Factors of progression to cirrhosis in patients co-infected with HIV and HCV. Identification and treatment

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ABSTRACT

Hepatitis C has particular connotations within patients co-infected with HIV. Moreover, for a patient co-infected with HIV, the acute hepatitis C virus (HCV) progresses more often to a chronic infection. Chronic hepatitis C is associated with more severe histological damage, and there is a more frequent and more rapid progression to cirrhosis and death by hepatic failure.

Key words: Hepatitis C, HIV, Treatment, prison.

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INTRODUCTION

Diverse factors determine the speed of progression of hepatic disease in co-infected patients. Factors associated with HCV (genotype, viral load, duration of infection) seem to have very little influence. Those associated with the infected host have a greater impact, especially the age of HCV infection and the immunodepression. Therefore, patients infected later in life and the most immunocompromised evolve more rapidly to cirrhosis. Likewise, those associated with the setting are important. Among them, alcohol is likely to increase the speed of the pathology progression and the antiretroviral therapy (ARV therapy), especially the HCV infection treatment, to reduce it. Some data suggest that protease inhibitors reduce the speed of the pathology progression more than other ARV therapies.

In order to reduce the speed of the hepatic disease progression in a co-infected patient with HIV, clinicians should advise to discontinue intake of alcohol. All patients who are eligible for treatment, including those with end-stage liver disease, must receive ARV therapy. It has been recommended for co-infected patients to receive ARV therapy at an earlier stage than those who are not infected with HCV and it seems quite reasonable to use protease inhibitors whenever possible, although no clinical trials support these two approaches. Hepatitis C antiretroviral therapy must be initiated as early as possible in all candidates, since it could be greatly beneficial for these patients.

HEPATITIS C NATURAL HISTORY IN HIV CO-INFECTED PATIENTS

Chronic hepatitis C shows a more rapid development and a greater rate of evolution to severe forms in HIV co-infected patients than in patients infected with HCV alone. In these two scenarios, the worst evolution becomes apparent from the acute hepatitis phase (1). Moreover, a larger proportion of acute Hepatitis C cases become chronic in co-infected patients. In fact, when patients show to be positive for HCV, they are then tested for HCV/RNA, and the proportion of patients who showed to be negative, that is to say, who have recovered from the infection is higher in HIV negative patients. Thus, within 203 patients HCV positive and co-infected with HIV, who have been consecutively tested for HCV/RNA by PCR in

our unit, 10% of them showed to be negative. On the contrary, this proportion reached 21% of the 135 patients mono-infected analysed during the same period.

The HCV chronic liver disease can develop with normal or elevated ALT levels, which is usually associated with more severe histologic damage. In HIV/HCV co-infected patients, the proportion with normal transaminase levels is lower (1). Thus, in a total of 291 HCV infected patients seen consecutively in our Unit, 183 HIV co-infected and 108 infected with HCV alone, 10% of the first group and 21% of the second showed normal transaminase levels. In accordance with what we have said before, the evolution to liver cirrhosis is more rapid and frequent in patients with HIV (1) (Figure 1). Likewise, mortality is higher and survival shorter in co-infected patients with cirrhosis. (2).

FACTORS ASSOCIATED WITH THE HCV DISEASE PROGRESSION IN HIV CO-INFECTED PATIENTS.

For exposition purposes, factors which determine the chronic HCV progression in co-infected patients with HIV can be classified in three groups. Firstly, those related to HCV, secondly, those dependent of the infected host and lastly, those we can call environmental or related to the setting. The real delimitation for these factors is not as easy since many of them are directly interrelated.

FACTORS ASSOCIATED WITH HCV

Factors associated with HCV have very little influence on the progression to chronic HCV in co-infected patients. Plasma viral load, genotype and duration of infection are included among them. The high levels of plasma viral load, which are probably a consequence of the immunodeficiency induced by HIV and the deterioration of the immune response that HCV entails, have been associated with a progression to hepatic fibrosis (3) in some works but not in the majority of them.

In mono-infected patients, genotype 1 has been associated in some works with a greater HCV viral load, genotype 3 with a more rapid progression and genotype 4 with a higher rate of chronic infection (4). However, we have not found studies within co-infected patients in which a relationship between genotype and disease progression could be observed.

In some studies (5,6) we have found a direct relationship between greater time of evolution and extent of histologic damage, but not on a constant basis (7-10). The reason why this association, perfectly plausible on the other hand, has not been constant, could be because the time of infection is largely associated with the variable age of infection, which is of a great influence on the progression of HCV.

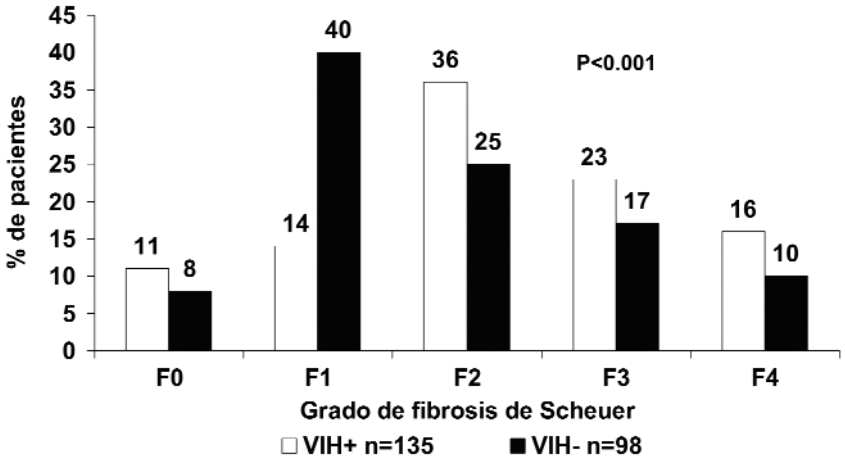

Figure I. Degree of hepatic fibrosis, (Knodell classification modified by Scheuer) in co-infected patients with HIV and mono-infected patients with HCV, consecutively treated in the Unit of communicable diseases of the University Hospital of Valme.

FACTORS ASSOCIATED WITH THE INFECTED HOST

They include, fundamentally, age of infection and immunodepression. Only one study observed a weak association between men and advanced stage of fibrosis (5), but this discovery has not been confirmed in other works.

Age of infection

In studies carried out on prognostic factors for hepatic fibrosis in HIV/HCV co-infected patients, it has been observed, on multiple occasions, that patients who have contracted the HCV infection at an earlier age show minor histological damage (3, 7, 9, 10). In a study conducted in our Unit within 152 HIV/HCV co-infected patients who have undergone a liver biopsy, we have observed that 48 % of them who contracted the HCV infection before the age of 20 showed advanced hepatic fibrosis (F3-F4); while this figure corresponded to 25% (p=0.02) in individuals who contracted hepatitis C after the age of 20 (9).

Degree of immunosuppression

Continually and in all the analysis conducted, a relationship between degree of immunodepression of patients, measured by the cell counts CD4+ nadir or by the biopsy, and degree of hepatic fibrosis has been found. Therefore the most immunocompromised patients show more severe histological damage (3-10).

In the work above mentioned carried out in our Unit, we have considered the rate of progression of liver fibrosis with regard to the CD4 cell counts in the biopsy. The rate or degree of progression corresponds to the quotient obtained by dividing the numeric value corresponding to phase of fibrosis obtained by means of Scheuer score by the estimate duration of infection in years. We have used a section value of 0.2 units of fibrosis per year, which corresponds to that of patients whose fibrosis develop a phase every five years. In this study, we observed that 52% of patients with CD4 + cell counts equal or inferior to 250 cells/mm3 presented a rate of progression of fibrosis superior to 0.2, while this percentage corresponded to 30% (p=0.03) (9).

We have verified that the more the CD4 cell counts diminish, the more the degree of specific CD8 response to HCV is low (11). On the one hand, we know that patients who achieve a weak gamma interferon response to HCV proteins are those who develop a greater degree of fibrosis (12). On the other hand, the immune system becomes hyperactive together with the degree of immunodepression, which causes, among other things, over-regulation of TNF-alpha, which could lead to hepatocyte apoptosis. In a study recently developed in our Unit, we have verified the relationship among percentage of hepatocyte Fas expression, a marker of development of apoptosis related to the TNF-alpha system, and degree of liver fibrosis (12).

The influence that immunodepression exerts on the liver disease progression is not only clear from the moment cirrhosis develops but also in the most advanced phases of the disease. Moreover, in a multicentre study carried out by 4 groups from the Sociedad Andaluza de Enfermedades Infecciosas – SAEI (Andalusian society of communicable diseases), we have observed that co-infected patients with liver cirrhosis and less than 100 CD4 + cell counts during their first course of decompensation show that death by hepatic failure is more frequent than in those with CD4 + cell counts above 100 (13).

FACTORS ASSOCIATED WITH THE SETTING

Within this group, intake of alcohol, antiretroviral therapy (ARV), cannabis consumption and anti-HCV antiretroviral therapy have been taken into consideration. Cannabis consumption has been associated with a greater speed of progression of liver fibrosis in mono-infected patients with HCV (15). To be verified within the co-infected population, this condition could be very relevant given the frequency of consumption of these substances in such group. However, at present, no study analysing the influence of cannabis consumption in HIV/HCV co-infected individuals has been conducted, therefore we will not go into this point in any depth.

Alcohol intake

Although in HCV mono-infected patients alcohol intake has been continually associated with progression of liver fibrosis, in co-infected patients results have been very variable (5, 6, 8-10). These differences are probably largely due to the fact that alcohol intake in patients is very difficult to collect, and errors are possibly numerous. Alcohol is a well-known stimulus for hepatic fibrogenesis and is likely to be an important factor in the disease progression in co-infected patients.

ARV therapy

ARV therapy has demonstrated to act like a protective factor for the rapid progression of hepatic fibrosis as showed in many studies (6, 7, 9, 10) in patients co-infected with HIV and HCV. This is completely coherent with the reverse role immunodepression plays. Data suggest that protease inhibitors decrease the progression of hepatic fibrosis to a greater extent than non-nucleosid analogues (6, 7, 9). In an Andalusian multicentre study, including 683 co-infected patients who have undergone a liver biopsy, we have observed that the rate of progression of fibrosis in patients treated with protease inhibitors during the whole preceding follow-up, was significantly inferior to those who had not received ARV. On the contrary, in patients who had received a nevirapine or efavirenz based treatment before the biopsy, the rate of progression has not been significantly different from that observed in patients who had not received ARV (data to be published).

The protective effect of ARV therapy on the progression of hepatic fibrosis has a clinical result. Moreover, in the so-called Bonn cohort, it can be seen that patients who had received ARV showed a significantly inferior mortality rate by hepatic failure than those who had been exposed to suboptimal ARV therapy or those who had not received any drug (16). The beneficial clinical effect that ARV therapy has on the hepatopathy evolution can even be seen in the most advanced phases of the hepatic disease. In the Andalusian multicentre study on cirrhosis in co-infected patients above- mentioned, we have observed that HIV/HCV co-infected patients with descompensated cirrhosis who had received ARV therapy showed a minor mortality rate by hepatic failure that those who had not (14).

Antiviral therapy against HCV

Many clinical trials have demonstrated that treatment with pegylated interferon and ribavirin achieves a sustained virological response ranging between 14% and 73% of patients co-infected with HIV and HCV, depending on viral genotype and study considered

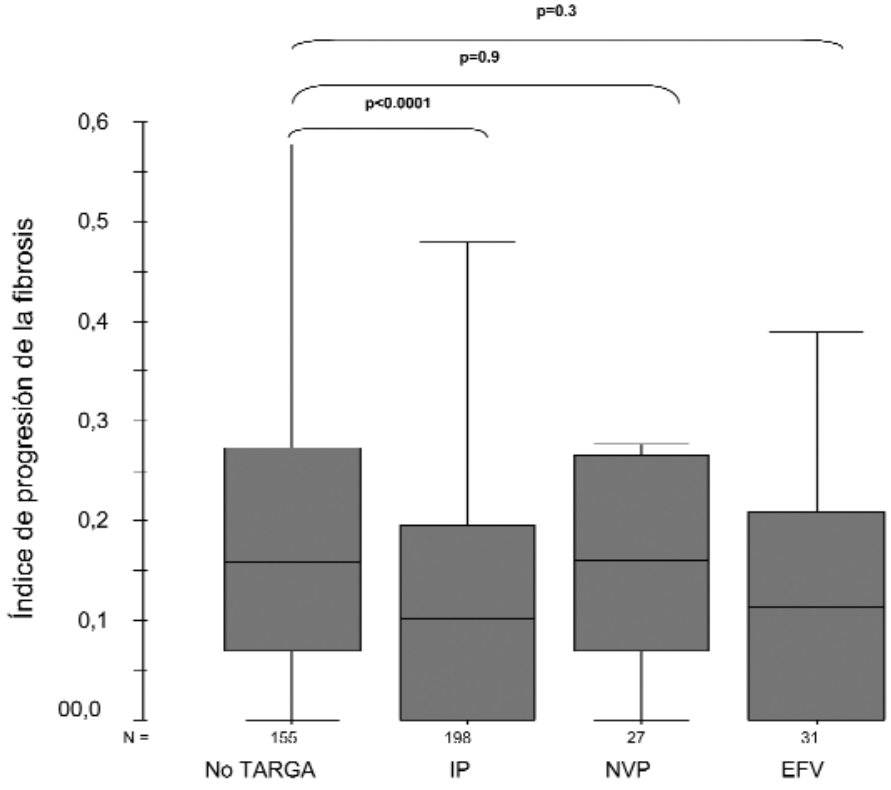

Figure II. Degree of progression of fibrosis (median, interquartile range and lower and higher values) in patients who had received HAART based on protease inhibitors (PI) before the biopsy, including nevirapine (NVP) or efavirenz (EFV) as tertiary drug, against those who have not received HAART (no HAART). Figures showed below the Box-and-Whisker graphs indicate the size of each population.

(17-20). The achievement of a sustained virological response involves histological improvement (18, 20) and reduction in the incidence of complications for the hepatic disease (21, 22) in patients mono-infected with HCV. Although there are no such hard data regarding co-infected patients, by extrapolation we could assume that antiretroviral treatment for Hepatitis C is one of the principal determining factors in the progression of the hepatic disease in this population as well.

CLINICAL TREATMENT

In order to reduce to the greatest extent the speed of hepatic fibrosis progression, we could act on the determining factors. To be precise, within the abovementioned factors, immunodepression degree, alcohol consumption, ARV therapy, and hepatitis C antiviral treatment can be modified. Duration of infection can also be modified, as it can be reduced as long as early action is taken.

ARV therapy and immunodepression

For the reasons given before, ARV therapy is a basic tool in order to reduce the speed of progression for hepatic disease by HCV. This measure should be applied to all patients, even those who show a more advanced hepatic disease, since even those achieve beneficial results in terms of survival (14,16). Although no clinical trials comparing different ARV therapy schemes have been conducted in co-infected patients, treatment should probably be based to the greatest extent on protease inhibitors, thus hepatotoxicity rate is minor and they seem to be more beneficial to the evolution of the hepatic disease (23).

Some authors think that ARV therapy should be initiated at an earlier stage in co-infected patients than in those infected with HIV alone (24). This approach is based on the idea that early treatment would prevent patients from achieving a higher degree of immunodepression, therefore we would prevent the progression of the hepatopathy.

Likewise, early ARV therapy would reduce the duration of HCV infection, at the moment it is contracted, therefore we would be fighting another factor associated with the progression of hepatic disease. Nevertheless, in order to evaluate the effectiveness of such approach, randomized clinical trials must be carried out by means of a comparison of strategies concerning early therapy schemes versus later ones. Finally, with regards to the two drugs accompanying PI, they must be chosen among the least hepatotoxic in the available therapeutical drug armory.

TREATMENT OF OTHER FACTORS CONCERNING THE SETTING

On the one hand, patients should be advised to discontinue intake of alcohol. Cessation therapies can be considered if the patient found it difficult to get out of the habit. If the profibrogenetic role of cannabis was confirmed in this population, the same way of action should be taken. Owing to the reasons above mentioned, chronic HCV antiviral therapy can play a fundamental role in the treatment of the liver disease progression in co-infected patients with HIV. Therefore, such therapy must be given to all the candidates. In this way, contraindications must be largely supported before excluding a patient. This is the case of low CD4 counts, considered an absolute contraindication for treatment with interferon and ribavirin, though some data allow us to put in doubt that such contraindication is well-supported (17). Anti-HCV therapy should be initiated as early as possible, so that CD4 counts have not decreased considerably, since it is greatly beneficial for the progression of liver fibrosis and allows to initiate treatment with interferon and ribavirin without the need of concomitant ARV therapy. This would achieve minor rate of interaction, less adverse reactions, better acceptance, and in all likelyhood, better results. In any case, if a patient should have received ARV therapy at an earlier stage, as soon as his HIV viral load is stabilized and a certain degree of immunoreconstruction is showed, we should reconsider chronic hepatitis C treatment as well.

CONCLUSIONS

Hepatitis C progresses more severely in co-infected patients than in mono-infected individuals, it becomes chronic at a higher rate and progresses more rapidly to cirrhosis and death by hepatic failure. HCV infection contracted late in life, alcohol intake and higher degree of immunodepression are some factors associated with a more rapid progression to cirrhosis. On the contrary, ARV therapy, especially that based on PI, reduces the speed of progression of HCV chronic hepatopathy in co-infected patients. Likewise, HCV erradication by means of a treatment based on pegylated interferon

and rebavirine is an effective measure in order to reduce the risk of cirrhosis.

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