

Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfecting subjects: an early report

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Abstract

Background—More severe liver disease together with a poor response rate to α interferon argue for the use of more potent anti-hepatitis C virus (HCV) therapies in human immunodeficiency virus (HIV)-HCV coinfecting patients, but the efficacy and safety of interferon-ribavirin combination therapy in HIV infected subjects are unknown.

Aim—To retrospectively evaluate the efficacy and safety of anti-HCV combination therapy in 21 HCV-HIV coinfecting patients receiving antiretroviral therapy, and to access the clinical relevance of in vitro inhibition of phosphorylation by ribavirin of potent inhibitors of HIV—that is, zidovudine, stavudine, and zalcitabine.

Patients—Twenty one patients were treated with combined antiretroviral therapy including zidovudine (n=8) or stavudine (n=13) (in association with protease inhibitors in 12). All received ribavirin (1000 or 1200 mg/day) and α interferon (3 MU three times/week) for chronic hepatitis C infection. All patients had not responded (n=20) or relapsed (n=1) after a previous six month course of α interferon therapy.

Methods—HIV viral load (Monitor test) and CD4 cells count were measured at the beginning and every three months during and after ribavirin plus α interferon therapy over a mean period of 11 (1) months. Clinical and biological adverse effects were recorded.

Results—There was no significant variation in HIV viral load or CD4 cell counts after three or six months of ribavirin therapy compared with baseline values. Of the 21 subjects, three (14%) had an increase in HIV viral load of more than 0.5 log leading to discontinuation of ribavirin in one. Eleven of 21 (52.4%) had initial negative HCV viraemia at three (n=10) or six (n=1) months but only six were polymerase chain reaction negative at the end of therapy, leading to rates for primary response and breakthrough of 23.8% and 28.5%, respectively. Six months after completion of therapy, three patients relapsed (14.3%) and three (14.3%) had sustained virological response. Median haemoglobin concentration decreased significantly after three and six months of ribavirin therapy (p= 0.0002 and p=0.0003,

respectively) leading to withdrawal of therapy in one patient.

Conclusions—These preliminary results show that: (1) despite in vitro interactions between ribavirin, zidovudine, and stavudine, significant variation in HIV replication does not usually occur in HCV-HIV coinfecting patients receiving ribavirin and different antiretroviral regimens, including zidovudine and stavudine; (2) α interferon and ribavirin combination therapy induced primary and sustained virological responses in 28.5% and 14.3% of treated subjects (who were previous non-responders to interferon therapy), respectively; (3) anaemia is a frequent adverse event. Such results should be confirmed in larger prospective trials.

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Keyword: ribavirin; human immunodeficiency virus; hepatitis C virus; zidovudine; stavudine; antiretroviral therapy

Hepatitis C (HCV) and human immunodeficiency (HIV) viruses share the same routes of transmission, explaining the high rate of HCV and HIV coinfection of 9-30%.¹ HCV related disease is more severe in HIV than in non-HIV infected individuals with a twofold higher rate of cirrhosis,² and may be associated with an increased risk of liver related death.³

More severe liver disease together with a poor response rate to α interferon of HIV-HCV coinfecting patients¹ argue for the use of more potent anti-HCV therapies to avoid histopathological deterioration. Anti-HCV combination therapy with interferon and ribavirin has shown promising results in immunocompetent (naive and relapser) patients with a marked increase in the virological sustained response rate⁴⁻⁷ but the efficacy and safety of such combinations in coinfecting subjects are unknown.

In vitro inhibition of phosphorylation by ribavirin of HIV reverse transcriptase inhibitor (that is, zidovudine (AZT), stavudine (D4T), and zalcitabine) to the active compound has been reported.⁸⁻¹⁰ The clinical impact of these findings is currently unknown and it may be hypothesised that ribavirin impairs the efficacy of antiretroviral drugs. Moreover, there may be

Abbreviations used in this paper: HIV, human immunodeficiency virus; HCV, hepatitis C virus; AZT, zidovudine; D4T, stavudine; PCR, polymerase chain reaction.

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Table 1 Baseline characteristics of human immunodeficiency virus-hepatitis C virus (HIV-HCV) coinfecting patients

Mean (SD) age (y)	40.2 (7)
Male	17 (81%)
Risk factor for HIV-HCV infections	
Intravenous drug use	17 (81%)
Transfusion	3 (14.3%)
Antiretroviral therapy	
Zidovudine	8 (38%)
Stavudine	13 (62%)
HIV-1 protease inhibitor	12 (57%)
Duration of antiretroviral therapy (months)	
Median (95% CI)	8.3 (6.0–10.5)
Range	3–22
Cirrhosis (No (%))	11 (52.4%)

a greater risk of anaemia in view of the haemolysis associated with ribavirin and the bone marrow suppression associated with nucleoside analogues. The aims of this study were: (1) to retrospectively evaluate the safety of anti-HCV combination therapy, especially the clinical relevance of these in vitro interactions, by reviewing the clinical, biological, virological, and immunological outcome of 21 coinfecting patients receiving an antiretroviral regimen, including at least D4T or AZT; and (2) to evaluate the efficacy of interferon and ribavirin combination therapy on HCV replication.

Patients and methods

PATIENTS

Twenty one HCV-HIV coinfecting patients receiving antiretroviral therapies, including at least D4T (n=8) or AZT (n=13), for a median period of 8.3 (3–22) months prior to introduction of ribavirin plus alpha interferon were studied. The main characteristics of the patients are summarised in table 1. There were 17 men and four women with a mean age of 40 (7) years. Risk factors for viral transmission were intravenous drug usage in 17, transfusion in three, and sexual contact in one. HCV genotype was 3a (n=7), 1a (n=6), 1b (n=4), 4 (n=2), and 2 (n=2). Twelve (57%) patients were treated with a HIV-1 protease inhibitor, including indinavir (n=5), saquinavir (n=5), or ritonavir (n=4) (two were given both ritonavir and saquinavir), in association with two nucleoside analogues.

Liver biopsy showed cirrhosis in 12 of 21 patients (57%) and mean activity and fibrosis scores were 2 (1) and 3 (1), respectively.

All patients had not responded (n=20) or relapsed (n=1) after a previous six month course of α interferon therapy. Patients re-

ceived anti-HCV therapy for a mean period of 8.5 (3) months, including ribavirin (1000 or 1200 mg daily) and α interferon (3 MU subcutaneously three times weekly).

MEASUREMENTS

HIV RNA plasma levels were assessed with a standard available commercial assay (Amplicor HIV-1 Monitor, Roche Diagnostic System Neuilly sur Seine, France) which has a detection limit of 200 copies of HIV-1 RNA/ml. HCV polymerase chain reaction (PCR) was performed using a standard commercial assay (Amplicor HCV Monitor, Roche Diagnostic System Neuilly sur Seine, France). CD4 lymphocyte counts were measured using dual colour flow cytometry.

HIV viral load and CD4 cell counts were measured three months before, at the beginning of the study, at three month intervals after ribavirin plus α interferon therapy, and three months after completion of therapy over a mean period of 9 (1) months.

STATISTICAL ANALYSIS

Changes in median HIV viral loads, CD4 counts, and haemoglobinaemia were compared by the Wilcoxon signed rank test. Results are expressed as median (range).

Results

Median HIV load and CD4 counts, performed in 21 patients three months before starting interferon and ribavirin therapy, were 2.8 (2.3–5.9) log₁₀ copies/ml and 293 (45–655) cells/ml, respectively. At the beginning of ribavirin and interferon therapy, CD4 counts were not different and HIV RNA plasma levels were significantly lower than three months earlier (p=0.3 and p=0.05, respectively).

There was no statistically significant change in HIV viral load or CD4 cell counts after three or six months of ribavirin therapy compared with baseline values (table 2, fig 1). However, an increase of more than 0.5 log copies/ml of plasma HIV-RNA (1.3, 0.6, and 0.6, respectively) was observed in three patients (14%) after 3–6 months of ribavirin. Two of these three patients had undetectable HIV viraemia prior to ribavirin. After three months of ribavirin plus interferon therapy, a median decrease of 68 (23–97) CD4 lymphocytes/ml was observed in 11 of 21 patients (52.4%; 95% CI 29.7–74.3%). After six months of anti-HCV

Table 2 Biological, virological, and immunological outcomes of human immunodeficiency virus-hepatitis C virus (HIV-HCV) coinfecting patients receiving interferon and ribavirin therapy

	Baseline	Month 3	p Value*	Month 6	p Value*
n†	21	21		17	
Haemoglobinaemia (g/dl)					
Median (range)	13.8 (10.5–16.7)	11.8 (7.8–16)	0.0002	11.8 (5–16)	0.0003
n†	21	21		17	
RNA HIV (log ₁₀ copies/ml)	2.3 (2.3–4.9)	2.3 (2.3–4.6)	0.3	2.3 (2.3–4.7)	0.6
HIV RNA negative (n (%))	12 (57)	10 (47.6)		10 (47.6)	
CD4 (cells/ml)					
n†	21	21		17	
Median (range)	330 (55–600)	336 (32–639)	0.6	298 (55–507)	0.2
HCV PCR					
n†	21	21		17	
No patients with negative PCR (%)	0 (0)	10 (47)		6 (35)	

*Compared with baseline.

†Number of tested patients.

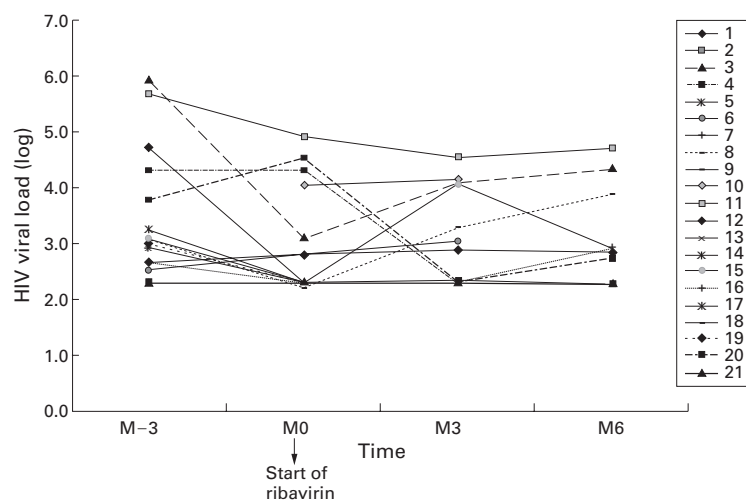


Figure 1 Human immunodeficiency virus (HIV) viral load three months before, at the start of ribavirin therapy, and three and six months after ribavirin therapy in individual patients (n=21).

therapy, the median decrease in CD4 was 57 (18–206) cells/ml in 10 of 18 tested patients (55.9%; 95% CI 30.7–78.5%). A decrease in haemoglobinaemia was observed after three and six months of ribavirin ($p=0.0002$ and $p=0.0003$, respectively). Ribavirin plus interferon were stopped in one case because of severe anaemia and in another case anaemia led to dose reduction of ribavirin and transfusion; in one other case, discontinuation of ribavirin was necessary because of both increased HIV viral load and decreased CD4 cell counts. In the latter, withdrawal of therapy was associated with a decrease in HIV viral load (8000 to 1800 copies/ml). For the two other patients who experienced an increase in HIV viral load during anti-HCV therapy, HIV viral load was not modified after completion of therapy. No other serious side effects were observed.

Eleven of 21 (52.4%) patients had initial negative HCV viraemia at three (n=10) or six (n=1) months but only six were PCR negative at the end of therapy, leading to rates of primary response and breakthrough of 23.8% and 28.5%, respectively. Six months after completion of therapy, three patients relapsed (14.3%) and three (14.3%) had sustained virological response.

Three months after completion of therapy, haemoglobinaemia and CD4 cell counts increased significantly ($p<0.003$ and $p<0.03$, respectively) while HIV viral load was not modified ($p>0.05$).

Discussion

Our results suggest that the ribavirin-interferon combination had a low in vivo impact, if any, on phosphorylation of nucleoside analogues and had a limited antiviral sustained efficacy in HCV-HIV coinfecting patients who were previous non-responders to interferon therapy.

Ribavirin (1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) is a guanoside nucleoside analogue which shows marked antiviral activity against different RNA and DNA viruses, including HCV, but has no anti-HIV activity.^{11,12} In vitro studies have demonstrated

that ribavirin inhibits intracellular phosphorylation of AZT, D4T, and zalcitabine, suggesting a decrease in their anti-HIV efficacy.^{8–10} The underlying molecular basis of such inhibition is under investigation and probably involves inhibition of thymidine kinase activity.¹⁰

The association of ribavirin and interferon with AZT or D4T for 3–6 months did not induce a significant change in HIV viral load or CD4 lymphocyte counts. This finding suggests that interactions between ribavirin and AZT or D4T may not influence HIV replication in vivo. However, three patients had an increase in HIV load of more than 0.5 log which could be related to impairment of AZT or D4T efficacy due to inhibition of phosphorylation and which led to discontinuation of ribavirin in one patient. It is noteworthy that an increase in HIV-1 RNA plasma levels cannot be related definitively to ribavirin but may be related to HIV resistance to antiretroviral therapy or to poor compliance with therapy. Similarly, as previously reported, the decrease in CD4 cell counts observed in 50% of patients was probably related to α interferon¹ rather than to ribavirin. Indeed, a decrease in CD4 cell counts was not observed in large trials in which HIV infected patients received only ribavirin.^{11,12}

Analysis of efficacy of anti-HCV combination therapy in coinfecting subjects showed 23.8% and 14.3% primary (HCV-RNA clearance at the end of therapy) and sustained virological response rates, respectively, in patients who were previous non-responders to interferon therapy. This very low sustained rate of response in non-responders parallels those obtained in the general population.¹³ Eleven of 21 (52%) patients had initial negative HCV viraemia during therapy. We believe that the discrepancies between an anti-HCV antiviral effect, at least initially, and the fact that many of these patients were interferon relapsers or non-responders could be explained, at least in part, by better immune status at the time of the combination therapy than at the start of interferon monotherapy (data not shown). Indeed, it is noteworthy that most patients (80%) received interferon therapy before HAART was available; most patients had a poorer immune status at the time of the first anti-HCV therapy. Moreover, among patients with initial negative HCV viraemia, nearly half experienced a breakthrough. Interferon and ribavirin therapy was well tolerated, except for ribavirin related haemolysis which requires monitoring of haemoglobin concentration and perhaps a decrease in initial dose to 600–800 mg/24 hours.

In conclusion, our preliminary data suggest that short term treatment with ribavirin is feasible with no major clinical impact on HIV disease in patients receiving zidovudine and zalcitabine but requires close monitoring of HIV viral load. Therapeutic trials with longer follow up and in vitro evaluation are warranted to confirm the safety and efficacy of anti-HCV combination therapy in coinfecting subjects.

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