR

Overall, 641/1701 (38%) patients achieved an SVR. SVR was achieved by 265/1070 (25%) patients infected with HCV genotype 1 or 4 and by 359/584 (61%) patients infected with HCV genotype 2 or 3. Of all the patient characteristics shown in Table 1 (not including ART during HCV treatment), univariate analysis showed HCV genotype, absence of AIDS-defining conditions and HCV RNA level to be independently associated with SVR. In a multivariate logistic regression model that included these variables and ribavirin dose (mg/kg/day), the odds ratio (OR) and 95% confidence interval (CI) were as follows: HCV genotype 2 or 3, OR 5.31 (95% CI, 4.17–6.76; $P<0.0001$); absence of AIDS-defining conditions, OR 1.75 (95% CI, 1.31–2.33, $P<0.0001$); and HCV RNA level <500 000 IU/mL, OR 1.73 (95% CI, 1.34–2.23, $P<0.0001$).

Table 1. Patient characteristics

Characteristic	Patients ($n=1701$)
Male sex, *n* (%)	1264 (75)
Age (years), 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 (46)
B	454 (27)
C	381 (22)
unknown	80 (5)
CD4 cell count, nadir (cells/mm^3), median (IQR)	204 (110–308)
CD4 cell count, baseline (cells/mm^3), median (IQR)	514 (390–720)
HIV RNA <50 copies/mL at baseline, *n* (%)	1219 (72)
HCV genotype, *n* (%)	
1 or 4	1070 (63)
2 or 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 NRTIs	19 (1)
2 NRTIs+1 NNRTI	690 (41)
2 NRTIs+1 protease inhibitor	461 (27)
3–4 NRTIs	190 (11)
other ART combinations	135 (8)
unknown	7 (<1)
Anti-HCV therapy, *n* (%)	
pegylated interferon 2b plus ribavirin	699 (41)
pegylated interferon 2a plus ribavirin	1002 (59)
Ribavirin (mg/kg/day), median (IQR)	14 (13–15)

IQR, interquartile range.

Effect of accompanying antiretroviral drugs on SVR

At the initiation of pegylated interferon plus ribavirin, 1495 patients were receiving concomitant ART and 37% achieved SVR, whereas 199 patients were not treated with ART and 44% achieved SVR. Taking the patients treated with ART as a reference and adjusting for HCV genotype, HCV RNA level, CDC clinical category and ribavirin dose (mg/kg/day), the adjusted OR (AOR) of SVR for patients not taking ART was 1.3 (95% CI, 0.91–1.88, $P=0.144$).

The number of patients treated with the different NRTI backbones at initiation of pegylated interferon plus ribavirin and the frequency of SVR are shown in Table 2. This table also shows the AOR of SVR for the different NRTIs, taking the backbone of tenofovir and lamivudine/emtricitabine as a reference and adjusting for HCV genotype, HCV RNA level, CDC clinical category and ribavirin dose (mg/kg/day). We found that, with the exception of regimens including zidovudine, the effect of other NRTI backbones had little effect on SVR. Overall, 389 patients received concomitant zidovudine and lamivudine as the NRTI backbone and 35% achieved an SVR. The AOR (95% CI) of SVR for zidovudine and lamivudine was 0.65 (0.46–0.93, $P=0.017$). HCV treatment discontinuations among patients with and without zidovudine in their NRTI backbone were 67/389 (17%) and 110/842 (13%), respectively ($P=0.065$). Likewise, the frequency of reductions in the dose of interferon and ribavirin among patients

Table 2. SVR after pegylated interferon plus ribavirin according to NRTI backbone (all patients)

NRTI backbone	*n*	% SVR	AOR[a]	95% CI	*P*
TDF+3TC/FTC	380	41.8	reference	—	—
3TC+d4T	264	38.6	0.90	0.61–1.32	0.588
AZT+3TC overall	389	35.0	0.65	0.46–0.93	0.017
AZT+3TC without ABC	242	36.0	0.63	0.42–0.94	0.023
AZT+3TC with ABC	147	33.3	0.69	0.43–1.12	0.131
3TC+ABC without AZT	115	37.4	0.72	0.43–1.21	0.213
ddI+d4T	47	21.3	0.54	0.23–1.26	0.153
ddI+3TC/FTC	36	25.0	0.59	0.23–1.52	0.273

TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; d4T, stavudine; AZT, zidovudine; ABC, abacavir; ddI, didanosine; AOR, adjusted odds ratio.
[a]Adjusted for HCV genotype, HCV RNA level, CDC clinical category and ribavirin dose (mg/kg/day).

with and without zidovudine in their NRTI backbone was 116/389 (30%) and 186/842 (22%), respectively ($P=0.004$). When we separately analysed patients who received zidovudine and lamivudine with abacavir ($n=242$) or without abacavir ($n=147$), we observed a significantly lower OR of SVR among the latter; the OR (95% CI) of an SVR for zidovudine and lamivudine without abacavir was 0.63 (0.42–0.94, $P=0.023$). No significant differences were found between the different NRTI backbones when we repeated this analysis for patients receiving a ribavirin dose of less than 800 mg/day, a ribavirin dose in mg/kg/day less than the median and a ribavirin dose in mg/kg/day less than the first quartile (data not shown).

We also analysed a subgroup of 628 patients who were particularly difficult to treat: those infected with HCV genotype 1 or 4 and with HCV RNA load >500 000 IU/mL. As shown in Table 3, no significant differences were found between the different NRTI backbones when we took the backbone of tenofovir and lamivudine/emtricitabine as our reference. We repeated this analysis for patients receiving a ribavirin dose <800 mg/day, a ribavirin dose in mg/kg/day less than the median and a ribavirin dose in mg/kg/day less than the first quartile, and no significant differences were found between the different NRTI backbones (data not shown).

Table 3. SVR after pegylated interferon plus ribavirin according to the different NRTI backbones including only patients with G1 or 4 and HCV RNA >500 000 IU/mL

NRTI backbone	*n*	% SVR	AOR[a]	95% CI	*P*
TDF+3TC/FTC	172	20.9	reference	—	—
3TC+d4T	104	19.2	0.84	0.44–1.61	0.594
AZT+3TC overall	157	18.5	0.83	0.46–1.50	0.542
AZT+3TC without ABC	89	18.0	0.76	0.37–1.55	0.444
AZT+3TC with ABC	68	19.1	0.94	0.44–2.04	0.880
3TC+ABC without AZT	54	25.9	1.20	0.53–2.70	0.660
ddI+d4T	21	9.5	0.43	0.09–1.97	0.278
ddI+3TC/FTC	23	17.4	0.87	0.27–2.77	0.810

TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; d4T, stavudine; AZT, zidovudine; ABC, abacavir; ddI, didanosine; AOR, adjusted odds ratio.
[a]Adjusted for CDC clinical category and ribavirin dose (mg/kg/day).

Table 4. SVR after pegylated interferon plus ribavirin according to the third drug used in the HAART regimen (NNRTI or protease inhibitor)

HAART regimens	*N*	% SVR	AOR[a]	95% CI	*P*
2 NRTIs+1 NNRTI	682	39.1	reference	—	—
2 NRTIs+1 unboosted PI	172	40.7	1.09	0.72–1.64	0.684
2 NRTIs+1 boosted PI	244	30.7	0.72	0.40–1.32	0.289
2 NRTIs+other	37	29.7	0.42	0.16–1.09	0.075
Other combinations	566	38.5	0.94	0.71–1.24	0.637

AOR, adjusted odds ratio; PI, protease inhibitor.
[a]Adjusted for HCV genotype, HCV RNA level, CDC clinical category, ribavirin dose (mg/kg/day) and use of zidovudine+lamivudine.

We finally performed an analysis of SVR after pegylated interferon plus ribavirin according to the third drug used in the HAART regimen, taking the regimen based on one non-nucleoside reverse transcriptase inhibitor (NNRTI) as the third drug as our reference (Table 4). No significant differences were found between those treated with an NNRTI and those treated with a protease inhibitor as the third drug.

Discussion

In this retrospective analysis of 1701 patients included in two large cohorts of HIV/HCV-co-infected patients who received pegylated interferon and ribavirin, 38% achieved SVR. The frequency of SVR was 25% for patients infected with HCV genotype 1 or 4 and 61% for patients infected with HCV genotype 2 or 3. We found that, with the exception of regimens including zidovudine, the effect of accompanying antiretroviral drugs had little effect on the virological response to pegylated interferon and ribavirin in this population group. Abacavir, in particular, was not found to compromise the outcome of HCV therapy.

We first addressed whether concomitant ART, as a whole, had any impact on SVR. This is a relevant question because HIV infects human hepatic stellate cells and promotes the expression of collagen I and proinflammatory cytokines,[38] which could, at least theoretically, hamper the treatment response. When we carried out an adjusted analysis, we found that receiving or not receiving ART did not affect the response to pegylated interferon plus ribavirin. One must take into account, however, that most of the patients not receiving antiretrovirals were ART-naive and had high CD4+ cell counts. We also explored whether any of the concomitant antiretroviral agents were associated with SVR rates. Among the different NRTIs at initiation of pegylated interferon plus ribavirin, zidovudine was the only drug that adversely affected SVR. According to our results, the most likely mechanism by which zidovudine reduced SVR rates in our cohort was the reduction in the dose of ribavirin, probably in response to the anaemia that occurs with co-administration of zidovudine and ribavirin, as shown elsewhere.[24,25]

We also addressed a very controversial issue, namely the effect of abacavir on SVR. As mentioned in the Introduction, the use of abacavir in the context of pegylated interferon plus ribavirin therapy has been found to affect the outcome of this treatment negatively in some studies but not in others. This issue was first raised in a retrospective analysis of a subgroup of 154 co-infected patients enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) HC02-Ribavic Study, who were treated with 1.5 mg/kg of pegylated interferon α-2b plus 800 mg/day of ribavirin.[31] Twenty-two patients in this study received abacavir-based ART. The authors focused on early virological responses defined by undetectable serum HCV RNA or a decrease of >2 $\log_{10}$ in serum HCV RNA at week 12. In the multivariate analysis, elevated baseline HCV viral load, HCV genotype 1 or 4 infection, abacavir-based ART and elevated baseline bilirubin were significantly associated with the risk of early HCV virological failure. In a retrospective multicentre study of HIV/HCV-co-infected patients who received pegylated interferon and ribavirin and HAART, the authors compared treatment outcomes between patients receiving an NRTI backbone consisting of abacavir plus lamivudine ($n=70$) or tenofovir plus lamivudine/emtricitabine

($n=186$).[32] The authors found a significantly higher frequency of SVR in the tenofovir plus lamivudine/emtricitabine group than in the abacavir plus lamivudine group in the subpopulation of patients harbouring HCV genotype 1 or 4 who received ribavirin doses <13.2 mg/kg/day.[32] In another retrospective multicentre study, the authors examined the influence of different NRTIs on the probability of achieving SVR in a group of 493 HIV/HCV-co-infected patients (78% on ART and 115 receiving abacavir) treated with pegylated interferon plus ribavirin.[33] The overall rate of SVR was 38%. Factors associated with lack of SVR in the multivariate analysis were higher baseline serum HCV RNA, HCV genotype 1 or 4 and lower ribavirin plasma trough concentrations (measured in plasma specimens drawn at week 4 using HPLC). A subanalysis performed in a subset of 99 patients with ribavirin plasma trough levels <2.3 μg/mL revealed that HCV load, genotype and abacavir were independent predictors of lack of SVR.

The results of the above-mentioned studies were very different from those reported by Laufer *et al.*,[34] who carried out a retrospective analysis of 244 HIV/HCV-co-infected patients treated with pegylated interferon plus weight-adjusted ribavirin. By intention-to-treat analysis, SVR was achieved by 46.2% of patients taking abacavir versus 46.7% of patients not taking abacavir ($P=1$). The only two factors in the multivariate analysis that were statistically associated with an increased risk of failure to achieve SVR were HCV genotype 1 or 4 and age >40 years. Specifically, the use of abacavir was not associated with higher rates of failure to achieve virological response at any of the timepoints evaluated (weeks 4, 12, 24, 48 and 72). Amorosa *et al.*[35] found similar results in a retrospective study of 212 ART-experienced HIV/HCV-co-infected patients treated with pegylated interferon plus ribavirin, 74 (35%) of whom received abacavir; the rates of SVR were not significantly different between abacavir users and non-users (15% versus 16%).

In our study, which included 262 patients taking abacavir, we did not find significant differences in SVR between patients treated with lamivudine and abacavir as their NRTI backbone and patients treated with tenofovir and lamivudine/emtricitabine as their NRTI backbone. The latter were taken as our reference after adjusting for important variables, such as HCV genotype, HCV RNA level, CDC clinical category and ribavirin dose. Of note, the results were the same when we repeated this analysis in a subgroup of patients infected with HCV genotype 1 or 4 and with an HCV RNA load of >500 000 IU/mL. If abacavir had had any effect on virological response to anti-HCV therapy, we would have expected a significant difference in SVR in the subgroup of patients treated with zidovudine, lamivudine and abacavir in comparison with those treated with tenofovir and lamivudine/emtricitabine as their NRTI backbone. Likewise, adjustment for zidovudine use was not reported in the studies of Bani-Sadr *et al.*[31] or Vispo *et al.*[33] We finally performed an analysis of SVR after pegylated interferon plus ribavirin according to the third drug used in the HAART regimen, taking as our reference the regimen based on one NNRTI as the third drug, and we did not find any more significant differences in SVR than in those treated with a protease inhibitor as the third drug.

Our study has the limitations characteristic of retrospective observational cohort studies, namely the potential for unmeasured confounding variables that could affect outcomes. The fact that this analysis does not include *IL28B* data is also a limitation. However, our study has several strengths. First, it included a larger number of patients than previously reported studies. Second, it was carried out within a collaborative group in which providers followed the same eligibility criteria for anti-HCV therapy. Third, the analysis included an adjustment for important covariates and a sensitivity analysis, the results of which were consistent with the findings of the primary analysis.

In conclusion, the results of our study, which was carried out in a large cohort and in a clinical practice setting, suggest that, with the exception of regimens including zidovudine, the effect of accompanying antiretroviral drugs has little effect on the virological response to pegylated interferon plus ribavirin in HIV/HCV-co-infected patients.

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None to declare.

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