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Sexual transmission is associated with spontaneous HCV clearance in HIV-infected patients☆

Nathan J. Shores[1,*], Ivana Maida[2,3], Vincent Soriano[3], Marina Núñez[4]

[1]*Division of Gastroenterology, Department of Medicine, Wake Forest University Health System, Winston-Salem, NC, USA*
[2]*Istituto Malattie Infettive, University of Sassari, Italy*
[3]*Infectious Diseases, Hospital Carlos III, Madrid, Spain*
[4]*Division of Infectious Disease, Department of Medicine, Wake Forest University Health Sciences, Winston-Salem, NC, USA*

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***Background/Aims*: There are conflicting data regarding the incidence and factors implicated in the spontaneous clearance of hepatitis C virus (HCV) after acute infection. The aim of this study was to determine the epidemiological factors that predict the resolution of acute HCV infection without therapy in patients with human immunodeficiency virus (HIV) infection.**

***Methods*: We conducted a retrospective, multivariate analysis of epidemiological data from HIV-infected patients presenting from 2000 to 2007 with evidence of past or present HCV infection. Data were collected from one American and two European HIV treatment clinics. A final cohort of 769 HIV-infected patients referred for treatment with available test results for antibody to HCV, HCV RNA, and hepatitis B surface antigen were included for the analysis. We calculated spontaneous clearance rates based on race, geographical location, gender, transmission risk factors, and hepatitis B virus coinfection.**

***Results*: Patients who admitted to a history of injection drug use spontaneously cleared the HCV infection significantly less often (11.6%) than those in whom sexual transmission was the presumed route of HCV infection (21.9%) ($p = 0.004$). This difference was more pronounced when heterosexual contact as the source of infection was analyzed separately. Multivariate analysis identified heterosexual HCV transmission (OR 2.81, 95% CI 1.55–5.09) and hepatitis B surface antigen carrier status (OR 10.3, 95% CI 4.29–24.73) as independent factors predicting spontaneous HCV clearance. No differences according to gender, race or geographical origin were observed.**

***Conclusions*: In summary, sexual transmission, particularly heterosexual, and hepatitis B virus coinfection were the only factors associated with spontaneous HCV clearance in this HIV-infected population.**

***Keywords*: HCV; HIV; Spontaneous clearance; Sexual transmission; Injection drug use; HBV; Coinfection; Intravenous drug use**

1. Introduction

Although recovery is not the usual course, acute hepatitis C virus (HCV) infection may resolve within 12 weeks, with normalization of aminotransferase levels, loss of detectable serum HCV RNA, and resolution of symptoms [1]. However, antibody to HCV (anti-HCV) persists. HCV is cleared spontaneously in approximately 26% of acute infections according to NHANES III data,

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* Corresponding author.
E-mail address: NShores@wfubmc.edu (N.J. Shores).

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but reported rates differ (0–42%) depending on the study population [2–15]. Since HCV and human immunodeficiency virus (HIV) share epidemiological factors, HCV screening is recommended in the HIV population, making their medical records an ideal resource for the evaluation of spontaneous clearance of HCV.

The literature indicates that spontaneous clearance of HCV occurs in HIV-infected patients, but data vary widely regarding the rate of clearance, i.e., 0–34% [3–7,10,11,14]. In prior studies of factors influencing spontaneous HCV clearance, race has consistently been implicated, with blacks and Asians clearing less than Canadian aboriginals [4,5,7,16–18]. However, for other factors such as gender, CD4 count, age at infection, and risk factor for viral infection, there are conflicting data [3–7,19,20]. HIV infection itself has also been shown to negatively impact on HCV resolution [7,21,22], while hepatitis B virus (HBV) coinfection appears to facilitate spontaneous clearance [5,14].

Limitations of the aforementioned reports include small samples, limited representation from only certain subgroups, and lack of inclusion of all potential relevant factors in the study designs. In the present study, we evaluated a large and epidemiologically diverse sample of HIV-infected patients and analyzed several factors reportedly influencing spontaneous HCV clearance.

2. Patients and methods

This is a retrospective, cross-sectional, multicenter study performed with data from one American academic medical center (Wake Forest University North Carolina Baptist Hospital, Winston-Salem, NC) and two European HIV clinics [Hospital Carlos III, Madrid (Spain); and University of Sassari, Sassari (Italy)]. The study was approved by each local institutional review board.

The records of all the HIV-infected patients from the three centers included between 2000 and 2007 were reviewed. Patients with a detectable antibody to HCV (anti-HCV) at initial HCV evaluation, and with available serum HCV RNA and hepatitis surface antigen (HBsAg) testing were included in this study. Patients were excluded if they lacked the above-mentioned laboratory test results. Patients with a history of anti-HCV therapy prior to the HCV RNA measurement were also excluded from the study. Epidemiological data, including age, gender, race, geographical location, and viral transmission risk factors were recorded. The transmission risk factor of 150 patients was not available.

All the patients had a positive HIV antibody determined by ELISA which was confirmed by Western blot, positive anti-HCV by EIA or ELISA, and HBsAg and quantitative serum HCV RNA were determined by polymerase chain reaction, with diverse lower limits of detection ranging from 5 to 600 IU/ml. HIV viral load, CD4 count, aminotransferase levels, and use of antiretroviral therapy at the time of the HCV RNA determination were recorded as well. Laboratory analyses were performed at the local laboratories or as send-out tests to reference laboratories, depending on the standard care at each institution.

Data were analyzed using descriptive statistical analysis: median and interquartile range for continuous variables and proportions for categorical variables. Comparisons between groups were made using chi-square or Fisher's exact tests for proportions and the Student's *t*-tests for continuous variables. Forward step-wise univariate and multivariate regression logistic analyses were performed to identify the independent predictors of spontaneous clearance. Differences were considered to be significant with p values <0.05. All the analyses were performed using SPSS (version 11.0, SPSS Inc., Chicago, IL).

3. Results

Out of 879 patients with a detectable anti-HCV, 769 had all the required data that were outlined above available for this analysis. The median age of the 769 HCV/HIV co-infected patients included in the study was 41 years. The majority were male, being treated with highly active antiretroviral therapy (HAART), and had relatively preserved CD4 counts. The characteristics of the patients according to HCV RNA status are summarized in Table 1. Both the groups (viremic and non-viremic) differed in race, geographical origin, HIV risk factor, proportion of HBsAg carriers, and aminotransferase levels.

White Americans, African Americans, and white Mediterraneans were HCV RNA negative in 23.5%, 15.9%, and 11.8% of the cases, respectively. Those with prior injection drug use (IDU) demonstrated the absence of HCV viremia significantly less often (11.6%) than patients for whom sexual transmission was the presumed route of HCV transmission ($p = 0.008$). In addition, HBV coinfection was significantly more frequent among subjects that spontaneously cleared HCV (15.7% vs. 3.9%, $p < 0.0001$).

We further analyzed the role of sexual transmission, and found that the difference between sexual and IDU transmission was driven by the subgroup of patients for whom heterosexual contact was the presumed HIV risk factor (Table 2).

Prevalence of undetectable HCV RNA among patients with a history of homosexual contact was comparable (13.5%) to that of the IDU group (11.6%) ($p = $ NS). We also explored racial and geographical factors and failed to demonstrate significant differences between the groups with adequate representation in our sample. The presence of HCV viremia was comparable for males and females as well.

In the multivariate logistic regression analysis that we chose, heterosexual transmission [OR 2.81 (95% CI 1.55–5.09); $p = 0.001$] and HBsAg carrier status [OR 10.3 (95% CI 4.29–24.73); $p < 0.0001$] were factors independently and strongly associated with the absence of HCV RNA (Table 2). A multivariate model including the variable "sexual contact" led to similar results (data not shown).

Interestingly, additional analyses showed no differences in clearance in the African American subgroup based on transmission risk factors. Thus, 15.2% of African American patients with reported IV drug use were non-viremic as opposed to 17.5% of AA's presumably infected via sexual activity [OR 1.18 (95% CI 0.51–2.78); $p = 0.70$].

4. Discussion

The hepatitis C virus has the ability to persist after acute infection, due to evasion of early and late immune