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Fluvastatin as an adjuvant to pegylated interferon and ribavirin in HIV/hepatitis C virus genotype 1 co-infected patients: an open-label randomized controlled study

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Objectives: Recent reports demonstrated *in vitro* the efficacy of fluvastatin in inhibiting hepatitis C virus (HCV) replication and a synergistic effect in association with interferon-α (IFN-α). *In vivo* the inhibition of HCV replication by statins has not been demonstrated. We evaluated in this open-label, randomized controlled study the efficacy of fluvastatin as adjuvant to pegylated-(PEG)-IFN and ribavirin in HIV/HCV genotype 1 co-infected patients.

Patients and methods: Forty-four HIV/HCV co-infected patients were randomized to receive, in addition to PEG-IFN-α 2b and ribavirin, 80 mg of fluvastatin once daily or no medication. Primary and secondary endpoints were the achievement of sustained virological response (SVR) and rapid virological response (RVR), respectively.

Results: By intent-to-treat analysis, 25% of the patients achieved an SVR. An SVR was observed in 8/21 patients in the fluvastatin arm and in 3/23 patients in the standard therapy arm ($P=0.08$). A significantly higher RVR rate was obtained in the fluvastatin arm compared with the standard therapy [7/21 (33%) and 1/23 (4%), respectively; $P=0.02$]. Baseline alanine aminotransferase (ALT) values and fluvastatin treatment arm were the only predictors of RVR at the univariate analysis; however, no predictors were independently associated with RVR or SVR at the multivariate analysis.

Conclusions: Fluvastatin addition to standard therapy did not significantly increase the SVR rate in HIV/HCV genotype 1 co-infected patients; however, it did significantly improve the RVR. Further studies are needed to confirm these promising results and to investigate the mechanisms of action of statins in HCV infection.

Keywords: statins, HIV/HCV co-infection, anti-HCV therapy

Introduction

The combination of pegylated interferon (PEG-IFN) with ribavirin yields an overall sustained virological response (SVR) rate in <50% of hepatitis C virus (HCV) genotype 1 carriers and in <30% of HIV co-infected subjects.[1–4] This unsatisfactory result requires the identification of novel compounds with direct anti-viral activity against HCV, such as protease and polymerase inhibitors, or against host enzymes necessary to viral replication. Cholesterol biosynthesis has been shown to play a critical role in HCV viral replication *in vitro*[5,6] and it has been demonstrated that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (e.g. statins), which inhibit cholesterol synthesis, suppress replication of HCV-1b replicons[7,8] possibly through the inhibition of geranylgeranylation of cellular proteins or through the destruction of lipid rafts critical for HCV replication. Among the five different statins studied, fluvastatin showed the greatest inhibitory effect on viral replication and exerted a synergistic activity in combination with IFN.[8] Interestingly, evidence indicates an immunomodulating effect of statins through the inhibition of the IFN-γ-induced expression of class II major histocompatibility complexes (MHC-IIs) on antigen-presenting cells, thus reducing T cell activation and secretion of pro-inflammatory cytokines.[9,10] Nevertheless, serum low-density lipoprotein (LDL) levels have been identified as a prognostic indicator of SVR to IFN-based therapy in patients with HCV infection, particularly by genotypes 1 and 2,[11] suggesting that lipid-lowering agents might favour HCV entry into the hepatocytes and translate into higher viral loads. *In vivo*, the inhibition of HCV replication by statins has not been demonstrated, and the available clinical data are limited and somewhat conflicting.[12–14] Recently, we demonstrated that fluvastatin did not show antiviral activity

against HCV after 4 weeks of therapy in HIV co-infected patients; conversely, it was associated with a significant, although probably not clinically relevant, increase in HCV viraemia.[15]

Since fluvastatin has been demonstrated to significantly inhibit the replication of HCV in synergism with IFN-α, this open-label, randomized controlled study was designed to evaluate the *in vivo* activity against HCV-RNA replication of fluvastatin as adjuvant to PEG-IFN and ribavirin treatment.

Therefore, we aimed to compare in this pilot study the efficacy and safety, in terms of SVR and adverse events, of PEG-IFN-α 2b plus ribavirin versus PEG-IFN-α 2b plus ribavirin plus fluvastatin in HIV/HCV genotype 1 co-infected patients. The secondary endpoint was the rate of achievement of a rapid viral response (RVR).

Patients and methods

Patient selection

Between March 2007 and April 2008 we prospectively enrolled 45 HIV/HCV co-infected outpatients attending the Infectious Diseases Department at L. Sacco Hospital, Milan. All had positive HCV-RNA, as confirmed by PCR analysis, genotype 1, elevated serum alanine aminotransferase (ALT) and a liver biopsy obtained within 6 months before enrolment. Inclusion criteria were ability to give written informed consent and absence of co-infection with hepatitis B virus (HBV) or other concomitant cause of liver disease. Exclusion criteria were decompensated liver disease and substance abuse. Patients were also excluded if they had ever taken cholesterol-lowering drugs or had been treated for HCV infection within the previous 6 months. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Intervention

After signing the informed consent form, patients were randomly assigned, according to a computer-generated random number table, in a 1:1 ratio to receive, in addition to standard PEG-IFN-α 2b (1.5 μg/kg once a week) and ribavirin (daily dose of 1000 mg for patients with body weight ≤75 kg or 1200 mg for patients who weighed >75 kg) treatment, either 80 mg of fluvastatin once daily or no medication. Recruitment and assignment of the patients to the open-label treatment arms were carried out by two of the investigators (L. M. and I. C.). Histological evaluation was performed by a single pathologist and was scored according to the Knodell–Ishak index.[16]

Aminotransferase (upper normal limit: 45 and 34 IU/L for men and women, respectively), γ-glutamyl transferase (γ-GT), total cholesterol, high-density lipoprotein (HDL), LDL and triglyceride levels were measured at baseline, after 4, 12 and 24 weeks and at the end of therapy. CD4+ T cell count and HIV-RNA were measured at baseline, after 4, 12 and 24 weeks and at the end of therapy. HCV-RNA quantification (Versant HCV-RNA 3.0, bDNA, Siemens Medical Solutions, Berkeley, CA, USA) and HCV-RNA PCR (COBAS AmpliPrep, Roche Diagnostics, Indianapolis, IN, USA) were performed at baseline and after 4 and 12 weeks. Thereafter HCV-RNA PCR was evaluated at week 24 and 48 (end of treatment) and 24 weeks after completion of treatment.

Objectives and outcomes

The primary measure of efficacy was the rate of SVR, defined as undetectable HCV-RNA in serum at the end of follow-up (24 weeks after therapy cessation) by an intent-to-treat analysis. Patients who did not achieve a reduction of HCV-RNA copies/mL of at least 2 $\log_{10}$ at week 12 and those who tested positive for HCV-RNA (PCR) at the end of 24 weeks of therapy were considered failures and therapy was discontinued. Secondary parameters of efficacy were: the rate of RVR, defined as negative HCV-RNA at week 4 of treatment; the rate of early virological response (EVR), defined as negative HCV-RNA or ≥2 $\log_{10}$ reduction of HCV-RNA from baseline at week 12 of treatment; sustained biochemical response, defined as the presence of normal ALT values at the end of 24 weeks of follow-up; and the rate of relapse, defined as patients with end-of-treatment response (ETR) but not reaching SVR.

Sample size calculation

Sample size calculation was carried out in order to detect a clinically important difference between treatment arms with regard to response to therapy. A total of 76 patients were thought to be needed. Based on known data the response rate in the standard therapy group was expected to be ∼30%. Assuming a response rate of ≥60% in the fluvastatin group, a total sample size of 76 patients would provide 80% power to detect that difference by means of a two-sided test at an alpha level of 0.05. However, we were not able to enrol all the 76 patients required by the statistical calculations, and the study enrolment was stopped at 45 patients due to the slowness of the enrolment procedure and the publication of the European AIDS Clinical Society guidelines that suggested a longer treatment period for HIV/HCV genotype 1 co-infected patients.[17]

Statistical analysis

Continuous variables are expressed as mean±SD; categorical variables are expressed as number of cases (%). Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA). Continuous data were analysed using Student's *t*-test if they appeared normally distributed and the Mann–Whitney test otherwise. Categorical variables were analysed using Fisher's exact test. All statistical tests were two-sided. Multivariate analyses were carried out using a logistic model and P values ≤0.05 were considered statistically significant.
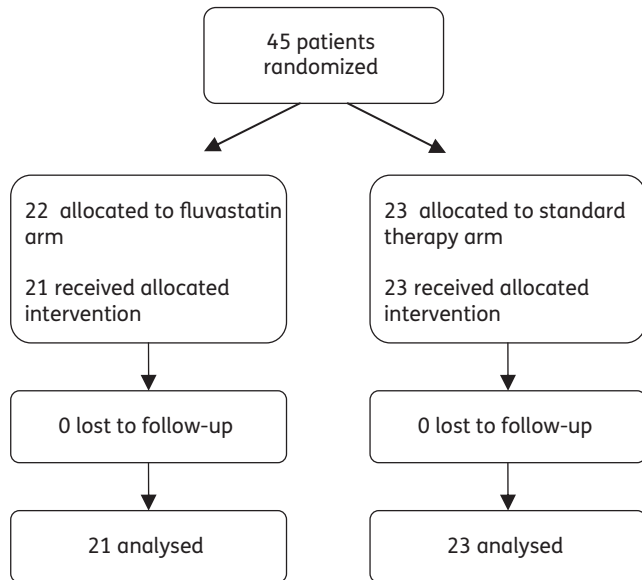
Results

Patient characteristics

Of the 45 patients enrolled in the study 23 were randomized to receive the standard therapy with PEG-IFN-α 2b plus ribavirin, and 22 were randomized to receive fluvastatin in addition to standard therapy. One subject withdrew from the study soon after the randomization assignment (to the fluvastatin arm) and was excluded from further analysis (Figure 1). Four patients (two in the fluvastatin group and two in the standard therapy group) were a non-responder or relapser to a previous treatment with standard IFN and ribavirin.

Table 1 shows the baseline characteristics of the two groups of patients. All the patients enrolled were Caucasian and both groups were well balanced for all the variables considered, without any statistically significant differences, including baseline HCV-RNA levels. All except three patients were on highly active antiretroviral therapy with a complete suppression of HIV replication (HIV-RNA < 50 copies/mL). Fourteen patients (32%) were on treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, 26 (59%) with a protease inhibitor-based regimen and all were treated with at least one nucleoside reverse transcriptase inhibitor (NRTI); one patient was on treatment with three NRTIs. Thirty-nine (88.6%) patients (20/21 in the fluvastatin arm and 19/23 in the standard therapy arm)

reached the 12 week visit and 34 (77.3%) patients completed 24 weeks of therapy (17/21 in the fluvastatin arm and 17/23 in the standard therapy arm). Ten patients discontinued treatment due to their own decision (2 patients) or to the onset of grade 3/4 side effects (8 patients). All were considered as treatment failure in the intent-to-treat analysis.

Figure 1. Flow diagram of the patients.

Virological and biochemical response

Response rates are summarized in Figure 2. In the global intent-to-treat analysis, 25% of patients reached SVR. In particular, SVR was achieved in 8/21 (38%) of the fluvastatin group versus 3/23 (13%) of the standard therapy group; $P=0.08$. Globally an RVR, EVR and ETR were obtained in 18% (8/44), 25% (11/44) and 38.6% (17/44), respectively. Of the patients achieving an RVR, 75% reached an SVR versus 14% of those who had not achieved an RVR ($P=0.0017$). The proportion of patients achieving an ETR but who relapsed during the follow-up was 14%, with a similar rate in the two groups.

Figure 2. Response rate by intent-to-treat analysis. RVR, rapid virological response at week 4; SVR, sustained virological response at week 24 after cessation of therapy.

Table 1. Baseline patient characteristics

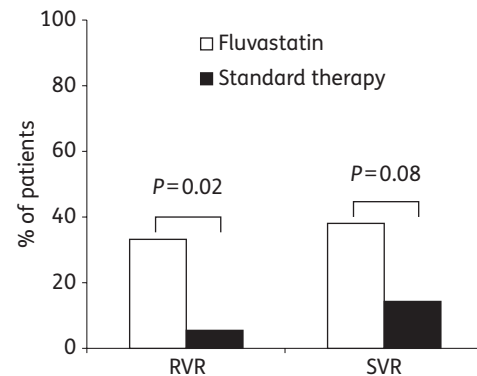| Variable	Fluvastatin group (21)	Standard therapy group (23)	Total (44)	P value[a]
Age, years	44.5 ± 4.02	45.52 ± 6.5	45.05 ± 5.4	0.5
Male sex	19 (90%)	20 (87%)	39 (89%)	1.0
BMI	23.8 ± 3.23	23 ± 3.3	23.4 ± 3.26	0.4
HIV-RNA, copies/mL	568 ± 1647	234 ± 818	386 ± 1279	0.4
CD4+, cells/mm^3	652 ± 258	569 ± 244	607 ± 251	0.3
HCV-RNA, $\log_{10}$ IU/mL	5.78 ± 0.6	5.76 ± 0.66	5.77 ± 0.6	0.9
Ishak fibrosis score				
0–2	13 (62%)	15 (65%)	28 (64%)	1.0
3–4	8 (38%)	8 (35%)	16 (36%)	1.0
ALT, IU/L	123 ± 79	86 ± 60	103 ± 71	0.1
Total cholesterol, mg/dL	155 ± 21	158 ± 34	157 ± 28	0.9
HDL, mg/dL	45 ± 13	40 ± 14	42 ± 13	0.3
LDL, mg/dL	76 ± 23.2	77 ± 24.9	76.5 ± 23.5	0.2
Triglycerides, mg/dL	177 ± 82	166 ± 74	171 ± 77	0.6

BMI, body mass index (calculated as weight in kg/height in m^2).
Values are expressed as mean $\pm$ SD for continuous variables and number of patients (%) for categorical variables.
[a]Fisher's exact test.

A significant difference in the RVR rate was found between the two groups: 33% (7/21) of patients in the fluvastatin arm obtained an RVR versus 4% (1/23) in the standard therapy arm ($P=0.02$). No significant differences emerged between the two groups in the proportion of patients achieving an EVR and an ETR.

Mean $\pm$ SD ALT values decreased from 103 ± 71 IU/L at baseline to 51.6 ± 26.8 IU/L at the end of therapy; the sustained biochemical response rate observed was 36%, with 25% of patients with an SVR not achieving ALT normalization at the end of follow-up.

Patients who received fluvastatin in association with the PEG-IFN/ribavirin regimen showed at week 24 a significant reduction of total cholesterol and LDL [from (mean$\pm$SD) 155.6 ± 21 mg/dL to 124.5 ± 9.2 mg/dL; $P=0.002$ and from 76 ± 23.2 mg/dL to 59 ± 23.3 mg/dL; $P=0.001$, respectively]; no significant change of these parameters occurred in the standard therapy group [from (mean$\pm$SD) 158 ± 34 mg/dL to 131 ± 39 mg/dL; $P=0.2$ and from 77 ± 24.9 mg/dL to 81 ± 28.3 mg/dL; $P=0.69$, respectively]. No significant change was observed for HDL and triglycerides during the study period.

Influence of pre-treatment variables on early viral dynamics

Since the degree of viral decay during anti-HCV therapy is known to mirror the sensitivity of the virus–host system to the treatment, we evaluated the influence of pre-treatment viral load, fibrosis score and randomization group on early viral dynamics calculated as the decline in viral load ($-\log_{10}$) between baseline, week 4 and week 12 (ΔHCV-RNA). As shown in Table 2, only grade of liver fibrosis was associated with a statistically significant variation in the viral kinetic decay. Although not significant, the influence of treatment group showed a higher decay between baseline and week 4 in the fluvastatin arm.

Pre-treatment variables associated with viral response

Univariate and logistic regression multivariate analysis for variables influencing both SVR and RVR were performed. At univariate analysis no significant correlation was found between SVR and all the parameters considered; in particular, the fluvastatin treatment arm showed an odds ratio (OR) of 3.89 compared with the standard therapy, but without reaching statistical significance ($P=0.07$). After adjusting for the main predictors of virological response (age, gender, HCV viraemia, total cholesterol levels at baseline and treatment arm), SVR was not significantly associated with any of these parameters.

At univariate analysis only baseline ALT values and the group of randomization were found to be significantly associated with RVR, whereas none of the other variables affected the response rate at week 4. However, no predictors were independently associated with RVR, when multivariate analysis was performed taking into consideration the two variables positively associated in the univariate analysis (Table 3).

Table 2. Viral kinetics decay (ΔHCV-RNA, $-\log_{10}$) according to pre-treatment variables and randomization arm

Week	Group			Viral load (IU/mL)			Fibrosis		
	fluvastatin	standard	P	$\leq$400000	>400000	P	$\leq$F2	>F2	P
4	−1.64	−1.01	0.06	−1.31	−1.31	0.96	−1.49	−0.78	0.09
12	−2.17	−1.87	0.49	−2.03	−2.01	0.96	−2.44	−1.22	0.04

Table 3. Pre-treatment variables associated with RVR at univariate and multivariate analysis

Variable	Univariate			Multivariate		
	P	OR	95% CI	P	AOR	95% CI
Age, years	0.32	0.92	0.77–1.08			
Sex (female versus male)	0.93	1.1	0.1–11.49			
Treatment arm (flluvastatin versus standard therapy)	**0.036**	10.5	1.61–94.9	0.09	6.99	0.72–68.09
BMI	0.39	1.12	0.85–1.47			
Baseline CD4 cell count, cells/mm³ ($\leq$300 versus >300)	0.73	1.48	0.14–14.89			
Baseline HCV-RNA, IU/mL (>400000 versus $\leq$400000)	0.74	0.76	0.15–3.78			
Baseline ALT, IU/L	**0.049**	1.01	1–1.02	0.12	1	0.99–1.02
Cholesterolaemia, mg/dL	0.76	0.99	0.96–1.02			
Triglycerides, mg/dL	0.38	0.99	0.98–1			
Fibrosis, Ishak score (0–2 versus 3–4)	0.87	1.16	0.18–7.38			

AOR, adjusted odds ratio; OR, odds ratio; CI, confidence interval.
For multivariate analysis only statistically significant values were included in the analysis.
Significant P values are shown in bold.

Table 4. Frequency of adverse events and treatment discontinuation

Variable	Fluvastatin group (21)	Standard therapy group (23)	Total (44)	P value[a]
Discontinuation				
own decision	1	1	2	1.0
adverse effect	3	5	8	0.7
Total adverse events	14	17	31	0.7
grade 3/4	6	8	14	0.7
General symptoms				
flu-like	14	10	24	0.1
asthenia	12	12	24	0.8
Haematological findings				
anaemia	4	6	10	0.7
leucopenia	9	8	17	0.7
thrombocytopenia	1	2	3	1.0
Neuropsychiatric symptoms				
depression	6	9	15	0.5
irritability	6	9	15	0.5

Values are expressed as number of patients.
[a]Fisher's exact test.

Safety evaluation

Seventy percent of the studied patients experienced some adverse effects (Table 4). The most frequently reported were fatigue and flu-like syndrome (54.5%); depression was reported in 34% of patients and five patients interrupted the treatment due to this adverse event. Among haematological disorders, anaemia (haemoglobin < 10.5 g/dL) was seen in 23%, 30% of whom required erythropoietin administration, leucopenia (< 2500 cells/mm^3) in 39%, 60% of whom required granulocyte-stimulating therapy, and thrombocytopenia (> 20% decrease from baseline) in 7% of subjects. Two patients were withdrawn because of thrombocytopenia and one for leucopenia. The side effect profiles were similar in both treatment groups.

Discussion

In agreement with published data for HIV/HCV genotype 1 co-infected patients,[18] the overall rate of SVR in our cohort was unsatisfactory (25%), particularly in the standard therapy arm (13%). This very low rate of SVR is similar to what was observed by Chung et al.[2] in HCV genotype 1 co-infected patients. Higher rates of response have been reported[3,4] considering genotype 1/4 as a single group, but the relatively higher response reported for genotype 4 might explain this difference.[19] Other possible explanations of the low response rate in our cohort might be the high HCV viraemia observed (42/44 > 400000 copies/mL), the presence of four patients who failed a previous IFN plus ribavirin treatment, and the small case file analysed. Patients in the fluvastatin arm had a higher, although not statistically significant, rate of SVR in comparison with those treated with standard therapy. Moreover, a significantly higher proportion of patients reached an RVR in the fluvastatin treatment group. Interestingly, the achievement of RVR was the only predictor associated with SVR, thus confirming the valuable role of early viral kinetics on the outcome of PEG-IFN plus ribavirin treatment.[20,21]

The inability of our clinical trial to definitely demonstrate, by multivariate analysis, a synergistic role for fluvastatin added to standard therapy might be related to the number of patients enrolled, which was not powered to demonstrate such a role.

The tolerability of the two treatment schedules was similar, confirming previous data on the safe use of statins in HCV- and HCV/HIV-infected patients.[22,23]

To date only one recent pilot study, conducted without a control group, has explored the effect of fluvastatin in association with PEG-IFN plus ribavirin in HCV-genotype-1-infected patients.[24] It is worth noting that a nearly double rate of SVR was observed in comparison with our results, possibly reflecting the influence of HIV co-infection in our cohort.

From our previous observation, fluvastatin monotherapy did not exert anti-HCV activity in HIV/HCV co-infected subjects;[15] nevertheless, in the present study, we observed a higher rate of RVR. It could be argued that statins, besides a weak direct antiviral effect, may enhance HCV infectivity of hepatocytes through the decrease in circulating LDL levels and the up-regulation of LDL receptors. This effect of statins might counterbalance the antiviral activity described in the replicon model.

However, other mechanisms among the pleiotropic actions of statins, such as their immunomodulatory effect or their ability to activate peroxisome proliferator-activated receptor (PPAR)-α,[25] may explain the synergistic effect obtained on RVR by the combination with PEG-IFN and ribavirin.

In conclusion, before definitively discarding statins as possible therapy for chronic hepatitis C in combination with PEG-IFN and ribavirin, an adequately powered randomized trial should be performed.

Transparency declarations

All the authors: no conflicts of interest to declare.

Author contributions

All the authors have significantly contributed to the work and have read and approved the manuscript. L. M. designed and wrote the study. I. C., M. C. and M. O. selected the patients and extracted clinical data. C. M. carried out the statistical analysis. S. A. and M. G. critically revised the manuscript and gave the final approval for the submission. L. M. had full access to the data and guarantees for them.

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