ELSEVIER

Antiviral Research 52 (2001) 189–198

Antiviral Research

www.elsevier.com/locate/antiviral

Management of hepatitis C in HIV-infected persons

Rafael Rodríguez-Rosado [a], Mayte Pérez-Olmeda [a], Javier García-Samaniego [b], Vincente Soriano [a,*]

[a] *Service of Infectious Diseases, Hospital Carlos III, Instituto de Salud Carlos III, C/Nueva Zelanda 54, 4° B, 28035 Madrid, Spain*

[b] *Liver Unit, Hospital Carlos III, Instituto de Salud Carlos III, Madrid, Spain*

Abstract

The life expectancy of HIV-infected persons has extended significantly since the introduction of highly active antiretroviral therapies. Although classical opportunistic infections are now rarely seen, the toxicity of antiretroviral drugs as well as liver disease caused by hepatitis viruses represent an increasing cause of morbidity and mortality among HIV-positive persons. Since the rate of hepatitis C virus (HCV) infection is high among HIV carriers (up to 75% among intravenous drug users), HCV/HIV coinfection is widely prevalent. Predisposing liver damage favors a higher rate of hepatotoxicity of antiretroviral drugs, which can limit the benefit of HIV treatment in some individuals. Overall, severe hepatotoxicity appears in around 10% of subjects who began triple combinations including either protease inhibitors or non-nucleosides. The progression to cirrhosis seems to occur faster in the setting of HIV infection, and conversely recent data demonstrate that HCV infection can accelerate the progression to AIDS in HIV-positive persons. Although clinicians have been reluctant to treat hepatitis C in HIV-infected people, this therapeutic nihilism is unwarranted. The availability of new more successful regimens to treat hepatitis C, in particular using the new pegylated forms of interferon in combination with ribavirin, open new hopes for the care of HIV–HCV-coinfected persons.

Keywords: Hepatitis C virus; HIV; HAART; Interferon; Ribavirin; Liver disease

1. Introduction

The hepatitis C virus (HCV) represents the most frequent etiology of cirrhosis in the developed world (Alter et al., 1999; WHO, 1997; Thomas et al., 2000). Several studies have concluded that most cases of chronic liver disease not related with alcohol are due to HCV. Overall, around 2% of the general population in developed countries is infected with HCV (Alter, 1997). This infection is currently the first cause of liver transplantation in Europe and the USA (Alter et al., 1999).

One of the most prominent characteristics of HCV infection is its high rate of evolution to chronicity. The virus is cleared only in less than 15% of exposed individuals; in the remaining, the infection produces chronic hepatitis, which can yield, later on, to cirrhosis and, eventually, hepatocarcinoma (Di Bisceglie, 1998; Thomas et al., 2000).

* Corresponding author. Tel.: +34-91-453-2500; fax: +34-91-733-6614.

E-mail address: vsoriano@dragonet.es (V. Soriano).

0166-3542/01/$ - see front matter
PII: S0166-3542(01)00184-X

HCV infection is common among HIV-infected people, mainly because both viruses share the same transmission routes (Soriano et al., 1999a). In HIV–HCV coinfected patients, the evolution of the hepatic disease produced by HCV shows a more rapid progression than in those not coinfected (Soto et al., 1997). The main characteristics of HCV infection in HIV-positive individuals are pointed out in Table 1. The evolution of HCV does not seem to improve significantly when HIV replication is adequately controlled (García-Samaniego et al., 1998). However, recent findings suggest that HCV viremia may decline after 1 year on successful HAART; therefore, a longer follow-up might be required to examine whether HCV-related liver disease might ameliorate when using HAART.

The results of the CHORUS database, which includes 4524 HIV-positive patients followed since August of 1997, have pointed out that HIV-infected persons who have responded to HAART with a CD4 count above 200 cells/μl have a projected survival of 32 years. US life tables in HIV-negative persons of the same median age (39 years old) indicate a projected survival of 36 years. These two projections are quite similar. However, the accelerated course of HCV infection could make greater the role of this virus as a cause of morbidity and mortality in HIV–HCV coinfected people. In fact, several reports have shown that hepatic disease, mainly that related to HCV, is currently among the main causes of hospitalization in HIV-infected patients (Soriano et al., 1999b).

Table 1
Characteristics of HCV infection in HIV-infected patients

Chronic hepatitis C is very common in HIV infected patients.
The prevalence of the infection with HCV in subjects with risk practices such as intravenous drug use, or previous blood transfusion reaches 80–100%.
HIV–HCV coinfected patients show a faster progression to cirrhosis than those HIV negative. The stage and progression rate of the hepatic fibrosis are greater in HIV-coinfected patients.
The liver disease produced by HCV constitutes a growing cause of morbidity and mortality and hospitalization for the patients infected with HIV.
The life expectancy of the HIV infected patients has significantly improved secondarily to the introduction of HAART regimens. Hepatotoxicity related with antiretroviral therapy is more frequent in patients with chronic hepatitis C, and can favor the removal of the antiretroviral medication.
The efficacy of therapy against HCV infection in HIV-infected patients without severe immunodeficiency is similar to that obtained in patients not coinfected with HIV.

Although HIV infection appears now adequately manageable with HAART, HCV infection can become one of the limiting factors for the tolerance of antiretroviral drugs in HIV–HCV coinfected people. Therefore, treating HCV infection in HIV-infected people also appears necessary for a sustained benefit of antiretroviral drugs (Soriano et al., 1999c).

2. Similarities and differences between HIV–HCV

2.1. Virology

Both viruses share several characteristics, besides transmission routes. The first one is that they are RNA viruses. HCV belongs to the Flaviviridae family, and contains a single RNA chain RNA, while HIV belongs to the Retroviridae family, with two RNA chains. Despite this similarity, the biological cycle and the replication process of both viruses show several important differences. Whereas HIV has an integration step into the host cell genome, the replication of HCV takes place in the cytoplasm, and there is no integration (Di Bisceglie, 1998). That makes easier to eradicate HCV than HIV infection.

Another similarity between both viruses is the existence of different genotypes and the so-called quasispecies. Most RNA viruses show in their replication cycle a relatively high error rate, with a low proof reading capacity (Domingo et al., 1996). The mutation rate of the polymerase RNA-dependent of HCV is of $1/10^4$ to 10^5 nucleotides; that means 1 mutation per each genome is transcribed. In the case of HIV, that rate is quite similar and produces a divergence in the nucleotide sequence higher than 30% when the most

distant variants are compared (Simmonds, 1995). This diversity has allowed the distinction of genotypes and subtypes, both in the case of HIV and HCV. For HCV six main genotypes and at least 30 subtypes have been described (Brechot, 1994; Simmonds, 1995). Within these subtypes, the viruses found in one infected subject also show significant differences among their sequences. The concept of *quasispecies* is based on this observation, that is the heterogeneous nature of all the viruses infecting one subject at a given moment (Domingo et al., 1996). The great genetic variability allows both viruses to quickly develop mechanisms to improve their adaptation to the environment, and in this way evade any immune or pharmacologic pressure. This is the reason why the most heterogeneous regions of both viruses are those codifying the envelope, which is the most immunogenic part (Brechot, 1994; Simmonds, 1995).

The classification of the different HCV variants is of clinical relevance. Distinct variants might show differences in cell tropism, virulence and sensitivity to antiviral drugs. In the case of HCV, the subtype 1b has been associated with a worse response to therapy than others. Conversely, HCV subtype 3a is the most frequently recognized among intravenous drug users in Europe, and tends to be more sensitive to treatment (Pawlotsky et al., 1995).

2.2. Epidemiology

It is estimated that approximately 2.7 million people are infected with HCV in the USA (Alter et al., 1999), and these figures approach 170 million worldwide (WHO, 1997; Alter, 1997; Thomas et al., 2000). The prevalence of HCV infection in HIV+ subjects varies depending on the different risk groups. HCV is responsible for most cases of chronic liver disease in HIV-infected patients. Among individuals infected parenterally (IDUs, hemophiliacs, blood transfusion receptors), the infection with HCV is much more frequent than in homosexual men. In this group, the prevalence of HCV infection is 5–8%, not significantly different from that in HIV-negative homosexual men (Marcellin et al., 1993). In this sense, sex does not appear to be an important route for HCV transmission. In contrast, the prevalence of HCV in IDUs rises up to 80–90%, and nearly 100% among hemophiliacs (Quan et al., 1993; Quaranta et al., 1994). It is important to keep in mind that IDUs represent one of the main reservoirs for HCV infection in developed countries. In the EuroSIDA cohort, which records data from more than 3000 HIV-infected subjects in Europe, a global rate of HCV infection of 33% has been recorded, but this approaches 80% when considering IDUs separately (Stubbe et al., 1998).

Most IDUs carrying HCV become infected within the first year of drug addiction practices. In one study, anti-HCV positivity rate was 78% at the end of the first year after starting needle sharing, 83% at the fifth year, and 94% after more than 10 years (Thomas et al., 1995).

3. Hepatic disease produced by HCV in HIV-infected patients

3.1. Natural history

Several studies have shown that there is a faster progression of HCV-related liver disease in HIV-coinfected patients. This observation was first reported by Martin et al. (1989). They described a rapid evolution to cirrhosis and liver failure in three old patients coinfected with HIV and HCV as a consequence of blood transfusions. The evolution to cirrhosis appeared 3 years after they became infected with HCV. Afterwards, Eyster et al. (1993) analyzed the outcome in a series of 223 hemophiliacs with a known date of infection with HIV and HCV, made by a retrospective analysis of sequential serum samples. Overall, 9% of those patients developed signs of hepatic failure 10–20 years after infection, without developing any AIDS-related condition. In that study, liver failure appeared to be significantly related with a low CD4 cell count. In another study conducted in HCV-infected hemophiliacs, Telfer et al. (1994) observed that those coinfected with HIV were 21 times more prone to develop hepatic failure than those not coinfected. Finally, in one Spanish study, 25% of subjects coinfected with HIV and

HCV developed cirrhosis 15 years after the date of infection, as compared with only 6.5% of those carrying HCV alone (Sánchez-Quijano et al., 1995).

A recent study conducted in France has examined the predictors of a faster evolution to liver cirrhosis, and other possible cofactors, such as alcohol consumption, in 122 HIV–HCV coinfected patients (Benhamou et al., 1999). The study was controlled by comparison with a similar group of HCV-monoinfected patients. Significantly more coinfected patients had greater fibrosis and necroinflammatory scores than their HCV-monoinfected counterparts. The average time until cirrhosis in the HIV/HCV coinfected group was 26 years, and 34 years in the monoinfected group. Interestingly, the slowest fibrosis rate was among those HIV-coinfected who received HAART (at least three drugs). Several factors were found to be related to the evolution to fibrosis. HIV seropositivity, alcohol consumption (>50 g/d), low CD4 counts (≤ 200 cells/μl), and older age at HCV infection (>25 years old) appeared as independent predictors of a faster fibrosis progression rate. Gender did not appear as an independent factor, in contrast with a previous study (Poynard et al., 1997). In a recent trial, not made in HIV-infected patients, a low serum albumin was related with a higher degree of liver damage in HCV infection (Khan et al., 2000). This parameter should be examined in HIV infection, since serum albumin is often reduced in advanced HIV infection.

3.2. Why is HCV liver disease faster in HIV-infected persons?

HCV infection is controlled by cytotoxic T lymphocytes (CTL), which eliminate the infected hepatocytes, and by cytokines produced by the T cells, which directly inhibit viral replication. The immune response against HCV appears in two ways: the CD4 Th1 cells produce cytokines which activate the CTL (CD8+) response, whereas the CD4 Th2 cells induce the production of specific antibodies against HCV. It has been suggested that a poor response of the CD4 Th1 subset might be related to the chronicity of HCV infection. This defective response might induce a change in the CTL that makes it more difficult to eliminate HCV. Following this rationale, it should be expected that there is a higher activity (virulence) of HCV infection in HIV-infected patients whose CD4 cells are defective in function and number (Eyster et al., 1993).

A greater variability of HCV sequences has been noticed in HIV+ patients with less than 200 CD4 cells/μl (Dove et al., 1999). That great variability might be associated with a more virulent (disease-causing) species of virus. In one study, the count of new clones and of HCV viral load were examined at baseline and after 1 year. Co-infected patients with low baseline CD4 counts had 89% new clones, whereas those with higher baseline CD4 counts had 60%. The control HCV-monoinfected group had 70%. In addition, coinfected subjects had a significantly greater increase in their median HCV-RNA titers during the 1-year interval than HCV-monoinfected patients (Dove et al., 1999).

Although the rate of progression of liver disease is not predicted accurately by HCV-RNA levels, mimicking what happens with HIV, the higher levels of HCV viremia predict a worse response to anti-HCV therapy. Does immune restoration operated by HAART have influence over HCV viremia? One study performed at our institution has analyzed this question. Sixteen coinfected persons who responded to HAART were included in the analysis. The median HCV-RNA viral load pre-HAART was approximately of 7 logs. It remained without significant changes at 3 months, but declined to less than 6 logs after 12 months of successful HAART (Pérez-Olmeda et al., 2000). Most likely, the immune restoration seen after introducing HAART causes firstly an enhanced destruction of HCV-infected hepatocytes, followed thereafter by an increased control of HCV replication.

4. Hepatocarcinoma

HCV is the main risk factor for the development of hepatocellular carcinoma (HCC) in developed countries. The way chronic hepatitis C

evolves to HCC is not accurately known. The HCV genome apparently does not contain oncogens and, contrary to what happens with hepatitis B virus, there is no evidence supporting an integration of the HCV genome into the chromosomes of hepatic cells (Fong et al., 1991). In this way, the most likely carcinogenic mechanism of HCV must be related with the presence of cirrhosis. The distorted ability of regeneration of liver cells, regardless of the etiologic agent, could interfere with their normal regenerative function, causing its malignant transformation.

HCC related with HCV appears more frequently in patients with advanced HCV disease, usually in the final stages of cirrhotic patients (Kiyosawa et al., 1990). The common age at diagnosis is between 65 and 75 years old. Recent data from patients coinfected with HIV and HCV suggest that they can develop HCC at a significantly younger age than those that are HIV-negative. Whether the treatment of HCV infection could prevent, or decrease, the risk of HCC in this population is unknown. A Japanese study has suggested that interferon (IFN) is not only useful to prevent the development of HCC in non-cirrhotic patients, but also in the cirrhotic ones, in which liver function could improve to some extent (Nishiguchi et al., 1995). However, the information available on the usefulness of IFN against HCV in HIV-coinfected patients with cirrhosis is very limited so far.

5. Hepatotoxicity of antiretroviral drugs in the setting of HCV infection

The availability of new drugs with a great inhibitor potency over HIV replication has also highlighted the significant rate of liver toxicity, which does not rarely lead to stopping or changing the antiviral regimen. In a recent study performed at our institution, hepatotoxicity (transaminases ≥ 2 fold) was seen in 14% of patients who started antiretroviral treatment including protease inhibitors (Rodríguez-Rosado et al., 1998). Hepatotoxicity was found more frequently in IDUs, and significantly correlated with the high prevalence of HCV infection in this population. Two other studies found transaminase levels above 200 IU/l in 8.5% of patients who started HAART (Savès et al., 1999; Sulkowski et al., 2000). Again, the presence of HCV infection was an independent predictor of this complication. These findings support the relevance of treating HCV infection in HIV-coinfected patients, in order to improve the tolerance of antiretroviral drugs and, secondarily, its benefit.

Table 2
Mechanisms of liver damage using antiretroviral drugs

Direct cytopathic effect (i.e. ritonavir).
Immune reconstitution syndrome in patients with chronic hepatitis C
Hypersensitivity syndrome (i.e. NVP, ABC)
Cholestatic action (i.e. IDV, NVP)
Mitochondrial toxicity and steatosis (i.e. d4T, AZT)

The mechanisms involved in the production of liver damage in subjects with chronic hepatitis C taking antiretroviral drugs are summarized in Table 2. Direct cytopathic damage can appear directly related with the specific drug in use (Savès et al., 1999). For instance, this is the case of ritonavir, but other agents can also have an intrinsic hepatotoxic effect. Direct hepatotoxicity is more frequent in HCV-coinfected patients, because of the underlying liver damage. On the other hand, a rapid immune reconstitution driven by HAART can increase aminotransferases as a consequence of an acute inflammatory response (John et al., 1996).

6. Treatment of chronic hepatitis C in HIV-infected patients

The increasing interest in HCV infection in HIV-infected patients has been specially outlined in the two latest consensus conferences on the treatment of chronic hepatitis C, which took place in the USA (1997) and in Europe (1999). Both documents encourage the treatment of hepatitis C in HIV-positive patients with good clinical and functional situation, without evident immunodeficiency (National Institutes of Health, 1997; Consensus Statement EASL, 1999).

The assessment of response to therapy is no longer biochemical (based on transaminase levels) but virologic. A complete response consists in the clearance of HCV-RNA in serum at the end of treatment. A sustained response means the maintenance of negative serum HCV-RNA 6 months after the end of treatment. This sustained virological response is the goal of anti-viral treatment in HCV.

α-IFN has for a long time been the standard of care for the treatment of chronic hepatitis C. The rate of sustained response in patients without HIV infection is around 20% (Poynard et al., 1996). In HIV-positive patients without severe immunodeficiency the response rate is quite similar (Table 3), but decreases when the CD4 cell count falls (Soriano et al., 1996). Patients coinfected with HIV and HCV presenting a sustained response do not have a higher risk of relapse after prolonged periods of follow-up, even in the immunodeficiency caused by HIV progress. This means that eradication of HCV is something really attainable (Soriano et al., 1997).

The combination of IFN and ribavirin, a nucleoside analog orally administered with a wide antiviral spectrum against DNA and RNA viruses, provides a significant increase in the sustained response rate, up to nearly 50% (McHutchinson et al., 1998). The benefit of this combination was initially explored in subjects suffering a relapse after a first cycle of IFN alone. However, the results of two wide controlled trials have shown the usefulness of the combination of IFN plus RBV as first-line therapy (McHutchinson et al., 1998; Poynard et al., 1998). Accordingly, the addition of RBV to IFN increases the antiviral benefit more than twice. Moreover, the incidence of secondary effects did not significantly differ from those of IFN alone, although the appearance of hemolytic anemia was more frequent in the group treated with RBV. This effect seems to be dose-related. Currently, several trials are analyzing if the antiviral efficacy of the combination is similar when the dose of RBV is reduced (to 600–800 mg/day), and whether the incidence of hemolytic anemia decreases. The combination of IFN and RBV has been recently approved as first line therapy for chronic hepatitis C in Europe and in the USA. The usefulness and safety of that combination in HIV-infected patients has not been accurately examined so far. In a pilot study performed in Spain (Pérez-Olmeda et al., 1999), which enrolled 18 patients with more than 300 CD4/mm^3, patients received a dose of IFN of 3 MU tiw and of RBV of 1–1.2 g/24 h. The rate of sustained response was 35%. All patients had been previously treated with IFN, and 6 of them never responded to it, while the other 12 were relapsers. Of note, 11 patients (66%) were receiving HAART concomitantly. The medication was well tolerated, but two subjects withdrew (one developed severe anemia, and the other suicidal ideation). Four patients were lost to follow-up. In another trial, conducted in France, end-of-treatment response of 50% was noticed in a group of 20 coinfected subjects (Landau et al., 2000). However, the population studied in this trial was very heterogeneous, and the results need to be interpreted carefully. Up to 45% of patients were cirrhotic, and 20% had received IFN previously without success, being the remaining naive patients.

Another optional strategy to improve the response rate consists in using induction-maintenance regimens. A higher dose of IFN in the first weeks of therapy, usually during at least 1 month,

Table 3
Response rate to interferon in patients with chronic hepatitis C, as a function of the HIV status

	HIV-positive ($n = 80$) (%)	HIV-negative ($n = 27$) (%)	P
Early response (3rd month OT)	38.8	44.4	0.6
Complete response (12th month OT)	32.5	37	0.7
Sustained response (12th month after stopping IFN)	22.5	25.9	0.7

OT, on treatment.

Table 4
Benefit of PEG-interferon-α over interferon-α for the treatment of chronic hepatitis C in HIV negative patients

	Interferon	SR (%)	PEG-interferon	SR (%)
Hoffman–La Roche	Roferon	19	Pegasys	39
Schering–Plough	Intron	12	PEG-Intron	23
Schering–Plough[a]	Intron	33	PEG-Intron	69

SR, sustained response.
[a] HCV genotype non-1, HCV RNA $< 2 \times 10^6$ copies/ml.

is followed by a smaller dose later on. That could improve the sustained response rate. This strategy is supported in the very short HCV replication half-life, of nearly 2.7 h. The pharmacokinetics of IFN, if administered only three times per week, explain why IFN only reaches the minimal active concentration for a few hours after each administration, making it more difficult to achieve a durable suppression of HCV replication. A more frequent administration could solve this problem.

Alternatively, the design and development of a new formulation of IFN can face the problem in a different way. The pegylated-IFN is covalently linked to a polyethyleneglycol molecule. That linkage makes the drug able to persist inside the body longer (Glue et al., 1999). The slower release of the drug allows its administration once weekly. Moreover, the overall activity seems to be increased significantly. Pegylated-IFN is currently in phase III/IV clinical trials, and is available in two different forms by two companies. The product manufactured by Hoffman–La Roche, (pegylated IFN α-2a) is called Pegasys (Zeuzem et al., 2000), and Schering–Plough's (pegylated IFN α-2b) Peg-Intron (Trepo et al., 2000). Both companies have recently reported preliminary results of Phase III clinical trials with their drugs, in all instances in subjects without HIV infection (Tables 4 and 5).

The response rates achieved with PEG-interferon-α alone are only slightly better than using IFN alone. The addition of RBV seems to significantly enhance the response. Side effects using pegylated IFN are similar to those appearing using standard α-IFN. These include "flu-like" symptoms such as fatigue, fever, headache, gastrointestinal disturbances, depression, neutropenia and thrombocytopenia. Of particular concern is neutropenia, which seems to be more common and severe.

Recently, preliminary results using the triple combination of pegylated α-IFN, RBV and Maxamine (histamine dihydrochloride) have attracted much interest. This new drug is an immune modulator that potentiates the action of natural killer (NK) cells and CD4 lymphocytes by blocking histamine receptors on phagocytic immune cells. This block in the release of "free radicals" from phagocytic cells reduces apoptosis in NK and CD4 cells. That results in strengthening the immune response against HCV, favoring its eradication. Maxamine is administered, as IFN, subcutaneously. The most common adverse events are transient flushing, temporary headache, lowered blood pressure, and a fast heart beat in some patients. The combination of Maxamine plus IFN shows similar benefit as the combination of IFN plus RBV (Lurie et al., 2000). As previously stated, the triple combination could be even more active.

Table 5
Benefit of adding ribavirin (RBV) to PEG-interferon-α (PEG) for the treatment of chronic hepatitis C in HIV-negative patients

	PEG (%)	PEG+RBV (%)
PEG Intron (Schering)	42	60
Pegasys (Roche)	39	80[a]

[a] Complete response. All other data refer to sustained response.

7. Indications for HCV therapy in HIV-coinfected patients

Accepted criteria for indicating therapy for chronic hepatitis C are a persistent increase in transaminase levels, a positive HCV-RNA in serum, and the presence of necroinflammatory and fibrotic activity in the liver biopsy specimen. The decision of treating HCV in HIV-coinfected patients should require these features, and consider new ones.

From a purely hepatologic point of view, patients with decompensated cirrhosis or with normal transaminase values should not receive any therapy for HCV infection. Conversely, patients with compensated cirrhosis and lack of contraindications for IFN and/or RBV could be candidates for therapy if they do not have advanced HIV disease.

From the HIV point of view, the immune and virologic situation should be assessed before decisions over the treatment of HCV infection are made. A sustained suppression of HIV replication and a CD4 count greater than 200–300 cells/μl seem to be required before recommending anti-HCV treatment in HIV-positive persons. If HIV disease is not under control or the CD4 count is very low, matters other than HCV are really more worrisome in the short-term, and need to be solved firstly. Moreover, the response of chronic hepatitis C seems to decline as the CD4 count falls. The percentage of response to HCV therapy is mildly smaller when the CD4 count is between 200 and 500 cells/μl. In these cases, the decision on treating HCV should be based on the presumable risk of progression of liver disease (based on histologic criteria, liver function tests, etc.) and patient's features (compliance, tolerability to the regimen, risk of interactions with other drugs, etc.), which could determine the response to treatment.

Patients with severe immunodeficiency, i.e. those with less than 200 CD4 cells/μl, should not be treated, in view of the very small chances of response to treatment, and the higher risk of developing AIDS-defining events. Besides, the administration of IFN occasionally produces a decrease in the number of CD4 cells, usually self-limited, which can worsen the outcome. The treatment of HCV should be offered to all HIV-positive patients with a preserved immune status or after obtaining a significant immune restoration using antiretroviral therapy (Soriano et al., 1999c).

8. Interactions and side effects related with anti-HCV therapy

The administration of standard doses of IFN for HCV infection (3–5 MegaU three times weekly) can induce—as previously stated—a rapid decrease in the CD4 count in nearly 10% of HIV-infected patients (Soriano et al., 1994). This drop usually occurs between weeks 6 and 14, and is usually self-limited. In most instances, this drop reflects a redistribution of CD4 cells, which move from the peripheral circulating compartment to the lymphoid organs, rather than a real destruction of those cells. In agreement with this hypothesis, the drop in CD4 cells is not associated with an enhancement in HIV replication.

With respect to RBV, there are few data in vivo about the potential interactions with anti-HIV drugs. This nucleoside analog does not have any activity over the cytochrome P450. However, in vitro studies have shown that RBV inhibits the phosphorilation of some nucleoside analogs, such as zidovudine and stavudine, both substrates of the thymidine–kinase. The impact of this phenomenon in vivo is not well known. Finally, a drop in the hemoglobin levels, secondary to hemolysis, appears as the most common adverse event associated with RBV treatment. This effect seems dose-related. In this sense, RBV should be used cautiously, mainly when other myelosuppressive drugs, such as zidovudine, are prescribed (Soriano et al., 1996).

References

Alter, M., 1997. Epidemiology of hepatitis C. Hepatology 26 (Suppl. 1), 62–65.

Alter, M., Kruszon-Morgan, D., Nainan, O., et al., 1999. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N. Engl. J. Med. 341, 556–562.

Benhamou, Y., Bochet, M., Di Martino, V., et al., 1999. Liver fibrosis progression in HIV and Hepatitis C virus coinfected patients. Hepatology 30, 1054–1058.

Brechot, C., 1994. Hepatitis C virus genetic variability: clinical implications. Am. J. Gastroenterol. 84, 41–47.

Consensus Statement EASL, 1999. International Consensus Conference on hepatitis C. J. Hepatol. 30, 956–961.

Di Bisceglie, A., 1998. Hepatitis C. Lancet 351, 351–355.

Domingo, E., Escarmís, C., Sevilla, N., et al., 1996. Basic concepts in RNA viruses evolution. FASEB J. 10, 859–864.

Dove, L.M., Phung, Y., Wrock, J., Kim, M., Wright, T.L., 1999. HCV quasispecies as a mechanism of rapidly progressive liver disease in patients infected with HIV. Hepatology 30, 456A.

Eyster, M., Diamondstone, L., Lien, J., et al., 1993. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with HIV. The Multicenter Hemophilia Cohort Study. J. Acquir. Immune. Defic. Syndr. 6, 602–610.

Fong, T., Shindo, M., Feinstone, S., et al., 1991. Detection of replicative intermediates of hepatitis C viral RNA in liver and serum of patients with chronic hepatitis C. J. Clin. Invest. 88, 1058–1060.

García-Samaniego, J., Bravo, R., Gómez-Cano, M., et al., 1998. Lack of benefit of protease inhibitors on HCV viremia in HIV infected patients. J. Hepatol. 28, 526–527.

Glue, P., Fang, J., Sabo, R., et al., 1999. PEG-IFN α 2b: phamacokinetics, pharmacodynamics, safety and preliminary efficacy data. Hepatology 30, 36A.

John, M., Flexman, J., French, M., 1996. Hepatitis C virus associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS 12, 2289–2293.

Khan, M., Farrell, G., Byth, K., et al., 2000. Which patients with Hepatitis C develop liver complications? Hepatology 31, 513–520.

Kiyosawa, E., Sodeyama, T., Tanaka, E., et al., 1990. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. Hepatology 12, 671–675.

Landau, A., Batisse, D., Van Huyen, J.P., et al., 2000. Efficacy and safety of combination therapy with interferon-alpha2b and ribavirin for chronic hepatitis C in HIV-infected patients. AIDS 14, 839–844.

Lurie, Y., et al., 2000. A phase II dosing regimen study of hystamine dihydrocloride (Maxamine) and interferon alfa-2b in naive chronic hepatitis C patients: 12- and 243-week analysis. In: Proceedings of the Tenth International Symposium on Viral Hepatitis and Liver Disease, Atlanta, GA, Abstract 111.

Marcellin, P., Colin, J., Martinot-Peignoux, M., et al., 1993. Hepatitis C virus infection in anti-HIV positive and negative French homosexual men with chronic hepatitis: comparison of second and third generation anti-HCV testing. Liver 13, 319–322.

Martin, P., Di Bisceglie, A., Kassianides, C., et al., 1989. Rapidly progressive non-A, non-B hepatitis in patients with HIV infection. Gastroenterology 97, 1559–1561.

McHutchinson, J., Gordon, S., Schiff, E., et al., 1998. Inteferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. N. Engl. J. Med. 339, 1485–1492.

National Institutes of Health, 1997. Consensus Development Conference Panel Statement: Management of hepatitis C, Hepatology 26 (Suppl. 1), 2–10.

Nishiguchi, S., Kuroki, T., Nakatani, S., et al., 1995. Randomised trial of effects of interferon-alfa on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 346, 1051–1055.

Pawlotsky, J., Tsakiris, L., Roudot-Thoraval, L., et al., 1995. Relationship between hepatitis C virus genotypes and sources of infection in patients with chronic hepatitis C. J. Infect. Dis. 171, 1607–1610.

Pérez-Olmeda, M., González, J., García-Samaniego, J., et al., 1999. Interferon plus Ribavirin in HIV-infected patients with chronic hepatitis C. J. Acquir. Immune. Defic. Syndr. 22, 308–309.

Pérez-Olmeda, M., Soriano, V., Muñoz, F., González-Lahoz, J., García-Samaniego, J., 2000. Influence of HAART on HCV-RNA levels in HIV+ patients. J. Hepatol. 32 (Suppl. 2), 113.

Poynard, T., Leroy, V., Cohard, M., et al., 1996. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 24, 778–789.

Poynard, T., Bedossa, P., Opolon, P., et al., 1997. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 349, 825–832.

Poynard, T., Marcellin, P., Lee, S., et al., 1998. Randomised trial of IFN-alfa 2b plus ribavirin for 48 weeks or 24 weeks versus IFN alfa 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 352, 1426–1432.

Quan, C., Kradjen, M., Grigoriew, G., et al., 1993. Hepatitis C virus infection in patients infected with the HIV. Clin. Infect. Dis. 17, 117–119.

Quaranta, J., Delaney, S., Alleman, S., et al., 1994. Prevalence of antibody to hepatitis C virus in HIV-1 infected patients. J. Med. Virol. 42, 29–32.

Rodríguez-Rosado, R., García-Samaniego, J., Soriano, V., 1998. Hepatotoxicity after introduction of highly active antiretroviral therapy. AIDS 12, 1256.

Sánchez-Quijano, A., Andreu, A., Gavilán, F., et al., 1995. Influence of HIV-1 on the natural course of chronic parenterally acquired hepatitis C. Eur. J. Clin. Microbiol. Infect. Dis. 14, 949–953.

Savès, M., Vandentorren, S., Daucourt, V., et al., 1999. Severe hepatitis cytolysis: incidence and risk factors in patients treated with antiretroviral combinations (Aquitaine Cohort, France 1996–1998). AIDS 13, F115–F118.

Simmonds, P., 1995. Variability of hepatitis C virus. Hepatology 21, 570–583.

Soriano, V., Bravo, R., García-Samaniego, J., et al., 1994. CD4+ lymphocytopenia in HIV-infected patients receiving interferon therapy for chronic hepatitis C. AIDS 8, 1621–1622.

Soriano, V., García-Samaniego, J., Bravo, R., et al., 1996. Interferon alpha for the treatment of chronic hepatitis C in patients infected with HIV. Clin. Infect. Dis. 23, 585–591.

Soriano, V., Bravo, R., García-Samaniego, J., et al., 1997. Relapses of chronic hepatitis C in HIV-infected patients who responded to interferon therapy. AIDS 11, 400–401.

Soriano, V., García-Samaniego, J., Rodríguez-Rosado, R., González, J., Pedreira, J., 1999a. Hepatitis C and HIV infection: biological, clinical, and therapeutic implications. J. Hepatol. 31 (Suppl. 1), 119–123.

Soriano, V., García-Samaniego, J., Rodríguez-Rosado, R., et al., 1999b. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. Eur. J. Epidemiol. 15, 1–4.

Soriano, V., Rodríguez-Rosado, R., García-Samaniego, J., 1999c. Management of chronic hepatitis C in HIV infected patients. AIDS 13, 539–546.

Soto, B., Sánchez-Quijano, A., Rodrigo, L., et al., 1997. HIV infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J. Hepatol. 26, 1–5.

Stubbe, L., Soriano, V., Antunes, F., et al., 1998. Hepatitis C in the EuroSIDA cohort of European HIV-infected patients: prevalence and prognostic value. In: Proceedings of the Twelfth World AIDS Conference, Geneva, Switzerland, Abstract 22261.

Sulkowski, M., Thomas, D., Chaisson, R., Moore, R., 2000. Hepatotoxicity associated with antiretroviral therapy in adults with HIV and the role of hepatitis B or C infection. J. Am. Med. Assoc. 283, 74–80.

Telfer, P., Sabin, C., Devereux, H., et al., 1994. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br. J. Haematol. 87, 555–561.

Thomas, D., Vlahov, D., Solomon, L., et al., 1995. Correlates of hepatitis C virus infections among drug users. Medicine (Baltimore) 74, 212–220.

Thomas, D., Astemborski, J., Rai, R., et al., 2000. The natural history of hepatitis C virus infection. J. Am. Med. Assoc. 284, 450–456.

Trepo, C., Lindsay, C., Niederau, M., et al., 2000. Pegylated interferon alfa-2b (Peg Intron) monotherapy is superior to interferon alfa-2b (Intron A) for the treatment of chronic hepatitis C. J. Hepatol. 32 (Suppl. 2), 29.

WHO, 1997. Hepatitis C: global prevalence. Wkly. Epidemiol. Rec. 72, 341–344.

Zeuzem, S., Feinman, S., Rasenack, J., et al., 2000. Evaluation of the safety and efficacy of once-weekly peg/inteferon alfa-2a (Pegasys) for chronic hepatitis C. A multinational, randomized study. J. Hepatol. 32 (Suppl. 2), 29.