

Chronic hepatitis C in patients with HIV/AIDS: a new challenge in antiviral therapy

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HIV-infected patients are living longer since the introduction of highly active antiretroviral therapy. However, coinfection with the hepatitis C virus (HCV) leads to increased morbidity from liver disease and higher overall mortality. The prevalence of chronic hepatitis C among patients with HIV/AIDS ranges from 7% (sexual transmission of HIV) to >90% (injection drug use). Uncontrolled HIV infection seems to accelerate the progression of HCV-induced liver fibrosis. Forty-eight weeks of combination therapy with pegylated interferon alpha (2a or 2b) plus ribavirin achieves a sustained viral response in coinfecting individuals in up to 38% with HCV genotype 1 and up to 73% with genotypes 2 or 3. The safety profile of this treatment is similar to therapy in HCV-monoinfected patients with influenza-like symptoms, cytopenia and neuropsychiatric symptoms dominating. However, HIV/HCV-coinfecting patients who also take zidovudine develop more profound anaemia than those on other HIV nucleoside analogue therapy. Didanosine and stavudine are associated with rare but serious mitochondrial toxicity, such as pancreatitis or lactic acidosis. It does not appear that the addition of ribavirin increases that risk. There is currently no evidence that in HIV/HCV coinfection one pegylated interferon product is superior to the other. Contrary to common perception, it is also unproven that HIV/HCV-coinfecting patients respond less well to therapy with peginterferon alpha plus ribavirin than HCV-monoinfected patients. Given the safety and efficacy of combination therapy with peginterferon plus ribavirin and the deleterious effects of chronic hepatitis C, all HIV/HCV-coinfecting patients should be evaluated for therapy.

Keywords: pegylated interferon, ribavirin, highly active antiretroviral therapy, drug interactions

Introduction

Patients infected with the human immunodeficiency virus (HIV) have experienced a dramatic decline in morbidity and mortality since the introduction of highly-active antiretroviral therapy (HAART) in 1996. With longer survival, they are increasingly threatened by non-HIV-related illnesses, chief among them coinfection with the hepatitis C virus (HCV). Compared with patients infected with HIV alone, HIV/HCV-coinfecting individuals have a higher rate of cirrhosis and hepatocellular carcinoma,¹ a shorter survival than HIV-negative persons with chronic hepatitis C once HCV-related liver decompensation occurs,² a higher rate of fulminant hepatic failure (without prior liver disease) in the context of HAART³ and a higher overall mortality.⁴ The HCV-related progression of liver fibrosis is more rapid in HIV/HCV-coinfecting patients with uncontrolled HIV viraemia compared with those with HCV alone.⁵

The prevalence of HCV coinfection among patients with HIV disease varies greatly and is largely dependent on the mode of transmission of HIV itself. It is high with parenteral transmission such as injection-drug use (91%) or transfusions (71%) but low with sexual transmission (7%).⁶

Therapy of chronic hepatitis C in HIV/HCV-coinfecting patients in 2005

Until 2004, only small, uncontrolled, observational studies had been published on the treatment of chronic hepatitis C in HIV/HCV-coinfecting individuals. In 2004, two randomized, controlled trials (RCTs) examined safety and efficacy of 48 weeks of standard interferon alpha-2b (IFN-2b) at 3 million international units (MIU) three times per week plus ribavirin at 800 mg/day compared with a 16 week delay of ribavirin⁷ or with daily IFN-2b.⁸ The rate of sustained viral response (SVR; HCV RNA <100 copies/mL or <50 IU/mL at post-treatment week 24) in both studies was disappointingly low at 11 and 9%. Early discontinuation was ~50%, mostly due to patient choice in light of lack of viral response at week 24 but also due to adverse events in 21–26% of patients.

In the same year, four RCTs were reported on therapy with pegylated IFN plus ribavirin, two with 40 kDa peginterferon alpha-2a (PEG-IFN-2a; Pegasys[®]) plus ribavirin and two with 12 kDa peginterferon alpha-2b (PEG-IFN-2b; PEG-Intron[®]) plus ribavirin (see Table 1). The largest trial to date (APRICOT,

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Table 1. SVR rates in six trials of pegylated IFN plus ribavirin for 48 weeks given to HIV/HCV-coinfected and to HCV-monoinfected patients

Therapy and trial name		SVR GT-1	SVR GT-2/3
PEG-IFN-2a + RBV for HCV/HIV coinfection			
APRICOT ⁹ (<i>n</i> = 868)	PEG-IFN-2a 180 µg/week + RBV 800 mg/day	29%	63%
	IFN-2a 3 MIU ×3/week + RBV 800 mg/day	7%	20%
		<i>P</i> < 0.001	<i>P</i> < 0.001
ACTG ¹¹ (<i>n</i> = 133)	PEG-IFN-2a 180 µg/week + RBV 600–1000 mg/day	14%	73%
	IFN-2b 3 MIU ×3/week + RBV 600–1000 mg/day	6%	33%
		<i>P</i> = NS	<i>P</i> = NS
PEG-IFN-2a + RBV for HCV monoinfection			
Hadziyannis ¹⁵ (<i>n</i> = 365)	PEG-IFN-2a 180 µg/week + RBV 800 mg/day (no standard IFN + RBV control arm)	41%	79%
PEG-IFN-2b + RBV for HCV/HIV coinfection			
RIBAVIC ¹² (<i>n</i> = 412)	PEG-IFN-2b 1.5 µg/kg/week + RBV 800 mg/day	17%	44%
	IFN-2b 3 MIU ×3/week + RBV 800 mg/day	6%	43%
		<i>P</i> = 0.006	<i>P</i> = NS
Barcelona ¹⁴ (<i>n</i> = 95)	PEG-IFN-2b 1.5 µg/kg/week + RBV 1000–1200 mg/day	38%	47%
	IFN-2b 3 MIU ×3/week + RBV 1000–1200 mg/day	7%	53%
		<i>P</i> = 0.007	<i>P</i> = NS
PEG-IFN-2b + RBV for HIV monoinfection			
Manns ¹³ (<i>n</i> = 1530)	PEG-IFN-2b 1.5 µg/kg/week + RBV 800 mg/day IFN-2b 3 MIU ×3/week + RBV 800 mg/day	42% 33%	82% 79%
		<i>P</i> = 0.02	<i>P</i> = NS

SVR, sustained viral response; HIV, human immunodeficiency virus; HCV, hepatitis C virus; GT, HCV genotype; NS, statistically not significant; IFN-2a/-2b, interferon alpha-2a/-2b; PEG-IFN-2a/-2b, peginterferon alpha-2a/-2b; RBV, ribavirin; MIU, million international units.

n = 868)⁹ compared 48 weeks of treatment with PEG-IFN-2a 180 µg once weekly plus ribavirin 800 mg/day with standard IFN-2a 3 MIU three times per week plus ribavirin 800 mg/day and PEG-IFN-2a plus placebo as safety control group. The SVR rate was higher in the pegylated than in the standard IFN arm, both overall (40% versus 12%, *P* < 0.001) and by HCV genotype (GT-1, 29% versus 7%, *P* < 0.001 and GT-2/3, 62% versus 20%, *P* < 0.001). Independent factors associated with SVR rate were genotype non-1 and baseline HCV RNA level <800 000 IU/mL. Indeed, in GT-1 with high HCV viral load (>800 000 copies/mL), the most common scenario in HIV/HCV-coinfected patients, the SVR rate was only 18%, compared with 61% with those having GT-1 and low viral load (≤800 000 IU/mL) or 61–63% in GT-2/3 with any viral load. Failure to achieve an early viral response (EVR), defined as a decline in HCV viral load by at least 2 log₁₀ or 100-fold or to <50 IU/mL led to an SVR in only 3%, giving the EVR measure a negative predictive value (NPV) for SVR of 97%. This rate is similar to the 97% NPV of the EVR measure found in the same therapy of PEG-IFN-2a plus ribavirin for HCV monoinfection.¹⁰ A smaller pilot study (ACTG A5071, *n* = 133)¹¹ also found a superior SVR rate with 48 weeks of PEG-IFN-2a plus ribavirin compared with standard IFN-2b plus ribavirin (27% versus 12%, *P* = 0.02).

The efficacy and safety of 48 weeks of PEG-IFN-2b at 1.5 µg/kg weekly plus ribavirin at 800 mg/day was compared with standard IFN-2b plus ribavirin 800 mg/day in another large study (RIBAVIC, *n* = 412).¹² PEG-IFN-2b plus ribavirin yielded an SVR rate of 27% versus 20% in the standard IFN-2b plus ribavirin group (*P* = 0.047). However, the superiority of PEG-IFN-2b

plus ribavirin was only seen on GT-1 (17% versus 6%, *P* = 0.006) but not in GT-2/3 (44% versus 43%, *P* = 0.88). The same phenomenon of similar SVR rates in GT-2/3 was observed in HCV monoinfection where PEG-IFN-2b versus IFN-2b, each combined with ribavirin, also had similar SVR rates (82% versus 79%, *P* = 0.89).¹³ A smaller study from the Universitat de Barcelona (*n* = 95)¹⁴ with the same combination therapy confirmed a higher SVR rate with PEG-IFN-2b plus ribavirin compared with IFN-2b plus ribavirin (44% versus 21%, *P* = 0.01) but again only in GT-1 (38% versus 7%, *P* = 0.007), not in GT-2/3 (47% versus 53%, *P* = 0.73). Of note, this study used a higher ribavirin dose of 1000–1200 mg/day (weight cutoff at 75 kg), and has so far achieved the highest SVR rate in GT-1 of 38%.

Toxicity of HCV therapy

Treatment with IFN-alpha (standard or pegylated) has long been known to cause significant side effects. These include initial influenza-like symptoms (45–62%) such as myalgia, arthralgia, headaches, anorexia, and fever, cytopenia (15–22%), neuropsychiatric symptoms such as depression (22–31%), and rarely thyroiditis (<1%) and other autoimmune phenomena. Treatment with ribavirin adds significant haemolytic anaemia (10–22%), dermatitis (20–24%) and cough (10%), and it requires birth control owing to its high teratogenicity. In combination therapy with pegylated IFN (alpha-2a or alpha-2b), these side effects appear to occur with a similar frequency in HIV-monoinfected and HIV/HCV-coinfected patients.^{9,10,12,13,15}

Interactions between peginterferon plus ribavirin and HAART

Zidovudine, IFN-alpha and cytopenia

Both zidovudine and IFN are myelosuppressive and cause mild anaemia when given alone. When ribavirin causing haemolytic anaemia is combined with IFN which inhibits the bone marrow's capacity to make up for the loss in red blood cells, profound anaemia may develop. This anaemia is more pronounced when zidovudine is taken concomitantly than when patients do not take zidovudine (maximum haemoglobin level drop 3.9 versus 3.1 g/dL in PEG-2a + ribavirin⁹ and 2.5 versus 1.0 g/dL with IFN-2b + ribavirin⁷). The rate of anaemia-related dose reductions of ribavirin is much higher in patients on zidovudine (60%) than in subjects not taking zidovudine (16%).⁷ Use of zidovudine does not influence the degree of IFN-induced neutropenia.

HIV dideoxynucleoside analogues (didanosine and stavudine), ribavirin, and mitochondrial toxicity

Since the first report in 2001,¹⁶ cases of mitochondrial toxicity such as pancreatitis or lactic acidosis (some fatal) have been observed by multiple authors in HIV/HCV-coinfected patients undergoing combination therapy with IFN + ribavirin. In almost all instances, this toxicity was associated with the concurrent use of didanosine, stavudine or both. The US Food and Drug Administration collected reports of 52 such events and found mitochondrial toxicity to be associated with the use of didanosine [odds ratio (OR) = 12.4], with didanosine plus stavudine (OR = 8.0), and with stavudine alone (OR = 3.3). The report points out that ribavirin leads to increased intracellular levels of didanosine-triphosphate.¹⁷ This led to a warning label in the didanosine prescribing information urging clinicians to use didanosine and ribavirin together only with great caution.

It is thus evident that co-administration of didanosine or stavudine during ribavirin therapy increases the risk of mitochondrial toxicity. But these data do not permit the reverse conclusion that addition of ribavirin to an existing HAART regimen with didanosine or stavudine increases mitochondrial toxicity. Indeed, a substudy of the APRICOT trial showed that this is not the case. Comparing the two groups who received PEG-IFN-2a plus either ribavirin or placebo, the incidence of pancreatitis, lactic acidosis and symptomatic hyperlactataemia was similar in both groups (2.4% versus 2.8%, $P = 0.78$). Among the 15 patients with such events, 11 were concurrently taking didanosine or stavudine.¹⁸ These data show that while didanosine and stavudine are associated with mitochondrial toxicity, the addition of ribavirin does not increase this risk.

Competition of ribavirin for intracellular phosphorylation enzymes

Before the recent studies of PEG-IFN plus ribavirin therapy were published, there was concern about the interaction between ribavirin and HIV nucleoside analogues. *In vitro*, ribavirin competes with intracellular phosphorylation enzymes and inhibits the conversion of zidovudine and stavudine into their active triphosphate forms. However, this *in vitro* observation was not confirmed in patients. A nested pharmacokinetic substudy of APRICOT found that in patients receiving ribavirin, there is no significant decrease in plasma levels of zidovudine, stavudine and lamivudine and no

inhibition of intracellular phosphorylation of zidovudine, stavudine and lamivudine.¹⁹

Influence of HCV therapy with peginterferon plus ribavirin on HIV infection

Not only were plasma levels and phosphorylation of nucleoside analogues not impaired during HCV combination therapy, there was also no impairment of HIV control during treatment. In APRICOT, the HIV viral load temporarily decreased by 0.7 log₁₀ during therapy with PEG-IFN-2a (with or without ribavirin) demonstrating that the weak antiretroviral property of IFN-alpha²⁰ is also in effect in HIV/HCV coinfection. The absolute CD4+ lymphocyte count temporarily declined during PEG-IFN-2a plus ribavirin therapy by 157 cells/mm³ but the CD4+ percentage rose by 3.0 percentage points. This discrepancy can be explained by lymphopenia induced by ribavirin (and to a lesser extent PEG-IFN) which then leads to a lower calculated absolute CD4+ cell count (=CD4+% times absolute lymphocyte count). The CD4+ percentage is a more stable and accurate parameter to estimate the cellular immune function. The other three trials had similar findings on HIV viral load and CD4+ cells. It can therefore be concluded that HCV combination therapy with PEG-IFN plus ribavirin does not impair the immune function or control of HIV infection in HIV/HCV-coinfected patients.

Influence of HIV disease on HCV viral response

In the two large trials with PEG-IFN plus ribavirin, both APRICOT⁹ and RIBAVIC,¹² none of the HIV-related parameters like CD4+ cell count or percentage, HIV viral load, antiretroviral treatment and CDC classification of HIV disease had an influence on SVR rate. The smaller ACTG A5071 study¹¹ found detectable HIV RNA are baseline to be independently correlated with a better SVR. The Universitat de Barcelona trial¹⁴ found absence of HIV protease inhibitor use to be independently associated with a better SVR, but only in patients infected with HCV genotypes 2 or 3. The reasons for these two associations are not clear, and these are not seen in the other, larger, studies. One possible explanation for the correlation between detectable HIV RNA and better SVR in ACTG A5071 may relate to the fact that patients with high CD4+ cell counts are often not taking HAART and have a low level of HIV viral load. These stable HIV patients may have less anaemia and neutropenia, possibly leading to fewer dose reductions and discontinuations of study medication.

Comparison of randomized controlled trials of HCV therapy in HIV/HCV coinfection

All four RCTs quoted above consistently show the same results. PEG-IFN plus ribavirin has superior SVR rates to standard IFN plus ribavirin, in PEG-IFN-2a plus ribavirin in all genotypes, and in PEG-IFN-2b + ribavirin only in genotype 1. PEG-IFN plus ribavirin is now considered the treatment of first choice in HIV/HCV-coinfected patients, as it has been already in HCV-monoinfected individuals. Upon further comparison of the four trials, it may be tempting to further conclude that treatment with PEG-IFN-2a plus ribavirin leads to higher SVR rates (APRICOT,⁹ GT-1, 29%; GT-2/3, 63%) than therapy with PEG-IFN-2b + ribavirin (RIBAVIC,¹² GT-1, 17%; GT-2/3, 44%). However, this conclusion

is invalid because primary endpoints can only be compared between randomized groups in one study, but not between groups from separate trials. Each trial has a different population with different baseline characteristics and has a different study design with different rules of how to manage treatment-related adverse events (e.g. dose reductions of PEG-IFN or ribavirin, use of growth factors, etc.). Many of these factors can directly influence the viral response. Only a randomized, controlled trial would be able to allow conclusions on differences in efficacy and safety between the two pegylated IFN products combined with ribavirin.

Similarly, there is a widespread belief that SVR rates to PEG-IFN plus ribavirin are lower in HIV/HCV-coinfected than in HCV-monoinfected patients. This notion may be suggested by a direct comparison of treatment with PEG-IFN-2a at 180 µg per week plus ribavirin at 800 mg/day in HCV monoinfection (Hadziyannis trial,¹⁵ GT-1, 41%; GT-2/3, 79%) and in HIV/HCV coinfection (APRICOT,⁹ GT-1, 29%; GT-2/3, 63%). Similar differences in SVR rates are seen with PEG-IFN-2b at 1.5 µg/kg per week plus ribavirin at 800 mg/day in HCV monoinfection (Manns trial,¹³ GT-1, 42%; GT-2/3, 82%) and in HIV/HCV coinfection (RIBAVIC,¹² GT-1, 17%; GT-2/3, 44%). However, again, this assumption is based on the comparison of SVR rates between separate studies with many differences in study population other than HIV status. Only a case–control study between two trials with the same treatment could provide the answer to the open question of whether HIV/HCV-coinfected patients have a different SVR rate than patients with chronic hepatitis C alone. One small case–control study examining viral kinetics during treatment with PEG-IFN plus ribavirin found a slower phase 1 and 2 viral decline in HIV/HCV-coinfected versus HCV-monoinfected patients but was too small to adequately control for confounding factors.²¹

Open questions for future research

The optimal length of therapy with PEG-IFN plus ribavirin in HIV/HCV-coinfected patients with GT-2/3 is not defined. For HCV-monoinfected GT-2/3 patients, Hadziyannis and colleagues showed that 24 weeks of therapy is sufficient as it has the same SVR rate as that of 48 weeks.¹⁵ The currently recommended length of treatment in HIV/HCV coinfection GT-2/3 is 48 weeks based on the above-quoted studies, but a European study is currently in progress that randomizes GT-2/3 HIV/HCV-coinfected patients to either 24 or 48 weeks of therapy.

Similarly, the Hadziyannis study showed that in GT-1, PEG-IFN-2a combined with a ribavirin dose of 1000–1200 mg/day leads to a higher SVR rate than with 800 mg/day of ribavirin (52% versus 41%). The same effect may apply to HIV/HCV-coinfected patients, but a higher ribavirin dose may also lead to more profound anaemia, especially in patients who take zidovudine as part of their HAART regimen. Randomized controlled studies addressing the issue of ribavirin dosing are currently being planned. The role of growth factors such as recombinant granulocyte-colony stimulating factor (G-CSF, filgrastim) and recombinant human erythropoietin (EPO, epoetin alpha) in the treatment of cytopenia during HCV therapy has also not been well defined. One randomized controlled study of HIV/HCV-coinfected patients with anaemia during combination HCV therapy found that, compared with standard of care, epoetin alpha at 40 000 IU weekly is able to raise the haemoglobin level at week 16 by 2.8 g/dL in patients receiving zidovudine, and by 1.3 g/dL in subjects not on zidovudine. The ribavirin doses at week 16 were similar in both groups.²² It is unclear if the use of

epoetin alpha has an influence on the SVR rate, and the drug is not currently approved for treatment of anaemia during HCV therapy.

Patients who do not achieve a viral cure after optimal HCV therapy may benefit from agents that can slow down or perhaps reverse the development of hepatic fibrosis. Based on a retrospective study that suggests a possible antifibrotic effect of IFN,²³ three ongoing randomized controlled studies examine the effect of half-dose PEG-IFN versus no treatment on fibrosis progression and clinical progression to end-stage liver disease in HCV-monoinfected patients (CO-PILOT, HALT-C and EPIC-3). Two similar randomized controlled studies (HRN-004 and SLAM-C) are currently being conducted in HIV/HCV-coinfected patients.

Promising new anti-HCV agents include oral HCV enzyme inhibitors, notably RNA-dependent RNA polymerase inhibitors and HCV protease inhibitors. Several investigational drugs are currently in phases I and II of clinical development. Conference abstracts of pilot studies in HCV-monoinfected subjects have reported a 1.2 log₁₀ decrease in HCV viral load with 14 days of therapy with the RNA polymerase inhibitor NM283 at 800 mg/day (Idenix, Cambridge, MA, USA),²⁴ and a 4.3 log₁₀ decline with 14 days of treatment with the protease inhibitor VX-950 at 2250 mg/day (Vertex, Cambridge, MA, USA) (Press Release, Vertex Pharmaceuticals, Chicago, 17 May 2005). It is hoped that, if successful, these new agents are also tested in HIV/HCV-coinfected patients in short order.

Conclusion

Patients with HIV/AIDS live longer with HAART, and increasingly HIV/HCV coinfection jeopardizes their health. Safe and effective therapy against chronic hepatitis C is now available for them with pegylated IFN (alpha-2a or alpha-2b) plus ribavirin. This therapy does not impair control of HIV infection or cellular immunity, however, anaemia may be worse in patients on zidovudine. It is unknown if there is a difference in SVR rates between HIV/HCV-coinfected and HIV-monoinfected patients.

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