Treating Hepatitis C Virus in HIV Patients: Are Side Effects a Real Obstacle?

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Abstract

Hepatitis C virus-related long-term complications are nowadays a leading cause of morbidity and mortality in HIV-infected persons. According to international guidelines, all HIV/HCV-coinfected patients should be evaluated and, if eligible, treated with pegylated interferon plus ribavirin. The management of anti-HCV treatment side effects, which may be even more serious in HIV patients, is very important to minimize treatment early discontinuations. The purpose of this review is to supply clinicians with an update, provided by the most recent and relevant literature, of underlying mechanisms, incidence, and advice about the management of pegylated interferon and ribavirin side effects in HCV/HIV-coinfected patients. **(AIDS Reviews 2007;9:16-24)**

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Key words

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Introduction

Chronic hepatitis C virus (HCV)-related liver disease is an important cause of comorbidity for HIV-infected patients. Coinfection with HCV and HIV is highly frequent, in particular among subjects at risk of parenteral transmission (hemophiliacs, ex-drug addicts), with a percentage of up to 90-100% according to case histories[1-3]. Moreover, complications of end-stage liver disease (ESLD) are currently one of the main causes of morbidity and mortality among coinfected subjects on HAART, as incidence and mortality due to opportunistic HIV-related diseases is dramatically reduced[4-8]. It has been suggested that the deficiency of cell-mediated immune response characterizing HIV infection actually favors the chronic development of acute HCV infection[9] and also the progression of chronic hepatitis to cirrhosis[10]. For these reasons, the published guidelines considering all coinfected patients as potential candidates for treatment with interferon (IFN) and ribavirin have gained unanimous consensus[11-13]. These recommendations are supported by recently published, randomized, controlled clinical trials showing the efficacy of combination treatment with pegylated interferon (PEG-IFN) and ribavirin in coinfected subjects, and its superiority over recombinant IFN and PEG-IFN monotherapies or recombinant IFN/ribavirin combination (Table 1). Nevertheless, the management of this treatment is often made difficult by numerous side effects, which frequently lead to treatment interruption or dose reduction that cause the exposure of patients to suboptimal doses of one or both of the drugs and compromise the potential efficacy of the treatment[14,15]. The greater incidence and seriousness of such undesirable effects in coinfected patients is often cited as a cause of reduced adherence and consequently as one of the principal factors of reduced efficacy of anti-HCV treatment in this particular population[16].

The aim of this review is to compare the incidence of side effects of anti-HCV treatment among mono- and coinfected subjects, with reference to the main ran-

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domized clinical trials, and to summarize the state of the art management of such effects, resulting from the international guidelines and the relevant literature.

Side effects in HIV/HCV patients treated with PEG-IFN and ribavirin

The main side effects of PEG-IFN and ribavirin therapy causing early discontinuation or drug dose reduction are: flu-like syndrome (temperature, widespread myalgia, asthenia), which occurs shortly after IFN injection and lasts for an average of 24-36 hours, hematologic effects (neutropenia, anemia, thrombocytopenia) and neuropsychiatric effects (insomnia, irritability, depression). A series of alterations of laboratory parameters can also occur in coinfected patients, such as lactic acidosis, pancreatic enzyme increase, sometimes symptomatic, or episodes of hepatic decompensation in cirrhotic patients, which have never been recorded in clinical trials on monoinfected patients (Table 2); it is possible that a common etiologic substrate for these events exists, such as mitochondrial damage induced by multiple factors. Figure 1 shows the incidence of the general and psychiatric side effects of PEG-IFNα-2a and -2b reported in the main trials regarding the treatment of monoinfected[17,18] and coinfected patients[19-23].

Leukocytopenia and neutropenia

The main cause of neutropenia during anti-HCV therapy is partially due to the direct myelotoxic action of IFN on bone marrow progenitors[24]. On the other hand, HCV infection can be associated with autoimmune cytopenias (in the first place with hemolytic anemia, but also with thrombocytopenia and neutropenia)[25] and it should not be forgotten that 10-50% of HIV-positive patients are recorded as having neutropenia (absolute neutrophil counts < 2000/ml) of variable severity[26]. In fact, in this category of subjects, numerous factors such as HIV-related myelodysplasia with downregulation of granulocyte colony stimulating factor (G-CSF) receptors in bone marrow precursors, or the concomitant use of potentially myelotoxic therapies (co-trimoxazole, ganciclovir, zidovudine) may contribute to decreased circulating neutrophils. All the clinical trials considered reveal a greater impact of PEG-IFN on the neutrophil count compared with recombinant IFN. The risk of neutropenia seems to be dose-dependent, as can be deduced from the registration PEG-IFNα-2b trial where neutropenia was reported in 18% of patients taking a PEG-IFN dose of 1.5 µg/kg and only in 10% of the patients enrolled in the low-dose PEG-IFN group. Moreover, the study by Schmid, et al.[27], specifically aimed at assessing the extent of myelosuppression caused by different IFN-therapy regimens, reveals how the leucopenia-inducing effect of PEG-IFNα-2a is statistically more significant at weeks 4, 8, and 48 compared with that of PEG-IFNα-2b, and how the neutrophil count nadir (± 52-55% neutrophils at baseline) is reached at around week 8 of treatment for all the regimens considered; the neutrophil count tends to return to pretherapy values within 24 weeks after the end of treatment. The clinical significance of neutropenia during IFN therapy is still under debate, since some authors[28] but not all[29,30] relate it to a greater risk of infection. Neutropenia is certainly one of the most frequent causes of dose reduction or IFN interruption (particularly if pegylated) during anti-HCV treatment in both co- and monoinfected patients (Table 2). A summary of the product characteristics of both PEG-IFN suggest a strategy for the management of neutropenia consisting in the progressive reduction of the drug dose, up to its suspension in the case of neutrophils < 500/ml[31,32]. No randomized clinical trials (whether in mono- or coinfected subjects) demonstrating the benefit of G-CSF on adherence to anti-HCV treatment and, consequently, on sustained virologic response (SVR) have been published until now, despite many proposals concerning this issue[33,34]. Therefore, although neither European nor U.S. guidelines for the treatment of chronic hepatitis C in coinfected patients strongly recommend its use[11,13], in clinical practice G-CSF is frequently required to maintain optimal adherence to anti-HCV treatment and, at the same time, to avoid exposure of patients to serious toxicity risks[12,35]. The leukocytopenia linked to IFN myelotoxicity also leads to a reduction of the absolute number (but not the percentage of total lymphocytes) of CD4+ T lymphocytes[19,21,22,36], which has proved to be completely reversible on suspension of IFN therapy[21,22,36].

Anemia

Anemia appears to be the main cause of the discontinuation or reduction of the ribavirin dose during anti-HCV therapy in coinfected patients (Table 2); it has a significant negative impact on the quality of life of patients treated[37] and it may increase morbidity in the case of patients with coronary heart disease[38]. During treatment with IFN and ribavirin, anemia can be induced by a multifactorial etiopathogenesis: the main

Table 1. Sustained virologic response in the main clinical trials conducted on HIV/HCV-coinfected patients

	ACTG5071 (N Engl J Med, 2004)[22]		APRICOT (N Engl J Med, 2004)[19]		RIBAVIC (JAMA, 2004)[20]		Laguno, et al. (AIDS, 2004)[21]		ICOS (Antivir Ther, 2005)[23]	
Study design	PEG-IFNα-2a + RBV 600-1000 mg vs. IFN 6 MU 3 MU x 3/W + RBV 600-1000 mg		PEG-IFNα-2a + RBV 800 mg vs. PEG-IFNα-2a + PL vs. IFNα-2a 3 x MU 3/w + RBV 800 mg		PEG-IFNα-2b + RBV 800 mg vs. IFNα-2b 3 MU x 3/W + RBV 800 mg		PEG-IFNα-2b 100-150 µg/W + RBV 800-1200 mg vs. IFNα-2b + RBV 800-1200 mg		PEG-IFNα-2b + RBV 800 mg vs. PEG-IFNα-2b + PL	
	PEG-IFN + RBV	IFN + RBV	PEG-IFN +RBV	PEG-IFN + PL	PEG-IFN + RBV	IFN + RBV	PEG + RBV	IFN + RBV	PEG-IFN + RBV	PEG-IFN + PL
Patients (n)	66	67	289	288	205	207	52	43	69	66
Cirrhotics (%)	11	9	15	16	39 (F3-F4)	39	29	31	14	18
Genotypes 1-4 (%)	77	78	67	68	61	62	63	64	53	51
SVR (ITT) (%)	27	12	40	20	27	20	44	21	22	9
SVR gen 1-4 (%)	14	6	29	14	17	6	38	7	11	9
SVR gen 2-3 (%)	73	333	62	36	44	43	53	47	34	9

PEG-IFN: pegylated interferon; RBV: ribavirin; IFN: interferon; PL: placebo; SVR: sustained virologic response; ITT: intent-to-treat; gen: genotype.

Table 2. Total dropout by incidence and by adverse events or laboratory anomalies in patients treated with PEG-IFN and ribavirin in the main clinical trials conducted on coinfected and monoinfected patients

	APRICOT (N Engl J Med, 2004)	RIBAVIC (JAMA, 2004)	Laguno, et al. (AIDS, 2004)	Fried, et al. (N Engl J Med, 2002)	Manns, et al. (Lancet, 2001)
Patients on PEG-IFN + RBV (n)	289	205	52	453	1025 (511 + 514)
Total DO incidence (%)	25	39	23	22	–
DO incidence by AE or lab anomalies (%)	15	17	17	10	13-14
Reduction of the PEG-IFN or RBV dose due to anemia or neutropenia (%)	11 (PEG-IFN) 7 (RBV)	7 (PEG-IFN) 10 (RBV)	9 (PEG-IFN) 13 (RBV)	20(PEG-IFN) 22 (RBV)	18-10 (PEG-IFN) 9-12 (RBV)

PEG-IFN: pegylated interferon; RBV: ribavirin; DO: dropout: AE: adverse events.

anemia-inducing mechanism consists in the extravascular hemolysis of erythrocytes where ribavirin concentrates in the form of ribavirin triphosphorylated compound, which, being unable to cross the cell membrane, remains "trapped" in the red blood cells causing adenosine triphosphate (ATP) depletion and consequent increased cell-membrane vulnerability to oxidative stress[39]. Further, it has been suggested that ribavirin might inhibit erythropoiesis by a downregulating mechanism of erythropoietin receptors[39]. A certain degree of anemia is also present, however, in patients treated solely with IFN, which, in turn, acts by inhibiting the proliferation of

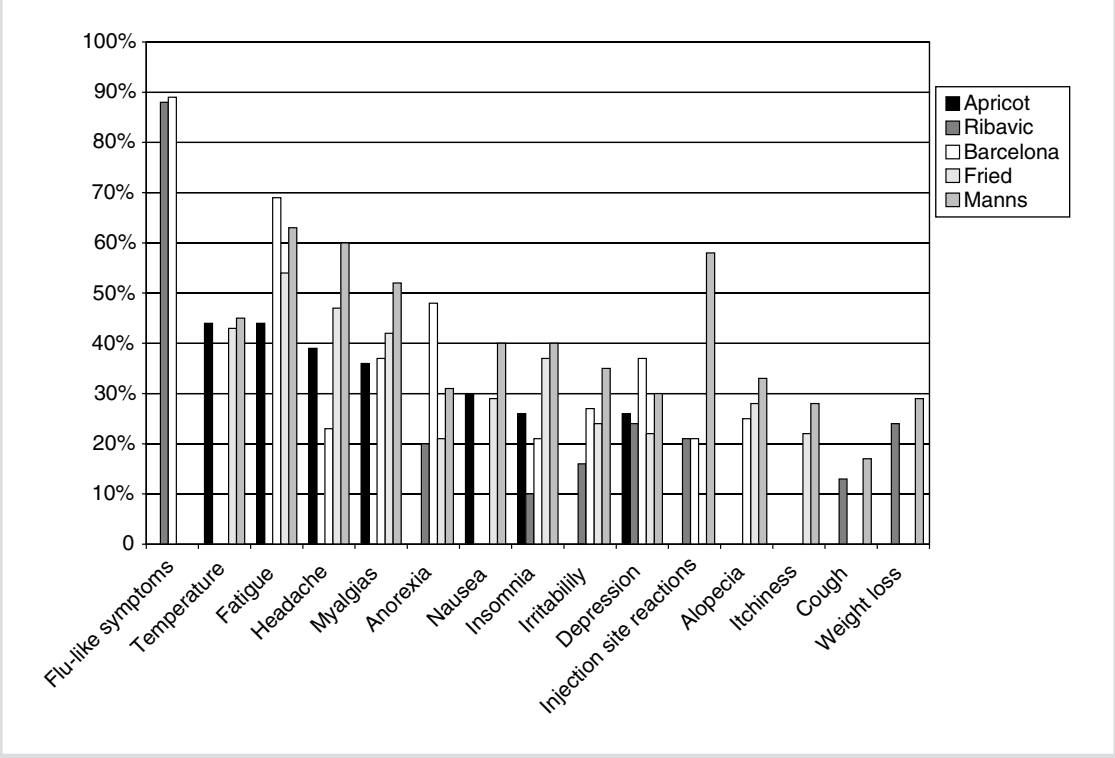

Figure 1. *Incidence of general and psychiatric side effects in the main clinical trials conducted in coinfected and monoinfected patients.*

erythroid progenitors[40] by favoring apoptosis in the erythroid cell line[41] and sometimes by provoking autoimmune hemolytic anemia[42].

In HIV-positive patients, anemia is the most common form of cytopenia, and it has been shown that it is related to increased mortality in these patients. Anemia can be caused by HIV-induced alterations of hematopoiesis, opportunistic infections, HIV-related neoplasias, nutritional deficits, or the use of anemia-inducing drugs such as zidovudine[43]. The timing and extent of the development of anemia in coinfected patients during IFN and ribavirin treatment do not appear to differ from those of monoinfected patients and neither do the management strategies. Emerging data show a close connection between the plasmatic concentration of ribavirin and the development of anemia in both monoinfected[44] and coinfected patients[45]. After the identification of the effective ribavirin therapeutic range, therapeutic drug monitoring should guide ribavirin dosages in most difficult cases. For the moment, however, the management of anemia during anti-HCV therapy still hinges on the progressive reduction of the ribavirin dose, as suggested by the IFNα-2a and -2b specifications[31,32] for values of Hb < 10 g/dl (or a 2 g Hb decline within four weeks in the case of patients with heart disease) and its suspension when the Hb value falls below 8.5 g/dl. However, in consideration of the negative impact of suboptimal doses of ribavirin on SVR (above all in the first weeks of therapy and in the case of HCV genotypes difficult to treat)[14,15], of the demonstrated erythropoietin efficacy for the treatment of ribavirin-induced anemia, improving quality of life and adherence[37,46], as well as a reduction in the compensatory production of erythropoietin on occurrence of anemia in patients treated with IFN and ribavirin as compared with patients with anemia due to other causes[47], the latest guidelines recommend erythropoietin use in coinfected patients[11,12,35]. In this context, management of antiretroviral therapy is also essential in order to prevent IFN- and ribavirin-related side effects: caution and possibly avoidance of the use of anemia- and neutropenia-inducing drugs such as zidovudine is consequently advised[11,12,35]. Of the new inosine monophosphate dehydrogenase inhibitors, Viramidine® (Valeant Pharma. Int.) appears to be the most promising: this is a ribavirin prodrug structurally similar to adenosine, activated mainly in the liver by the adenosine-deaminase enzyme; it is phosphorylated in circulating erythrocytes far less efficiently[48,49], and therefore its anemia-inducing activity is lower than that of ribavirin. Encouraging results were provided by a phase II clinical trial demonstrating a similar efficacy of ribavirin and Viramidine in association with PEG-IFN in the treatment of patients affected by chronic hepatitis C, but with significantly lower Viramidine toxicity. However, the results of the VISER I study conducted on 970 HCV-positive IFN-naive patients, randomized to receive PEG-IFNα-2b + ribavirin 1000/1200 mg/d or PEG-IFNα-2b + Viramidine 600 mg 2/d, were recently presented. The study confirmed the lower toxicity profile of Viramidine, but in the intent-to-treat analysis, Viramidine was less efficient in providing SVR compared to ribavirin[50].

Thrombocytopenia

Both from epidemiologic and clinical points of view, thrombocytopenia is certainly the least important form of IFN-related cytopenia (Fig. 2). In all the clinical trials examined, the percentage of patients who had to reduce or suspend IFN due to severe thrombocytopenia was ≤ 5-6%; the problem was more frequent with the use of PEG-IFN and was on average more significant in coinfected than in monoinfected patients. The main cause of thrombocytopenia is the direct myelosuppressive action of IFN, which is accompanied by a blunted thrombopoietin response when thrombocytopenia occurs[51]. It must be remembered, however, that diverse pathogenetic mechanisms of thrombocytopenia can coexist in HCV-positive patients, such as spleen sequestration in the case of hepatic cirrhosis, diminished thrombopoietin production by the "suffering" liver, or the co-presence of autoimmune reactions, which can even benefit from treatment with IFNα[52]. At the moment, no guidelines exist for the use of recombinant IL-11, which acts as a thrombopoietin growth factor and which has been approved in the USA by the Food and Drug Administration only for use with cancer patients. One small trial has explored its benefits in the case of HCV-positive patients affected by IFN-related thrombocytopenia with positive results, but it should be mentioned that water retention appeared to be its most frequent side effect, which means that use of this molecule is not very practical in the case of cirrhotic patients[53]. In the case of severe thrombocytopenia, therefore, a progressive reduction of the IFN dose as reported in the PEG-IFNα-2a and -2b specifications should be made. The use of recombinant IFN in thrombocytopenic patients is suggested only by the U.K. guidelines, in consideration of the lower bone marrow toxicity demonstrated by this molecule[12].

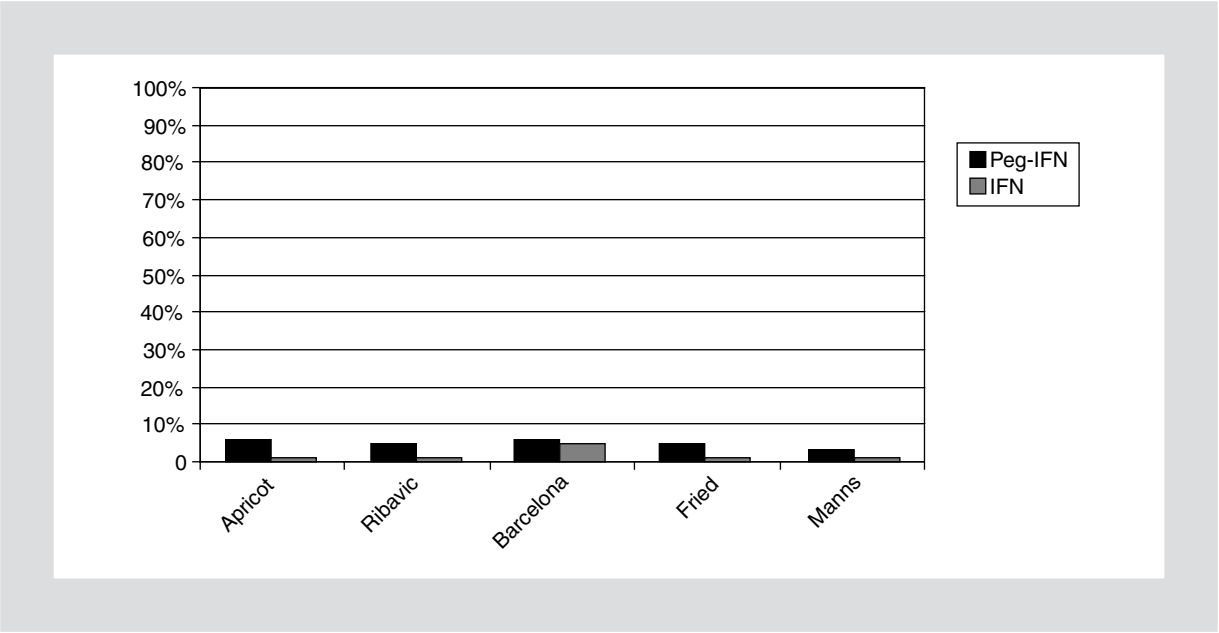

Figure 2. *Reduction of PEG-IFN dose due to severe thrombocytopenia: comparison of the main clinical trials in mono- and coinfected patients. PEG-IFN: pegylated interferon; IFN: interferon.*

Mitochondrial toxicity

In HIV/HCV-coinfected patient populations, mitochondrial damage is frequent, particularly during HAART treatment, and is caused by a multifactorial etiology. The HCV infection induces mitochondrial dysfunction mediated by direct oxidative damage of core proteins on the mitochondria[54], by the production of intracellular oxidant agents linked to viral replication in infected cells[55], and by the activation of diverse cell apoptosis pathways, such as the fatty acid synthase (FAS) system[56]. The HCV infection involves a depletion of mitochondrial DNA (mtDNA), demonstrated in the peripheral blood mononuclear cells (PBMC), regardless of therapy with reverse transcriptase inhibitors, which certainly enhance the effect by inhibiting mtDNA-polymerase-γ[57]. Data showing an additive effect of the two viral infections on mtDNA depletion have recently been published[58]. This supports the greater frequency of side effects involving mitochondrial damage (such as lipoatrophy and hyperlactatemia) found in coinfected subjects[59]. Furthermore, a worsening of these symptoms has been reported during treatment with IFN and ribavirin, even without the concomitant use of didanosine (ddI)[60]. The effect of nucleoside reverse transcriptase inhibitors (NRTI) is amplified by the interaction between these drugs and ribavirin, which promotes, through inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH), the phosphorylation of ddI, the increase of intracellular concentration of 2`,3`-dideoxyadenosine-5`-triphosphate (ddATP) and, as a result, an inhibition of the DNA polymerase-γ[61]. For these reasons, it is understandable how adverse events associated with mitochondrial toxicity (such as asymptomatic or symptomatic hyperlactatemia with various degrees of severity, pancreatitis, hepatic steatosis and hepatic damage, which in cirrhotic subjects can even lead to decompensation) occur exclusively in coinfected patients (Table 3). A recently published prospective study has highlighted that risk factors concerning events connected with mitochondrial toxicity are essentially an antiretroviral regimen including ddI or stavudine (d4T) (but only when associated with ddI), abnormal levels of lactic acid prior to IFN therapy, and diabetes mellitus[62]. A retrospective analysis of the factors precipitating hepatic decompensation in the patients enrolled in the APRICOT study has, on the other hand, highlighted the presence of advanced liver disease and, as in the previous study, the concomitant use of ddI as risk factors[63]; further, the APRICOT study did not reveal differences between the three treatment regimens proposed in relation to the risk of hepatic decompensation. On the basis of these data, the current guidelines discourage the use of ddI and, if possible, of d4T (especially in association with ddI) in coinfected patients who must undergo IFN treatment. The aim of this recommendation is to avoid the abovementioned side effects or

Table 3. Incidence of side effects attributable to mitochondrial toxicity and hepatic decompensation in the main clinical trials in mono- and coinfected patients

% of all patients treated	APRICOT (N Engl J Med, 2004)	RIBAVIC (JAMA, 2004)	Laguno, et al. (AIDS, 2004)	Fried, et al. (N Engl J Med, 2001)	Manns, et al. (Lancet, 2001)
Mitochondrial toxicity (pancreatitis, hyperlactatemia, hepatic steatosis)	0.8	3	4	0	0
Hepatic decompensation	1.6	2	0	0	0

Table 4. Incidence of psychiatric side effects in the main clinical trials in mono- and coinfected patients

% of all the patients treated	APRICOT (N Engl J Med, 2004)			RIBAVIC (JAMA, 2004)		Laguno, et al. (AIDS, 2004)		Fried, et al. (NEJM 2001)			Manns, et al. (Lancet,2001)		
Group for study	PEG-IFN + RBV	PEG-IFN + PL	IFN + RBV	PEG-IFN + RBV	IFN + RBV	PEG-IFN + RBV	IFN + RBV	PEG-IFN + RBV	PEG-IFN + PL	IFN + RBV	PEG-IFN HD + RBV	PEG-IFN LD + RBV	IFN + RBV
Insomnia	26	21	29	10	17	21	19	37	23	39	40	40	41
Irritability	–	–	–	16	21	27	42	24	25	28	35	34	34
Depression	26	20	22	24	29	37	51	22	20	30	31	29	34

Peg-IFN: pegylated interferon; RBV: ribavirin; IFN: interferon PL: placebo.

episodes of decompensation in the case of cirrhotic patients. Obviously, among these patients, only those without signs of decompensation are considered eligible for anti-HCV treatment by the current guidelines (Child-Turcotte-Pugh stage A)[11,12,35]. In the case of stable HIV infection and an uncompromised immune system, delaying antiretroviral therapy could also be a good choice in order to simplify the treatment.

Psychiatric effects

There are many evidences that both HIV and HCV have an impact on brain function[64]. However neuropsychiatric symptoms in coinfected patients are the result of a complex relationship between substance abuse, impact of infection, and depression.

According to a case-control study, patients with HIV/HCV coinfection have a diminished quality of life similar to that of monoinfected patients[64]. Coinfected patients frequently experience symptoms such as depression and asthenia, producing a reduced quality of life. However, this quality of life impairment seems to be related to sociodemographic conditions (unemployment, poverty, past or current drug abuse) rather than to the presence of the double viral infection[65]. Recombinant or PEG-IFN therapy produces numerous neuropsychiatric side effects and, among these, depression is certainly one of the main ones[66]. Interferon-α alters many neuroendocrine pathways involved in the etiology of depression, such as the serotoninergic and noradrenergic systems, the hypothalamus-hypophysis-suprarenal and the hypothalamus-hypophysis-thyroid axes and the cytokine network acting on the limbic structures[67]. During IFN therapy, depression seems to be the principal factor predicting a reduced health-related quality of life[68] and increasing the risk of dropout from IFN therapy[69] in monoinfected patients. For this reason, besides being a clinical problem (it can occur in particularly severe forms and may be accompanied by suicidal tendencies), the management of psychiatric symptoms that can emerge during IFN and ribavirin therapy is of great importance. Table 4 summarizes the incidence of the more frequent psychiatric disorders recorded in the main clinical trials conducted on coinfected and monoinfected patients. As can be noted, little difference is observed between the use of PEG-IFN or recombinant IFN (which was associated with a greater number of psychiatric side effects in some of the studies mentioned before[66]). Coinfected patients do not appear to be more prone to this category of side effects

than monoinfected patients. Finally, it has been demonstrated that in monoinfected patients, the risk of developing depression during IFN treatment can be predicted from the psychological condition at baseline[70]. Treatment for IFN-mediated depression hinges on selective serotonin reuptake inhibitors (SSRI) which, besides having remarkable efficacy, have also shown good tolerability and safety levels[71,72]; of the SSRI, citalopram and escitalopram seem to be preferable in coinfected patients, since they are probably devoid of pharmacologic interactions with antiretroviral drugs[73,74]. Up to now, very little data regarding the management of IFN-mediated depression in coinfected patients has been published, but it would appear that treatment with SSRI could also be considered efficacious and safe in this population[75], and European guidelines strongly advise its use in clinically significant cases of depression[11]. Interferon treatment of patients with severe psychiatric disorders is unadvisable, and a pretreatment psychiatric assessment can probably be helpful for clinicians to correctly select the candidate patients for IFN therapy. Randomized clinical trials are certainly necessary in order to assess the efficacy and advisability of preventive antidepressant treatment in patients considered at risk of developing IFN-induced disorders.

Conclusion

All HCV/HIV-coinfected patients should be considered as potential candidates for treatment with IFN and ribavirin. Early detection and correct management of side effects is essential to increase the efficacy of anti-HCV treatment in this patient population.

References

1. Sulkowski M, Brinkley-Laughton S, Thomas D. HCV and HIV coinfection: Prevalence, genotype distribution and severity of liver disease in an urban HIV clinic. Hepatology 2000;32:204.
2. Troisi C, Hollinger F, Hoots W, et al. A multicenter study of viral hepatitis in a U.S. hemophiliac population. Blood 1993;81:412-8.
3. Sherman K, Rouster S, Chung R, Rajicic N. HCV prevalence among patients infected with HIV: a cross-sectional analysis of the U.S adult AIDS Clinical Trials Group. Clin Infect Dis 2002;34:831-7.
4. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with HIV infection. Clin Infect Dis 2001;32:492-7.
5. Cohen M, French A, Benning L, et al. Causes of death among women with HIV infection in the era of combination antiretroviral therapy. Am J Med 2002;113:91-8.
6. Martin-Carbonero L, Soriano V, Valencia E et al. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. AIDS Res Hum Retroviruses 2001;17:1467-71.
7. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr 2000;24:211-7.
8. Bonacini M, Louie S, Bzowej N, Wohl A. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. AIDS 2004;18:2039-45.
9. Thomas D, Astemborski J, Rai R, et al. The natural history of HCV infection: host, viral, and environmental factors. JAMA 2000;284: 450-6.
10. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in HIV and HCV coinfected patients. The Multivirc Group. Hepatology 1999;30:1054-8.
11. Alberti A, Clumeck N, Collins S, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV coinfected patients. J Hepatol 2005; 42:615-24.
12. Nelson M, Matthews G, Brook G, Main J. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and HCV infection. HIV Med 2005;6(Suppl 2):96-106.
13. Tien P; Veterans Affairs Hepatitis C Resource Center Program; National Hepatitis C Program Office. Management and treatment of HCV infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. Am J Gastroenterol 2005;100:2338-54.
14. Davis G, Wong B, McHutchinson J, et al. Early virologic response to treatment with PEG-IFNα-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003;38:645-52.
15. Opravil M, Torriani F, Sasadeusz J, et al. Treatment exposure and sustained virologic response in genotype 1 patients treated with PEG-IFNα-2a (40 kDa) plus ribavirin in APRICOT (AIDS PEGASYS Ribavirin International Coinfection Trial). Program and abstracts of the 45th ICAAC; December 16-19, 2005; Washington, DC [abstract V-1179].
16. Sherman K. Implications of PEG-IFN use in special populations infected with HCV. Semin Liver Dis 2003;23(Suppl 1):47-52.
17. Manns M, McHutchinson, Gordon S, et al. PEG-IFNα-2b plus ribavirin compared with IFNα-2b plus ribavirin for initial treatment of chronic hepatitis c: a randomized trial. Lancet 2001;358:958-65.
18. Fried M, Mitchell M. PEG-IFNα-2a plus ribavirin for chronic HCV infection. N Engl J Med 2002;347:975-82.
19. Torriani F, Rodriguez-Torres M, Rockstroh J, et al. PEG-IFNα-2a plus ribavirin for chronic HCV infection in HIV-infected patients. N Engl J Med 2004;351:438-50.
20. Carrat F, Bani-Sadr F, Pol S, et al. PEG-IFNα-2b vs. standard IFNα-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292:2839-48.
21. Laguno M, Murillas J, Blanco J, et al. PEG-IFNα-2b plus ribavirin compared with IFNα- 2b plus ribavirin for the treatment of HIV/HCV coinfected patients. AIDS 2004;18:F27-36.
22. Chung R, Andersen J, Volberding P, et al. PEG-IFNα-2a plus ribavirin vs. IFNα-2a plus ribavirin for chronic HCV infection in HIV-coinfected persons. N Engl J Med 2004;351:451-9.
23. Cargnel A, Angeli E, Mainini A, et al. Open, randomized, multicenter Italian trial on PEG-IFN plus ribavirin versus PEG-IFN monotherapy for chronic hepatitis C in HIV coinfected patients on HAART. Antivir Ther 2005;10:309-17.
24. Ernstoff M, Kirkwood J. Changes in the bone marrow of cancer patients treated with recombinant IFNα-2 Am J Med 1984;76:593-6.
25. Ramos-Casals M, Garcia-Carrasco M, Lopez-Medrano F, et al. Severe autoimmune cytopenias in treatment-naive HCV infection: clinical description of 35 cases. Medicine (Balt) 2003;82:87-96.
26. Levine A, Karim R, Mack W, et al. Neutropenia in HIV infection: data from the women's interagency HIV study. Arch Int Med 2006;166:405-10.
27. Schmid M, Kreil A, Jessner W, et al. Suppression of hematopoiesis during therapy of chronic hepatitis C with different IFNα mono and combination therapy regimens. Gut 2005;54:1014-20.
28. Puoti M, Babudieri S, Rezza G, et al. Use of PEG-IFN is associated with an increased incidence of infections during combination treatment of chronic hepatitis C: a side effect of pegylation? Antivir Ther 2004;9:627-30.
29. Soza A, Everhart J, Ghany M, et al. Neutropenia during combination therapy with IFNα and ribavirin for chronic hepatitis C. Hepatology 2002;36:1273-9.

30. Cooper C, Al-Bedwawi S, Lee C, et al. Rate of infectious complications during IFN-based therapy for hepatitis C is not related to neutropenia. Clin Infect Dis 2006;42:1674-8.
31. Pegasys® (PEG-IFNα-2a) [package insert]. Nutley, NJ: Hoffmann-La Roche, Inc., 2002.
32. PEG-Intron® (PEG-IFNα-2b, recombinant) [package insert]. Kenilworth. NJ: Schering Corporation 2002.
33. Armstrong W, Kazanjian P. Use of cytokines in HIV-infected patients: colony-stimulating factors, erythropoietin, and interleukin-2. Clin Infect Dis 2001;32:766-73.
34. Golia P, Talal A, Jacobson I, et al, A preliminary study of growth factors versus dose reduction for PEG-IFNα-2b and ribavirin associated neutropenia and anemia in HIV/HCV coinfected patients. Gastroenterology 2003;124:766.
35. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV coinfection. AIDS 2004;18:1-12.
36. Moreno L, Carmen Q, Moreno A, et al. PEG-IFNα-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. AIDS 2004;18:67-73.
37. Afdhal N, Dieterich D, Pockros P, et al. Proactive Study Group. Epoetin-α maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology 2004;126:1302-11.
38. Dieterich D. Treatment of hepatitis C and anemia in HIV-infected patients. J Infect Dis 2002;185(Suppl 2):128-37.
39. De Franceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic HCV infection: role of membrane oxidative damage. Hepatology 2000;31:997-1004.
40. Kato K, Kamezaki K, Shimoda K, et al. Intracellular signal transduction of IFN on the suppression of hematopoietic progenitor cell growth. Br J Haematol 2003;123:528-35.
41. Tarumi T, Sawada K, Sato N, et al. IFNα induced apoptosis in human erythroid progenitors. Exp Haematol 1995;23:1310-8.
42. Pellicano R, Smedile A, Peyre S, et al. Autoimmune manifestations during interferon therapy in patients with chronic hepatitis C: the hepatologist's view. Minerva Gastroenterol Dietol 2005;51:55-61.
43. Fangman J, Scadden D. Anemia in HIV-infected adults: epidemiology, pathogenesis, and clinical management. Curr Hematol Rep 2005;4:95-102.
44. Lindhal K, Schvarcz R, Bruchfeld A, et al. Evidence that plasma concentration rather than dose per kilogram body weight predicts ribavirin-induced anemia. J Viral Hepatol 2004;11:84-7.
45. Rendon A, Nunez M, Romero M, et al. Early monitoring of ribavirin plasma concentrations may predict anemia and early virologic response in HIV/HCV-coinfected patients. J Acquir Immune Defic Syndr 2005;39:401-5.
46. Sulkowski M, Dieterich D, Bini E, et al. Epoetin-α once weekly improves anemia in HIV/HCV-coinfected patients treated patients treated with IFN/ribavirin: a randomized controlled trial J Acquir Immune Defic Syndr 2005;39:504-6.
47. Trivedi HS, Trivedi M. Subnormal rise of erythropoietin in patients receiving IFN and ribavirin combination therapy for hepatitis C. J Clin Gastroenterol 2004;38:595-8.
48. Wu G, Larson G, Walzer H, et al. Phosphorylation of ribavirin and Viramidine by adenosine-kinase and cytosolic 5'-nucleotidase II: implication for ribavirin metabolism in erythrocytes. J Agents Chemother 2005;49:2164-71.
49. Gish G. Treating HCV with ribavirin analogs and ribavirin-like molecules. J Agents Chemother 2006;57:8-13.
50. Benhamou Y**,** Pockros P, Rodriguez-Torres M, et al. The safety and efficacy of Viramidine® plus PEG-IFNα-2b versus ribavirin plus PEG-IFNα-2b in therapy-naive patients infected with HCV: phase III results. J Hepatol 2006;44(Suppl 2):273.
51. Peck-Radosavljevic M, Wichlas M, Pidlich J, et al. Blunted thrombopoietin response to IFNα induced thrombocytopenia during treatment for hepatitis C. Hepatology 1998;28:1424-9.
52. Garcia-Suarez J, Burgaleta Chernanz N, et al. HCV-associated thrombocytopenia: clinical characteristics and platelet response after recombinant IFNα-2b therapy. Br J Haematol 2000;110:98-103.
53. Rustgi V, Lee P, Finnegan S, et al. Safety and efficacy of recombinant human IL-11 (Oprevlekin) in combination with IFN/ribavirin in hepatitis C patients with thrombocytopenia. Hepatology 2002; 36:361.
54. Okuda M, Li K, Berd M. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by HCV core protein. Gastroenterology 2002;122:366-75.
55. De Maria N, Cantoni A, Fagioli S. Association between reactive oxygen species and disease activity in chronic hepatitis C. Free Radical Biology Med 1996;21:291-5.
56. Hayashi N, Mita E. FAS system and apoptosis in viral hepatitis. J Gastroenterol Hepatol 1997;12.223-6.
57. Cotè H, Brumme Z, Craib K, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med 2002;346:811-20.
58. De Mendoza C, Soriano V. The role of HCV in mitochondrial DNA damage in HIV/HCV-coinfected individuals. Antivir Ther 2005; 10(Suppl 2):M109-15.
59. Garcia Benayas T, Blanco F, Soriano V. Weight loss in HIV-infected patients N Engl J Med 2002;347:1287-8.
60. De Mendoza C, Sanchez-Conde M, Timmermans E, et al. Mitochondrial DNA depletion in HIV-infected patients is more pronounced with chronic hepatitis C and enhanced following treatment with PEG-IFN plus ribavirin. Antivir Ther 2005;10:557-61.
61. Balzarini J, Lee C, Herdewijn P, et al. Mechanism of the potentiating effect of ribavirin on the activity of 2'-3'-dideoxyinosine against HISEE. J of Biological Chemistry 1991;266:21509-14.
62. Laguno M, Milinkovic A, de Lazzari E, et al. Incidence and risk factors for mitochondrial toxicity in treated HIV/HCV-coinfected patients. Antivir Ther 2005;10:423-9.
63. Mauss S, Valenti W, De Pamphilis J, et al. Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during IFN-based therapy. AIDS 2004;18:F21-5.
64. Fleming A, Christiansen D, Nunes D, et al. Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. Clin Infect Dis 2004;38 :572-8.
65. Breitstein P, Montessori V, Chan K, et al. Quality of life, depression and fatigue among persons coinfected with HIV and hepatitis C: outcomes from a population-based cohort. AIDS Care 2005;17:505-15.
66. Dieperink E, Willwmbring M, Ho S, et al. Neuropsychiatric symptoms associated with hepatitis C and IFNα: a review. Am J Psychiatry 2000;157:867-76.
67. Loftis J, Hauser P. The phenomenology and treatment of IFN-induced depression. J Affect Disord 2004;82:175-90.
68. Dan A, Martin L, Crone C, et al. Depression, anemia and health-related quality of life in chronic hepatitis C. J Hepatol 2006;44: 491-8.
69. Zdilar D, Franco-Bronson K, Buchler N, et al. Hepatitis C, IFNα and depression. Hepatology 2000;31:1207-11.
70. Raison C, Borisov A, Broadwelll S, et al. Depression during PEG-IFNα plus ribavirin: prevalence and prediction. Am J Psychiatry 2005;66:41-8.
71. Gleason O, Yates W, Isbell M, et al. An open-label trial of citalopram for major depression in patients with hepatitis C. J Clin Psychiatry 2002;63194-8.
72. Schramm T, Lawford B, Macdonald G, Cooksley W. Seratraline treatment of IFNα-induced depressive disorder. Med J Aust 2000; 173:359-61.
73. Gutierrez M, Rosenberg J, Abramowitz W. An evaluation of the potential for pharmacokinetic interaction between escitalopram and the cytochrome P450 3A4 inhibitor ritonavir. Clin Ther 2003;25: 1200-10.
74. Yu B, Chen G, He N, et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003;31:1255-9.
75. Laguno M, Blanch J, Murillas J, et al. Depressive symptoms after initiation of IFN therapy in HIV-infected patients with chronic hepatitis C. Antivir Ther 2006;9;905-9.