HEPATITIS C IN PATIENTS CO-INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS. A REVIEW AND EXPERIENCE OF A BRAZILIAN AMBULATORY

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SUMMARY

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share the same transmission mechanisms. The prevalence of HCV in the HIV-infected population varies from region to region, throughout the world, depending on different exposure factors to both viruses. Co-infection with HIV accelerates the progression of the disease caused by HCV, appears to worsen the progression of the HIV infection and increases HCV transmission. Therefore, clinical management and treatment of HCV is a priority in medical facilities that receive HIV-infected patients. Clinical management of these patients involves specific diagnostic procedures and appropriately trained medical staff. The indication of treatment should meet specific clinical and laboratory criteria. There are a number of drugs currently available to treat hepatitis C in co-infected patients.

KEYWORDS: HIV; Hepatitis C; Review; Brazil.

Epidemiology and transmission mechanisms: Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share the same transmission mechanisms: parenteral, sexual and vertical. Thus, the prevalence of HCV in the HIV-positive population depends on risk factors involved in the transmission of HIV and HCV, respectively. HIV-infected patients present prevalence rates for HCV that are much greater than the rates for the general population. These rates in the co-infected population may range from 4% to 90%[76]. In the United States, it is estimated that about 30% of the HIV-infected patients are also co-infected with HCV[58,65]. In Europe, 33% of the 3,048 patients studied in the cohort of patients from Euro SIDA presented HCV co-infection[64]. In Argentina, FAINBOIM *et al.*[17] studied 484 HIV-infected patients and observed that 58.5% of them were co-infected with HCV. Moreover, it was observed that 234 (48.3%) of these patients were intravenous drug users (IDU).

In Brazil, there is little data concerning HIV/HCV-infected patients. Generally speaking, the prevalence ranges from 17.5 to 95% in different studies[6,39,44,52,73]. A study conducted by our center, analyzing 1,457 patients that were HIV-positive and treated at "Casa da Aids", from January to December 1996, revealed that 17.7% (258) were HCV positive[36].

Patients with risk factors for parenteral transmission (users of intravenous drugs and blood and blood product recipients) present the highest prevalence of HIV/HCV co-infection[1,31]. The materno-fetal transmission of HCV increases in the presence of HIV. The risk of materno-fetal transmission has been assessed by different studies. On average, the materno-fetal transmission risk is estimated as 6% in negative-HIV mothers[41]. In HIV co-infected mothers, the risk is greater. On average, it is estimated as 14%, ranging from 5% to 36%[41]. Many studies have demonstrated that HCV viremia is significantly greater in HIV co-infected patients[4,53]. It is believed that the HCV viral load of the mother is related to the risk of materno-fetal transmission of the virus.

There are a number of studies in the literature relating HCV transmission and risk behavior for sexually transmitted diseases (STD)[18,69] or HCV-infected sexual partners[10,24,50]. The population infected with HIV generally present high-risk behavior for the transmission of STD and frequently present HCV-infected partners. Thus, the HIV-infected population, even without parenteral exposure factors, can have a greater association with HCV infection than the non HIV-infected population.

Some authors believe that the sexual transmission of HCV can be facilitated by the presence of an HIV-infected sexual partner, however, studies in this area are controversial. EYSTER *et al.*[15], LISSEN *et al.*[28] and SOTO *et al.*[62], observed that sexual partners of co-infected subjects presented a higher risk of being positive to HCV than the regular partners of patients infected only with HCV. The results, however, were not statistically significant considering the studied groups. Also, WYLD *et al.*[77] did not observe any association between HCV transmission and presence of HIV among regular sexual partners.

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In order to assess the risk factors associated with hepatitis C in HIV infected patients, we conducted a case-control study at our place of work. We analyzed the exposure factors to HCV in 118 HIV/HCV co-infected patients and in a group of 117 HIV infected patients. The risk factors that were associated with HCV infection, when data were submitted to multivariate analysis were: above the age of 30, use of intravenous illicit drugs, use of inhaled illicit drugs, anal sexual intercourse, sexual partners with a past history of liver disease, sexual partners with past history of blood transfusion, and sexual partners with a history of IDU[37]. Thus, our results reinforced the theory that the sexual transmission of HCV is facilitated by the presence of HIV.

Future prospective studies in serum-discordant populations concerning HIV and HCV will help us understand the questions concerning this transmission mechanism.

In a similar study using the same 118 cases, they were compared with 233 controls positive to HCV in order to evaluate the risk factors associated with HIV infection. We concluded that HIV infection among patients co-infected with HCV was associated with the female gender, civil status divorced/widowed, to past or current use of illicit drugs and to the habit of sharing pipes or syringes[55].

Natural history of HCV infection in HIV-infected patients: The HIV infection interferes and modifies the natural history of the HCV infection. After HCV infection, about 15 to 20% of the mono-infected subjects present spontaneous viral clearance. Some authors have reported that clearance is detected in 5% to 10% of HIV/HCV co-infected patients[70,74]. A study conducted among our population confirmed this information. We identified RNA-HCV by PCR (polymerase chain reaction) technique in 192 co-infected patients that presented positive HCV serology[36].

Based on our results, 95.3% of the patients presented positive reagent results to the ELISA test[34]. HIV infection has been associated with high viremia by HCV, leading to a more accelerated progression of hepatic disease, cirrhosis, liver failure and hepatocarcinoma[2,13,16,21,63,68].

The studies referred to above suggest that HIV infection can accelerate the natural course of HCV infection. However, it should be pointed out that the mechanisms responsible for hepatic abnormalities that could lead to a faster progression of liver disease are still not fully understood. The opportunistic infections, co-infections with other hepatotrophyc viruses, the use of hepatotoxic drugs (among them, the antiretroviral therapy) and alcohol abuse are common situations faced by HIV positive patients that could contribute to accelerated hepatic degeneration.

BICA *et al.*[3] and MARTIN-CARBONERO *et al.*[30] reported that in some specific populations of co-infected patients, the main cause of death and hospitalization among HIV-infected patients is HCV-related chronic hepatic disease[3,30].

Impact of the hepatitis C virus infection in the evolution of the disease caused by HIV: Clinical studies which have examined whether there is an influence of HCV on HIV disease progression showed discordant results. Whereas some authors have demonstrated an association between HCV infection and faster HIV disease progression[22,51], others have not[14,29,66].

HCV might act as a co-factor for HIV disease progression through several mechanisms. First, non-specific immune stimulation driven by chronic HCV infection might enhance HIV replication[12]. Second, the infection of immune cells by HCV could favor CD4 T-cell depletion and partly undermine the immune recovery that follows successful antiretroviral therapy[26]. Third, HCV could compromise the benefits of antiretroviral drugs as a result of a higher incidence of liver toxicity and treatment discontinuation[65].

Diagnosis: All HIV-infected patients should perform serology for HCV infection[8,9]. The third generation immunoenzyme serology method should be used for the detection of anti-HCV antibodies. Patients who present positive results for anti-HCV should be submitted to HCV-RNA detection to confirm the diagnosis of current viral replication. The absence of anti-HCV antibodies in HIV co-infected patients does not exclude the possibility of HCV infection, especially in subjects with advanced HIV disease. HCV occult infection can occur in this situation[19]. Thus, HIV infected patients, with HCV negative serology, who present elevated serum aminotransferase levels or a history of high-risk behavior, should be submitted to PCR, for a definitive diagnosis of HCV infection[67,68,70,71]. It should also be highlighted that viremia for HCV can be intermittent. Thus, we suggest that patients with positive HCV serology, or even with negative serology but with clinical evidence of HCV infection, should be submitted to at least two HCV-RNA detections within six months before the diagnosis of current viral replication can be excluded[67].

Clinical management of HCV infection in HIV co-infected patients: After the diagnosis of hepatitis C, clinical management of co-infected patients should include complete information about other aspects of the disease, in addition to information concerning the specific treatment. The patients should be informed about the HIV and HCV transmission mechanisms and about infection prevention and transmission modes.

They should also be submitted to serology to detect antibodies for hepatitis A and B infection. If there is no serologic evidence of previous or current infection by these viruses, the patient should be vaccinated against them. The patient should also be instructed not to drink alcohol, since it is believed that alcohol intake can accelerate the progression of the liver disease caused by HCV[49].

Clinical and laboratory assessment of these patients should include, in addition to a comprehensive physical examination, the performance of liver function tests, in accordance with the guidelines provided by specific manuals[8].

Liver biopsy: Liver histology allows the staging of HCV hepatic damage and predicts, in the short-mid term, who will develop cirrhosis. At the same time, it may rule out other causes of liver damage. However the role of liver biopsy for treatment decision purposes is controversial in HIV-HCV co-infected patients[59,60]. Some authors have suggested that liver biopsy is a dispensable method for clinical management of the disease. They argue that owing to the quick progression of the disease in this specific population, the biopsy is unnecessary and could increase morbidity and treatment costs[48,58].

However other authors have recommended that all patients should be submitted to liver biopsies whenever they are candidates for specific

treatments and do not present any contraindication for this procedure[20,67]. Their recommendations for the performance of a liver biopsy also include patients with ALT within the normal ranges[67,71].

In our center, we conducted liver biopsies in all patients who have HCV-RNA and indication for specific treatment approaches, even in the presence of normal ALT levels. Liver biopsy was performed on 156 co-infected patients and we diagnosed active chronic hepatitis in 112 patients (71.7%), reactional liver in 31 patients (19.8%) and other diagnoses in 13 patients (8.3%). These other diagnoses, were granulomatous hepatitis (3 patients), acute hepatitis (4 patients), steatohepatitis (6 patients). Among the 156 patients submitted to biopsy, 139 (89.2%) presented high levels of ALT and 17 (10.8%) presented ALT levels within the normal range. Among the 17 patients with normal ALT, the results of the liver biopsy were: reactional liver in seven, chronic hepatitis with minimum activity in six, chronic hepatitis with moderate activity in one, cirrhosis in one, and granulomatous disease in two patients[38].

We believe that liver biopsy is an essential tool for clinical management of the disease since it enables the identification of patients that really require treatment, in addition to leading to the diagnosis of other conditions related to HIV-infected patients.

TREATMENT

Criteria for treatment indication: After the introduction of new antiretroviral therapies, an increase in the survival rates of HIV-infected patients has been observed all over the world. As a result, hepatitis C gained more attention.

As previously discussed HIV co-infection accelerates the evolution of liver pathology caused by hepatitis C virus, leading to the onset of cirrhosis, clinical pictures of liver imbalance and hepatocarcinoma. Thus, all HIV positive persons should be considered as candidates for anti-HCV therapy[59,60].

Treatment criteria should follow, as a whole, the same recommendations as for HCV mono-infected populations[41]. Similarly, the contraindication criteria for treatment follow the same recommendations for the HCV mono-infected population[41].

Thus, patients that have HCV-RNA and histologic evidence of chronic liver pathology should be treated[59,60].

There are no clinical data concerning treatment efficacy and the safety of patients with chronic liver disease and normal ALT levels.

According to a recent international consensus conference on chronic viral hepatitis and HIV infection, treatment in patients with repeated normal alanine aminotransferase levels should be carried out in the context of study protocols or when a liver biopsy has proved the presence of clinically significant fibrosis, F2 or above[60]. At the same conference it was also observed that anti-HCV therapy should be prescribed only when the CD4 cell count is above 350 cells/μL. In individuals with CD4 cell counts between 200 and 350 cells/μL, and already under long-term antiretroviral therapy, the decision to treat HCV might be individual. In individuals with CD4 cell counts of less than 200 cells/μL anti-HCV therapy should be deferred.

Most authors reported that the best therapeutic results are obtained in patients with CD4 cell counts above 200 cells/mm^3 [32,56,58,59].

In our center, we recommend treatment for patients that have CD4 cell count above 200 as has been recommended by the British HIV Association[42].

Available medications: The therapeutic options in this group of patients are the same as those available for HCV mono-infected patients.

Alpha interferon monotherapy: Monotherapy with alpha 2a or alpha 2b interferon has been tried by many authors in studies that included a small number of patients and very heterogeneous clinical conditions to allow for the comparison of results[5,32,56,57]. Generally speaking, the authors suggested that the efficacy of monotherapy was not different when co-infected and mono-infected patients are considered and they observed that the best therapeutic response occurred in patients whose CD4 cell level was over 500 cells[20,32,56].

Alpha interferon associated with ribavirin: Few studies have analyzed the efficacy and safety of IFN and ribavirin combinations in HIV co-infected patients[25,40,42,45,56].

The trials conducted so far have studied few patients. Most of the authors suggested that the efficacy of this combination in co-infected patients is about 22% (16 - 40%). The authors used different therapeutic regimens and groups of patients with different levels of immunosuppression and liver necro-inflammatory activity, which could explain the variation in results[20]. In fact, controlled studies enrolling more patients and with different levels of immunosuppression are required in order to more clearly define which patients could really benefit from the use of IFN/ribavirin.

The spectrum of adverse events related to the use of interferon and ribavirin in this population is not different from that of the mono-infected population, as we observed previously in our center[33].

Pegylated interferon associated with ribavirin: Another option for the treatment of hepatitis C in HIV co-infected patients is pegylated interferon, associated with ribavirin or by itself. Owing to its easy administration (once a week) and its greater efficacy in treating mono-infected patients, its use in co-infected patients could represent a great advance in the treatment of these patients[27,75].

Available data from large clinical trials and from a few studies already completed show that response rates to anti-HCV therapy are lower in HIV-co-infected patients, even using the new peg-IFN formulations with ribavirin. Overall, sustained response rates are in the range of 26-40%[11,46,47,54,72]. Relapses seem to be more frequent in this population[61].

The reasons why anti-HCV therapy provides a poor response in the setting of HIV infection may vary. As both peg-IFN and ribavirin act, at least in part, as immunomodulatory agents, subtle immune defects derived from HIV infection might negatively impact on the performance of these drugs, even in patients with high CD4 cell counts and undetectable plasma HIV-RNA levels under antiretroviral therapy[23].

In addition, there is a high rate of anti-HCV treatment discontinuation in some of the trials conducted in HIV-co-infected patients. Preliminary studies with the use of pegylated interferon in co-infected patients revealed that the rate of treatment interruption ranged from 12 to 42%[11,47,72].

Although this may reflect a higher rate of serious adverse events in this population compared with HIV-negative individuals, it might also reflect the fact that some physicians are not sufficiently familiar with the management of side-effects of anti-HCV therapy.

Efforts to minimize side-effects with pre-emptive symptomatic treatments and the appropriate management of complications are thus critical to ensure the completion of anti-HCV therapy in most patients.

Pegylated versus conventional interferons: Recent results from large trials have shown that pegylated interferons seem to have greater efficacy over standard interferons[11,47,72].

According to different authors, the treatment of choice for HIV-HCV co-infected patients is the combination of pegylated interferon plus ribavirin, following doses and schedules used for HCV-monoinfected patients[59,60].

The benefit of extending therapy (more than six months for HCV genotypes 2 or 3; and more than 12 months for HCV genotypes 1 or 4) in early virological responders should be examined in clinical trials[59,60].

The primary goal of therapy is viral eradication. Other aims of therapy may include the treatment of extrahepatic manifestations of HCV, a potential reduction in the probability of transmission and regression in the degree of fibrosis present. We intend to somewhat restrain the progression of the chronic liver disease and, as a result, prevent or at least postpone the onset of severe and advanced forms (liver failure, liver cirrhosis, and hepatocarcinoma)[43].

A study conducted in Brazil observed that even co-infected patients that present persistent viremia after treatment can have significant histologic improvement[35].

The prevention of more advanced forms of the disease is particularly important in the population of co-infected patients, where the possibility of liver transplant is more restricted. Thus, in our opinion, the treatment of hepatitis C in the co-infected population should start as soon as the clinical indications are identified.

Adverse events related to the use of interferon and ribavarin in co-infected patients: Co-infected patients can present the same adverse events related to interferon and ribavarin use, already described for mono-infected patients[11,47,72]. In addition, co-infected patients can also develop CD4 cell decrease, pancreatitis and lactic acidosis during the treatment with interferon and ribavirin[7,59]. These events are not described in the treatment of mono-infected patients. Therefore, the treatment of the co-infected population requires continuous laboratory and clinical follow-up, plus a qualified medical team to clinically manage the patients.

Prevention: The use of intravenous illicit drugs should always be discouraged. The transmission of hepatitis C virus may happen through contaminated instruments used in this situation. People who insist on using intravenous drugs should be instructed about hygiene and safety measures for their use. The use of inhaled drugs should also be discouraged, since there is evidence of HCV transmission through this mechanism, especially in HIV-infected populations[37]. HIV-infected patients are instructed about safe sex practices, which should be enough to prevent HCV transmission.

RESUMO

Hepatite C em pacientes co-infectados pelo vírus da imunodeficiência humana. Revisão sobre o tema e experiência de um ambulatório brasileiro

O virus da hepatite C e o HIV compartilham os mesmos mecanismos de transmissão. A prevalência da infecção pelo vírus da hepatite C em pacientes co-infectados pelo HIV varia em diferentes regiões do mundo, a depender dos diferentes fatores de exposição para ambos os vírus. A co-infecção com o HIV acelera a progressão da doença causada pelo vírus da hepatite C, agrava a progressão da infecção causada pelo HIV e aumenta o risco de transmissão do vírus da hepatite C. Portanto, a atenção clínica e o tratamento da infecção pelo vírus da hepatite C deveriam ser prioridade nas unidades de atendimento a pacientes infectados pelo HIV. O manejo clínico desses pacientes envolve procedimentos diagnósticos específicos e equipe médica treinada para esse fim.

O tratamento dessa condição deve seguir critérios clínicos e laboratoriais específicos. Atualmente já são disponíveis medicamentos para o tratamento da hepatite C em pacientes co-infectados pelo HIV.

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