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HIV and HCV: from Co-infection to Epidemiology, Transmission, Pathogenesis, and Treatment

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Abstract: Human immunodeficiency virus (HIV) is the infectious agent causing acquired immunodeficiency syndrome (AIDS), a deadliest scourge of human society. Hepatitis C virus (HCV) is a major causative agent of chronic liver disease and infects an estimated 170 million people worldwide, resulting in a serious public health burden. Due to shared routes of transmission, co-infection with HIV and HCV has become common among individuals who had high risks of blood exposures. Among hemophiliacs the co-infection rate accounts for 85%; while among injection drug users (IDU) the rate can be as high as 90%. HIV can accelerate the progression of HCV-related liver disease, particularly when immunodeficiency has developed. Although the effect of HCV on HIV infection is controversial, most studies showed an increase in mortality due to liver disease. HCV may act as a direct cofactor to fasten the progression of AIDS and decrease the tolerance of highly active antiretroviral therapy (HARRT). Conversely, HAART-related hepatotoxicity may enhance the progression of liver fibrosis. Due to above complications, co-infection with HCV and HIV-1 has imposed a critical challenge in the management of these patients. In this review, we focus on the epidemiology and transmission of HIV and HCV, the impact of the two viruses on each other, and their treatment.

Key words: Acquired immunodeficiency syndrome (AIDS); Human immunodeficiency virus (HIV); Hepatitis C virus (HCV); Epidemiology; Co-infection;

EPIDEMIOLOGY AND TRANSMISSION

Both HIV and HCV pose great threat to human health world-wide. There are approximately 40 million people who have been infected by HIV, while an estimated 3% of the world's population is infected by HCV. Due to shared routes of transmission, co-infection of the two viruses occurs frequently, especially among individuals who have high risks of blood exposures. Many previous studies have shown that 13-43% of HIV-infected patients are also infected with HCV in the United States and Europe (11, 33, 38, 42). The prevalence of chronic hepatitis C among HIV patients varies depending on the route of infection. This ranges from 7% in sexual transmission of HIV

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(12) and soars in hemophiliacs (52) to more than 90% in IDUs (39, 44, 54).

Recipience of blood products is the predominant route for co-infection. A set of data has been given that on routine testing of blood products from HIV-infected hemophiliacs treated before the discovery of HCV in the early 1990s, HCV RNA and antibodies were detected in the serum of over 90% of patients (17). In 1999, new screening methods involving nucleic acid amplification to detect HIV and HCV RNA were implemented in the United States under an investigational new drug protocol approved by the Food and Drug Administration (FDA) (4). Due to the abilities of these new methods in the identi- fication of contaminated donors in the infectious window period before seroconversion (5), the trend that the prevalence of individuals infected with HIV and/or HCV is declining significantly in the current blood donor population. Thus, the importance of recipience of blood products as the source of HIV and/or HCV infection trails off (49).

Intravenous drug usage represents another important route causing the take-up of HCV and/or HIV (1). The probability of transmission from needlestick injuries after exposure to HCV-or HIV-contaminated blood is 2-8% and 0.3%, respectively.

Though sharing the same routes of transmission, the preference of the two viruses varies. HCV is 10 times more infectious than HIV on blood-to-blood contact and can be more effective *via* the needle-stick transmission (15-30/1000 *vs.* 3/1000 accidental injuries) (6). In contrast, HIV is more apt to use the sexual and perinatal routes for transmission (18, 37).

Unlike HIV, there is little evidence to support efficient spread of HCV *via* sexual contact. However, acute hepatitis C has been detected among homosexual HIV-positive men, indicating that HCV can be sexually transmitted. The risk of transmission probably depends on the number of sexual partners and the performance of sexual practices that are prone to injuries. In total, about 4-8% of all HIV-infected homosexual are also infected with HCV.

The overall vertical transmission rate of HCV has been estimated at 5%. Moreover, the risk of HCV vertical transmission is higher in infants born to HIV co-infected mothers (2). This higher rate of vertical transmission may result from the higher HCV viral load in mothers with immunosuppression secondary to HIV infection.

MUTUAL INFLUENCE AND THERAPY

Impact of HIV infection on the natural history of HCV pathogenesis

The natural history of HCV infection succeeded by liver disease progression is a long period of time, in some cases it even exceeds 30 years. 80% of the acute HCV infection will convert to chronic infection. 20% of the converted cases may develop cirrhosis within 20-30 years, with an annual rate of 1-4% further deteriorating to hepatocellular carcinoma (19). Among cirrhosis patients, 6% will develop hepatic decompensation, while 3-4% will die or require liver transplantation (10). In summary, infection with HCV has 3 outcomes: self-limited (spontaneous clearance of viraemia), persist without causing clinical disease (asymptomatic healthy carrier), or lead to cirrhosis or hepatocellular carcinoma.

Co-infection with HIV appears to adversely affect every stage in the natural history of HCV infection. Although there is clearance of HCV RNA from the

blood among approximately 20% of acute HCV infected patients, this ratio is only 5-10% regarding HIV, especially less frequently in those with lower $CD4^+$ cell counts (45). Another study on HCV and HIV dynamics in co-infected subjects demonstrated that the estimated HCV virion half-life was longer in the co-infected group, suggesting that co-infection may contribute to a slower clearance of HCV (47). In addition to making an increase of HCV viral load in serum (8, 23) or liver (43), HIV co-infection will on average cause 10 fold higher titers of HCV viraemia compared with that of HCV mono-infected cases. Darby and colleagues (9) studied death from liver disease and hepatocellular carcinoma among 4865 men with hemophilia who were exposed to HCV-contaminated blood products. Results showed that the cumulative risk for liver-related death was 1.4% (HCV mono-infected) and 6.5% (co-infected) respectively, indicating that co-infection with HIV is responsible for more end-stage liver diseases.

The consensus from these studies is that HIV has an effect in altering the rate of fibrosis and cirrhosis progression. Considering its undoubted association with accelerated liver disease and reduction in survival in HCV infected patients, HIV infection can severely affect the natural history of HCV pathogenesis.

Effects of HAART therapy on HCV viral load and related liver diseases

As HAART therapy is adopted in patients co-infected, it is strongly hoped that the improved immune response would be helpful in reducing HCV levels. However, the effect of HAART on serum HCV load remains controversial. Most studies could not get supportive evidence on the change in HCV RNA titers after HAART therapy (14, 46), while transient (32) or sustained increase (30) or decrease, even clearance in some cases (13, 53) in HCV load were observed. However, HAART therapy has been reported to reduce intrahepatic HCV viral load (28). Patients who had been treated with protease inhibitors had a 3- to 4-fold lower intrahepatic HCV load than that observed in other groups. No difference was observed in the plasma HCV load between both groups (48).

In 2003, Mohsen and colleagues (26) investigated the link between HIV infection and the fibrosis progression rate in HCV patients. In their study, a total of 153 HCV infected and 55 HIV-HCV co-infected patients were identified from two London hospitals. The estimated median fibrosis progression rate was 0.17 units/year in HIV-HCV co-infected and 0.13 in HCV mono-infected patients. They declared that HIV infection modified the natural history of HCV by accelerating the rate of fibrosis progression by 1.4 folds and the development of advanced fibrosis by 3 folds.

Brau and colleagues recruited 274 co-infected patients and stratified them depending on $CD4^+$ counts and HIV viral load at biopsy to assess fibrosis progression rate (3). They concluded that HIV viral load but not $CD4^+$ count was an independent predictor of hepatic fibrosis.

In another study, Verma and co-workerscompared 85 HIV-HCV co-infected subjects with 296 HCV mono-infected patients over 10 years (50). Co-infected patients were grouped into four, receiving either no therapy, or reverse transcriptase inhibitors (NRTIs), or HAART, or initially NRTIs and subsequently HAART. Groups were well matched as regard to age, HCV disease duration, alcohol consumption,

body mass index, and HIV parameters. Those in the HAART-only group had similar HCV-related disease severity compared with HCV mono-infected subjects and endured less advanced disease as regard to fibrosis stage (P<0.0009), fibrosis progression rate (P<0.0001), necroinflammation (P<0.0001) and prevalence of cirrhosis (P<0.006) compared with patients who didn't receive HAART therapy at all.

However, Macias and colleaguesobserved that the usage of nevirapine was responsible for more advanced hepatic fibrosis (21). This discordance may due to the small sample size they recruited. Anyway, this result has not been repeated yet.

It is important to acknowledge that HAART can attenuate hepatic fibrosis in HIV-HCV co-infected patients. More importantly, patients who received HAART as soon as possible after HIV diagnosis and who successfully suppressed the viral load of HIV are more likely to have slower fibrosis progression compared with those whose HAART therapy are delayed or ineffective.

Impact of HCV infection of AIDS progression

Although it is well accepted that HIV is responsible for the deterioration of HCV disease, there are conflicting reports on the effect of HCV infection on the HIV progression (38, 40).

Before HAART therapy, co-infection with HCV had been shown to confer an increasing risk for progression to AIDS in HIV-infected patients (20). However, other studies have failed to certify this (51).

Greub and colleagues (16) reported that among 3,111 HIV-positive patients receiving HAART, HCV-infected persons had a modestly increased risk for the progression to a new AIDS-defining event or death, arthralgia, headaches, anorexia, and fever, and even among the subgroup with continuous suppression of HIV replication. But two further studies demonstrated that HCV co-infection in HIV patients is not statistically associated with survival (31, 41).

Considering co-infected patients differing in important respects, it is easy to explain the contradictory findings above. And the widespread usage of HAART therapy and the various routes of HCV infection make it hard to understand how HCV infection modifies the outcomes of HIV progression.

HCV treatment in co-infected cases

Since the adoption of HAART therapy in 1996 has substantially prolonged survival in patients with HIV, liver disease like cirrhosis and hepatocellular carcinoma (HCC) in this cohort becomes a frequent yet important cause of morbidity and mortality (15). Considering its benefits on viral eradication, even in HIV-HCV co-infection cases (22, 35) and reduction in the risk for liver failure and liver cancer, the 2002 National Institutes of Health Consensus Development Conference Panel on the management of hepatitis C recommended that HIV-HCV co-infected persons should be considered for HCV treatment (27).

Lacking the experience in treating HIV-HCV co-infection patients, it is a good choice to follow therapies being approved for use in patients with HCV.

After treating co-infected patients with interferon alpha (INF-α) for 12 months, Soriano and colleagues found that 18 out of 90 patients (20%) got a sustained virologic response (SVR) (36). However, receiving the treatment with INF-α, patients have to endure its significant side effects. These include the initial influenza-like symptoms (45%-62%) such as myalgia, cytopenia (15%-22%) neuropsychiatric symptoms

such as depression (22%-31%), and rarely thyroiditis (＜1%) and other autoimmune phenomena.

Ribavirin (1-beta-D-ribofuranosyl- 1H-1, 2, 4-triazole-3-carboxamide), a guanoside nucleoside analogue, can exert tremendous antiviral activity against many viruses including HCV, but not HIV. Its antiviral activity may be related to the restoration of a previously suppressed cellular immune response. Compared with INF-α monotherapy, combination therapy with INF-α plus ribavirin is more effective (25, 29). *In vitro* studies have demonstrated that ribavirin inhibits intracellular phosphorylation of HIV reverse transcriptase inhibitor (AZT, D4T, and zalcitabine), suggesting a decrease in their anti-HIV efficacy. Zylberberg and colleagues found that despite *in vitro* interactions between ribavirin and AZT, D4T, significant variation in HIV replication does not usually occur in HIV-HCV co-infected patients receiving ribavirin and different antiretroviral regimens. They also found that INF-α and ribavirin combination therapy induced primary and sustained virological responses in 28.5% and 14.3% of treated subjects (55). The adverse events caused by ribavirin are that it adds significant haemolytic anaemia (10%-22%), dermatitis (20%-24%) and cough (10%), and it also requires birth control owing to its high teratogenicity.

Pegylated interferon in combination with ribavirin is the current treatment for chronic HCV. The addition of polyethylene glycol to the INF-α molecule allows once weekly subcutaneous injection that provides continuous exposure to INF-α. Crespo and colleagues found that Peginterferon alpha-2b plus ribavirin was more effective than INF-α-2b plus ribavirin in HIV-coinfected patients (7). Nearly at the same time, Sherman *et al*. treated 312 patients, who failed in either conventional interferon monotherapy or conventional interferon plus ribavirin combination therapy, with peginterferon alpha-2a (40-kDa) 180 μg/week plus ribavirin 800 mg/day for 24 or 48 weeks, and the result showed that the overall SVR rates were 23% (48/212) for non-responders and 41% (41/100) for relapsers. It is an acceptable response rate being achieved in clinical practice (34). To optimize this therapy, Mauss and Rockstroh recommended the usage of higher ribavirin doses and longer treatment periods (24).

For years, progress has been made in treating HCV in HIV-HCV co-infected cohort. However, severe adverse effects and high discontinuation rates have been reminding us to optimize antiretroviral therapy before the start of interferon-based therapy, to prepare active management of adverse events and to motivate the patient to participate in.

CONCLUSION

With the advent of HAART therapy restoring the patients' immune response, HCV-associated liver diseases have become the main threat to take the lives of HIV-HCV co-infected patients. The more obvious and severe as the situation is, more attentions and efforts are kept on emitted to this field.

Though sharing routes for transmission, so far, there have not been enough evidence to consider HIV and HCV as close interacted with each other inside the body, at least unlike what we have thought they should do. Different transmission routes of the two viruses and many independent factors (e.g. age and alcohol addiction) complicate the patients investigated, which is a big trouble in studying the cross-talk of the two viruses. Further research is needed to make it clear

whether there does exist such a kind of interaction and inter-affection between HIV and HCV. And if so, effort is demanded to better understand these affairs.

INF-α and ribavirin are good candidates to slow down the pathogenesis of HCV. Combination of these two plus the addition of polyethylene glycol can achieve a better effect. However, both INF-α and ribavirin have strong adverse effects. Combination doesn't solve the problem of side effects. New treatments with the same or better advantage but less adverse effects are expected.

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