HIV/HCV COINFECTION

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Epidemiology

Around one third of HIV patients worldwide suffer from chronic hepatitis C (HCV). HIV and HCV are transmitted by percutaneous exposure to contaminated blood, through sexual intercourse, and to a lesser extent, from mother to infant. The prevalence of HCV infection varies with the mode of transmission of HIV. HCV has been reported in up to 90% of HIV-infected hemophiliacs and 90% of HIV-positive injection drug users (IDU). In contrast, the incidence of HCV infection among HIV-infected homosexual men has increased recently, and unprotected anal intercourse, traumatic sexual practices, and concomitant sexually transmitted diseases have been the main risk factors for HCV acquisition. Several outbreaks of acute hepatitis C among men who have sex with men (MSM) have recently been reported in Berlin, London, Paris and Amsterdam.

On the other hand, the rates of coinfection vary considerably, both between and within countries, depending on rates of IDU within the population studied. In the United States, a cross-sectional analysis of two large HIV trials (n=1687 subjects) demonstrated that the overall prevalence of HCV coinfection was 16%. Approximately 80% of these patients were infected with HCV genotype 1, and 75% had high HCV RNA levels (ie, >800,000 IU/mL)\(^{(1)}\). Similar HCV prevalence rates have been demonstrated among HIV-infected populations in France, Germany, Switzerland and Greece. We studied the prevalence of HCV infection in a series of 892 HIV positive Argentinian patients detecting 30% of anti-HCV+ (ELISA) and 20% of HCV RNA+ (PCR)\(^{(2)}\); an eloquent difference in comparison with the 0.6-0.9% prevalence of HCV infection among the control general population in Argentina. The most prevalent HCV genotypes among coinfected individuals were type 1 (80%), 3 (12%) and 4 (6%). We found no case bearing genotype 2.

One other investigation comparing the virological characteristics of HIV-HCV coinfected patients vs. HCV monoinfected patients, we detected significantly higher viral load and higher fibrosis score in HIV/HCV coinfected patients. In addition, a higher prevalence of genotype 1a and 3a (40% and 20% respectively) was also reported. Lastly, genotype 1 HCV coinfected patients had a significantly higher viral load (p <0.05) compared with that of the other HCV genotypes\(^{(3)}\). A vast majority of our studied population was represented by IDUs. This data coincides with information from European and Asiatic investigators who also reported a predominance of genotype 1 and 3 in intravenous drug abusers associated a higher HCV viral load in HIV-HCV coinfected patients when compared with HCV monoinfected patients.

Natural History

The widespread use of highly active antiretroviral therapy (HAART) since 1996 has dramatically changed the natural history of HIV infection; given the increased survival of HIV-infected individuals, HCV now has enough time to cause severe liver damage. Cross sectional studies have shown that higher CD4 cell counts and undetectable human immunodeficiency virus (HIV) plasma viral load are associated with a slower rate of liver fibrosis progression in HIV/HCV-coinfected patients under HAART\(^{(4)}\). In contrast, after acute HCV infection, progression to chronic HCV infection is increased from 70–85% in those not infected with HIV to over 90% in HIV infected individuals, particularly in those with advanced immunosuppression. Accordingly, lower CD4 cell counts and lack of HAART have been reported to be independent predictors of liver-related mortality in this population. Pineda et al. demonstrated that both a significant increase in CD4 counts after HAART initiation and the proportion of time with undetectable HIV RNA during follow-up were independent markers of good liver disease outcomes. Therefore, a dynamic assessment of the response to HAART (changes in CD4 counts and time with undetectable HIV RNA) might be used to adopt therapeutic decisions for HCV-HIV–coinfected patients\(^{(5)}\).

On the other hand, among the 10% of HIV-HCV-coinfected individuals who have normal transaminases, up to 30% may have significant liver fibrosis on biopsy. Thus, a normal alanine aminotransferase (ALT) level in HIV-HCV coinfection should not provide reassurance that liver fibrosis progression is unlikely. Liver fibrosis progression is accelerated in HIV/HCV-coinfected patients, with a more rapid progression to cirrhosis compared with HCV-monoinfected persons. Among 67 HIV/HCV-coinfected patients undergoing paired liver biopsies separated by a median of 2.8 years, Sulkowski and colleagues demonstrated that 28% of patients had an increase of at least two modified Ishak stages of hepatic fibrosis. Among those with mild fibrosis on initial biopsy, 26% had a two-stage progression on follow-up biopsy. Once HIV-HCV-coinfected persons have developed cirrhosis, the risk of hepatic decompensation is higher than for HCV monoinfected individuals. Further, survival following decompensation is poor, despite effective HAART.

Diagnosis and Monitoring of HCV Infection

All HIV-infected patients should be tested at least initially...
for the presence of HCV antibody. Thereafter, testing should be repeated as often as required based on an accurate assessment of ongoing risk exposure. HCV antibody may be negative, despite active HCV viremia, in 10–15% of immunosuppressed patients. Consideration should be given to HCV-RNA testing despite negative HCV antibody in cases of unexplained transaminase elevation in patients with CD4 counts <200 mm⁻³, when acute hepatitis C is suspected, or among subjects with a high risk of acquiring HCV (e.g. IDU). Quantitative HCV RNA level, does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important prognostic information about the response to antiviral therapy.

Non-invasive procedures to assess liver fibrosis (FibroScan and serum biochemical markers) are generally accurate in discriminating between lack of fibrosis and advanced fibrosis but are less precise in distinguishing between intermediate fibrosis stages⁷⁰. Their predictive value is particularly good for advanced hepatic fibrosis and cirrhosis. However, serum fibrosis markers are generally less reliable in coinfected patients, given the inflammatory nature of HIV disease and/or the frequent prescription of drugs in this population that may interfere with some fibrosis markers in the blood.

Liver biopsy remains the preferred test for evaluation of HCV-related disease and is useful to assess prognosis and guide HCV treatment decisions. It can provide important information that may not be available from other clinical or laboratory assessment, particularly in immunosuppressed individuals. The decision to biopsy is thus usually made on an individual basis; it is most often taken when the risk–benefit ratio with treatment is unclear, for example in patients with liver disease associated with HCV genotype 1 and high viral load. In patients for whom HCV treatment is deferred, the most appropriate intervals to monitor such patients have not been determined, but because of unpredictable fibrosis progression, even among those with limited fibrosis, serial liver biopsy should be considered every 2–3 years⁷⁷.

Hepatitis C Virus Treatment

Treatment guidelines endorsed by the National Institutes of Health, the US Public Health Service, the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the European Consensus Conference Panel state that HCV should be treated in the HIV-infected patients.

Like monoinfected patients, combination pegylated interferon plus ribavirin for 48 weeks represents the standard of care for treating chronic HCV in HIV-infected individuals. One of the most important benefits of HCV therapy is a reduction in the risk for liver-related complications⁷⁹.

What Patients Should be Treated?

Standard HCV therapy in HIV-HCV-coinfected individuals is with either Pegylated Interferon (PEG-IFN) (alpha-2a or alpha-2b) plus ribavirin (RBV). Both forms of PEG-IFN have been studied in large trials in HIV-HCV-coinfected populations and, although no head-to-head comparison has been performed, their efficacy appears similar, with sustained virological response (SVR) rates of between 27% and 44% overall. In the absence of PEG IFN and Ribavirin contraindications, HCV treatment should be offered to persons with a high likelihood of achieving a SVR, i.e. patients infected with genotype 2 or 3 and those infected with genotype 1 if the viral load is low (<400,000 – 500,000 IU/mL); patients with significant hepatic fibrosis (bridging fibrosis or cirrhosis); persons with stable HIV infection not requiring antiretroviral therapy who are motivated to undergo therapy; acute HCV infection; cryoglobulinemic vasculitis; and/or cryoglobulinemic membranoproliferative glomerulonephritis⁷⁷.

Three randomized controlled trials (ACTG, APRICOT and RIBAVIC) were published in 2004 demonstrating that pegylated interferon plus ribavirin is the optimal therapy for chronic HCV among HIV-infected patients. Lower HCV treatment response rates in HIV-HCV-coinfected populations are probably related to multiple factors, including higher HCV viral load, immunosuppression, increased toxicity/ poorer treatment adherence, and suboptimal dosing of ribavirin. Adequate exposure to RBV is crucial to maximize responses to anti-HCV therapy. Weight-based dosing seems well able to balance the highest efficacy and the lowest limiting toxicities of the drug, namely anemia. Pharmacokinetic studies have shown a good correlation between RBV plasma levels and HCV RNA responses. Therefore, the use of fixed low doses of RBV (800 mg/day) in most trials conducted in coinfect patients in the past could explain lower SVR. Recently, PRESCO study examined whether administration of weight-based ribavirin (1,000 mg/d if body weight <75 kg and 1,200 mg/d if body weight >75 kg) in combination with PEF IFN, improves the SVR rate in HIV/HCV-coinfected patients. Substantial improvements in virologic outcomes were reported, with SVR achieved in 72.4% of HCV genotype 2– or 3–infected patients and 35% of genotype 1– or 4–infected patients. Only 3% of patients stopped HCV therapy because of severe anemia⁸⁰. As such, recent HIV/HCV management guidelines now recommend weight-based ribavirin dosing in HIV-positive persons undergoing combination HCV therapy⁸⁰.

Data from randomized controlled trials indicate that the pre-treatment CD4 cell count is not strongly associated with SVR. However, the efficacy and safety of PEG IFN/RBV in persons with CD4 cell counts <200 cells/μL has not been established. Therefore, for HIV infected patients with CD4 cell counts <200 cells/μL, initiation of HAART should be considered before HCV treatment⁷⁷.

Predictors of Treatment Outcome

Baseline serum HCV RNA and HCV genotype are the main predictors of SVR to PEG IFN–RBV in coinfect as in HCV monoinfected patients. Several other variables, however, may
influence treatment responses, although generally to a lesser extent. They can be grouped in three categories, determining a better outcome as follows: a) host (younger age, non-black ethnicity, lower body mass index, lack of insulin resistance), b) HCV status (elevated ALT, less advanced hepatic fibrosis), and c) treatment schedule (optimal doses of PEG IFN and/or Ribavirin, enough length of therapy, good adherence). On the other hand, prediction of SVR through early virological testing has allowed treatment to become increasingly individualized in HCV monoinfection. Based on HCV genotype and HCV viral load reduction on treatment at week 4 (Rapid Virological Response-RVR) and/or week 12 (early virologic response—EVR), therapy may either be shortened or discontinued, thereby minimizing cost and toxicity\textsuperscript{(10)}.

A recent Spanish study in HIV-HCV coinfection-population found RVR to provide a PPV for SVR of 69%, 90%, and 83% in genotypes 1, 3, and 4, respectively. Similar to HCV monoinfection, the NPV of RVR for a SVR is considerably lower than NPV of EVR, with levels of 70%, 43%, and 70% for genotypes 1, 3, and 4. Thus, individuals without a RVR should be continued on therapy for at least 12 weeks to assess EVR. RVR may be particularly useful in some subsets of HIV-HCV coinfected individuals\textsuperscript{(11)}.

On the other hand, a reduction <2 log IU/ml in HCV RNA at week 12 and/or the presence of detectable viremia at week 24 both predict lack of SVR; accordingly these patients should be advised to stop prematurely anti-HCV therapy.

In conclusion, the current treatment of chronic HCV infection in HIV-positive persons should be PEG IFN plus weight based RBV for 48 weeks. Patients infected with HCV genotype 2–3 and RVR could benefit from shorter (24 weeks) courses of therapy. In contrast, carriers of HCV genotypes 1 and 4 with early virological response (week 12) but not RVR (week 4) might benefit from extended (60–72 weeks) courses of therapy\textsuperscript{(12)}.

Adverse events (AE) and interactions of hepatitis C virus therapy

Approximately 12–25% of coinfected patients in clinical trials discontinued therapy early because of an adverse effects, and serious adverse events occurred in 17–29%. The most common AE of HCV therapy include fatigue, depression, irritability, insomnia, and weight loss. Leukopenia and thrombocytopenia are dose-related AE of PEG IFN\textsuperscript{(13)}. In particular, use of granulocyte colony-stimulating factor was allowed in two of the pivotal HIV/HCV coinfection treatment trials to improve leukopenia. Anemia is also a common AE during combination anti-HCV therapy. It arises because of the suppression of erythropoiesis induced by interferon and the reversible hemolysis induced by RBV. Reduction of the RBV dose had been recommended if anemia developed during HCV therapy, but this is associated with reduced SVR rates. Erythropoietin could be given to patients suffering from anemia induced by PEG INF/RBV (20,000–40,000 U/week).

Didanosine and zidovudine have been found to have important interactions with PEG IFN and RBV. Didanosine (DDI) has been associated with severe mitochondrial toxicity leading to pancreatitis, hepatic failure, and death, particularly among patients taking ribavirin. Therefore, DDI is contraindicated in patients receiving HCV treatment. Concomitant use of zidovudine and HCV therapy has been associated with higher rates of anemia. If other antiretroviral regimens are available (based on tolerability and HIV resistance), discontinuation of zidovudine prior to PEG IFN/RBV should be considered; if zidovudine is continued, hemoglobin levels should be monitored closely to detect significant anemia. Lastly, conflicting data exist regarding the role of abacavir as a disturbing component to a good virological response of HCV treatment generated through a intracellular competitive mechanism between Abacavir-RBV.

Hepatotoxicity induced by HAART treatment

Severe hepatotoxicity (ACTG grade 3 or 4) after HAART initiation, usually not a frequent event, ranges in incidence from 2–18%, and is particularly important because it may result in the need to interrupt or discontinue HAART. Hepatotoxicity can occur with all antiretroviral agents, but is frequently linked to the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), and in particular nevirapine, as part of a hypersensitivity syndrome\textsuperscript{(14)}. In the protease inhibitor class, hepatotoxicity has been linked to the use of full dose ritonavir and tipranavir/low dose ritonavir (r) combination, with other ritonavir boosted combinations such as lopinavir (LPV/r), fosampranavir (FOS/r), and atazanavir (ATZ/r) at much lower risk. In the nucleoside reverse transcriptase inhibitors (NRTI) class, stavudine and didanosine are particularly linked to mitochondrial damage; cases of liver failure linked to hepatic steatosis, pancreatitis, and severe metabolic acidosis have also been described. Despite all concerns regarding the relatively high incidence of liver toxicity using antiretroviral drugs in HIV-positive patients with chronic HCV infection, the benefits outweigh this risk. Many reports have clearly demonstrated lower rates of liver-related mortality in coinfected patients taking HAART, even in those with end-stage liver disease. In most cases, HAART can be successfully continued with regular monitoring and/or drug substitution.

Current concepts and recommendations for the management of HCV in HIV-infected patients

\textbullet{} Anti-HCV testing should be performed in all HIV-infected patients;

\textbullet{} HCV RNA testing should be performed to confirm HCV infection in HIV-infected patients who are seropositive for anti-HCV, as well as in those who are seronegative and have evidence of unexplained liver disease;

\textbullet{} Information on liver fibrosis staging is important for therapeutic decisions in coinfected patients;

\textbullet{} HCV should be treated in the HIV/HCV-coinfected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy;
√ The current treatment of chronic HCV infection in HIV-positive persons should be PEG IFN plus weight based RBV for 48 weeks;
√ The achievement of SVR can be predicted on the basis of negative serum HCV RNA at week 4 of therapy;
√ Patients infected with HCV genotype 2–3, and RVR could benefit from shorter (24 weeks) courses of therapy. In contrast, carriers of HCV genotypes 1 and 4 with early virological response (week 12) but not RVR (week 4) might benefit from extended (60–72 weeks) courses of therapy;
√ While didanosine should never be used with RBV, zidovudine should also be avoided when possible;
√ In most cases, HAART is associated with low hepatotoxicity and can be successfully continued with regular monitoring and/or drug substitution; and
√ HIV-infected patients with decompensated liver disease may be candidates for orthotopic liver transplantation.

References