Similar Progression of Fibrosis Between HIV/HCV–Infected and HCV–Infected Patients: Analysis of Paired Liver Biopsy Samples

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See related article, de Vries–Sluijs TEMS et al, on page 1934 in *Gastroenterology*.

BACKGROUND & AIMS: Fibrosis progression might be accelerated in patients who are coinfected with human immunodeficiency virus (HIV) and HCV (HIV/HCV). However, no studies have directly compared fibrosis progression by paired liver biopsy between patients infected with HIV and HCV versus those infected with only HCV. **METHODS:** Liver biopsy samples were collected from patients with HIV/HCV (n = 306) and those with HCV; biopsies from 59 without a sustained virologic response (SVR) or cirrhosis were matched with those from patients with only HCV (controls) for initial fibrosis stage, demographics, and HCV treatment. For HIV/HCV patients, categorical variables at baseline and the area under the curve of continuous variables per unit time were analyzed for associations with fibrosis progression. **RESULTS:** Liver biopsies from HIV/HCV patients had more piecemeal necrosis than controls ($P = .001$) and increased lobular inflammation ($P = .002$); HIV/HCV patients also had shorter intervals between liver biopsies (4.7 vs 5.9 years, $P < .0001$). Between the first and second biopsies, fibrosis remained unchanged or progressed 1 or 2 units in 55%, 18%, and 18% of HIV/HCV patients, respectively, compared with 45%, 30%, and 9% of controls. The fibrosis progression rate was similar between HIV/HCV and control patients (0.12 ± 0.40 vs 0.091 ± 0.29 units/y; $P = .72$). In paired biopsies from 66 patients, including those with SVR, there were no associations between fibrosis progression and demographics; numbers of CD4+ T cells; levels of aspartate aminotransferase or alanine aminotransferase; use of highly active antiretroviral therapy; response to HCV therapy (no treatment, SVR, or nonresponse); baseline levels of FIB-4; or histologic features including inflammation, fibrosis, or steatosis. **CONCLUSIONS: On the basis of analysis of liver biopsy samples, fibrosis progression was similar between HIV/HCV-infected and HCV-infected patients; no clinical or laboratory parameters predicted disease progression.**

Keywords: Hepatitis C Disease Progression; Coinfection; Human Immunodeficiency Virus.

With the advent of highly active antiretroviral therapy (HAART), which combines various nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors, the morbidity and mortality related to human immunodeficiency virus (HIV) have significantly decreased.[1] As a result, patients are now living longer with HIV infection, and other comorbidities, and hepatic events have emerged as a key issue in the management of HIV-infected patients.[2] As a result of shared routes of transmission, coinfection with chronic HCV in those infected with HIV is common.[3]

Several studies have examined the natural history of HCV in monoinfected subjects. These have found that disease progression was associated with age at infection, male gender, overweight, excess alcohol consumption, hepatic inflammation, steatosis, and presence of fibrosis.[4–8] Conversely, treatment-induced sustained virologic response (SVR) can be associated with improved histology.[9] Although some studies assessed fibrosis progression based on estimated disease duration in cross-sectional analysis of single biopsies,[4] others used a paired biopsy approach,[5–9] comparing change in fibrosis during a known time period.

Although early reports suggested that the natural history of HCV in those coinfected with HIV was more progressive,[10,11] more recent studies suggest that fibrosis progression in those with controlled HIV is similar to those with HCV alone,[12,13] affected by excess alcohol use, age at infection, baseline fibrosis, inflammation, and steatosis as well as SVR to anti-HCV therapy[10–12,14–19] and unique factors associated with HIV therapy.[12,14,19–22] Although early studies suggested that low CD4 levels were associated with advanced fibrosis,[10,14,15] more recent data in patients without HIV suggest that advanced fibrosis might result in low CD4 rather than vice versa.[23] Studies on disease progression by paired biopsy analysis in those with coinfection suggest that 16%–50% have fibrosis progression.[15,21,22,24] However, few studies directly compare fibrosis progression by paired biopsy between those with coinfection and those with HCV alone.[25,26] To address this gap in knowledge, we performed a longitudinal cohort study to compare fibrosis progression by paired biopsy in patients with HIV-HCV and HCV alone and assessed factors associated with fibrosis progression in those with HIV-HCV coinfection.

Abbreviations used in this paper: ALP, alkaline phosphatase; APRI, AST to platelet ratio; AUC, area under the curve; HAART, highly active antiretroviral therapy; HAI, histologic activity index; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NR, non-responder; NRTI, nucleoside/nucleotide analogue reverse transcriptase inhibitor; SVR, sustained virologic response.

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Patients and Methods

Study Population

This single center study derived its population from HIV-HCV coinfected and HCV monoinfected patients seen between 1998 and 2009. All patients were aged >18 years and positive for HCV RNA by commercial assay. All those with HIV were positive for anti-HIV antibodies. Patients were excluded from analysis if they had a prothrombin time prolonged >2 seconds from control, presence of ascites, thrombocytopenia (platelet <70,000), active or recent (within 3 months) opportunistic infection related to HIV, renal failure defined as creatinine >2.5, were HBV surface antigen positive, had any other form of chronic liver disease, or had inability to give informed consent. Those with HIV and advanced disease with less than 1-year expected survival were also excluded. Alcohol abuse was defined as more than 50 g/day. Those without cirrhosis on initial biopsy were offered a follow-up biopsy to assess disease progression.

Of 306 coinfected subjects biopsied, 66 without cirrhosis at baseline underwent a second biopsy as part of a prospective study and composed the paired biopsy group. Because HCV therapy can modify disease progression,[9,16–18] we included only the 59 who were HCV treatment naïve or prior non-responders (NRs) to at least a 12-week course of therapy. Because NRs have a similar progression to those who are treatment naïve,[22] these groups were combined. During the same time period, 233 patients with HCV alone who were also treatment naïve or prior NRs underwent paired biopsy at our center as part of routine care. From this group, we retrospectively identified a control group at random by using a computer-generated algorithm matched to the coinfected group for age (±4 years) and baseline Knodell fibrosis score. In addition, we identified a more strictly defined control group matched on age, gender, race, and baseline Knodell fibrosis score.

Liver Histology

A percutaneous liver biopsy was performed in the standard fashion. Formalin-fixed, paraffin-embedded liver tissue was stained by hematoxylin-eosin and Masson's trichrome. In both coinfected and monoinfected subjects, histologic activity index (HAI) for total inflammation (piecemeal necrosis, lobular inflammation, and portal inflammation) and fibrosis was assessed by Knodell score[27] and deemed adequate for size by 1 of 2 dedicated liver pathologists (M.A.C. and A.S.M.). In those coinfected with HIV-HCV, we also used the Ishak HAI for inflammation and fibrosis[28] and the modified Brunt scoring system for steatosis[29] to assess predictors of fibrosis disease progression.

Variables Examined

At the time of initial biopsy, the following information was collected: age; gender; race; and for those with coinfection pathologic alcohol use, the presence of diabetes, hypertension, lipodystrophy, dyslipidemia, and both past and current antiretroviral use. Before biopsy, biochemical tests for complete blood count, AST, ALT, alkaline phosphatase (ALP), bilirubin, albumin, complete blood count, HCV RNA and HCV genotype were performed by commercial assays. For those with HIV coinfection, CD4 and CD8 lymphocyte counts and HIV RNA were also obtained. Coinfected patients were seen every 3–6 months. AST to platelet ratio (APRI) and FIB-4 were calculated as previously described.[30,31] This study was approved by the Office of Research Subjects Protection at the Virginia Commonwealth University Health System.

Statistical Analysis

Demographic, clinical, laboratory, and histologic data are presented as mean and standard deviation for approximately normally distributed data, median and interquartile range for skewed quantitative data, and proportions for categorical data as indicated. The primary outcome was defined as a worsening in Knodell fibrosis score between biopsies. For those with no (stage 0) fibrosis, we assessed for a ≥1-stage increase. In those with portal fibrosis (stage 1), we assessed for either a 1-stage decrease or a ≥1-stage increase. In those bridging fibrosis (stage 3), we assessed for a ≥1-stage decrease or a 1-stage increase to cirrhosis (stage 4). To account for varying time between biopsies, a fibrosis progression rate was calculated by subtracting the first biopsy score from the second and dividing by the years between biopsies. In coinfected patients, area under the curve (AUC) per unit time was computed for quantitative variables that were measured longitudinally. Sub-

Table 1. Characteristics of Coinfected Patients With a Single Biopsy and With More Than 1 Biopsy at the Time of the First Liver Biopsy

Characteristic	Single biopsy (n = 240)	Paired biopsy (n = 66)	*P* value
Age (*y*)[a]	47 (8.5)	43 (8.7)	.022
Male (*%*)[b]	78 (72–83)	73 (60–83)	.42
White (*%*)[b]	20 (15–26)	20 (11–31)	1
Weight (*kg*)[b]	79 (16)	77 (16)	.62
BMI[a]	26 (4.7)	26 (5.2)	.72
Alcohol abuse (*%*)[b]	28 (22–34)	21 (12–33)	.34
HCV genotype 1 (*%*)[b]	80 (75–85)	83 (72–91)	.72
HAART use (*%*)[b]	83 (78–87)	79 (67–88)	.47
NRTI (*%*)[b]	81 (75–86)	79 (67–88)	.73
NNRTI (*%*)[b]	33 (27–39)	30 (20–43)	.77
Protease inhibitor (*%*)[b]	45 (39–52)	38 (26–51)	.33
CD4 (cells/μL)[c]	440 (270–670)	500 (290–700)	.32
HIV <400 (*%*)[b]	65 (58–71)	51 (36–66)	.1
AST (*U/L*)[c]	58 (43–95)	72 (48–100)	.094
ALT (*U/L*)[c]	61 (42–90)	80 (50–110)	.0075
ALP (*U/L*)[c]	110 (82–140)	110 (91–150)	.24
Platelet (cells/μL)[a]	210 (84)	210 (69)	.63
APRI[c]	0.58 (0.35–1.1)	0.69 (0.46–1.3)	.25
FIB-4[c]	1.9 (1.2–3.2)	1.8 (1.1–2.9)	.55
Total HAI inflammation[a]	6.4 (2.9)	6.3 (3)	.9
Ishak fibrosis stage (*%*)[a]			.083
0	17 (12–22)	15 (8–26)	
1	36 (30–43)	36 (25–49)	
2	19 (14–25)	24 (15–36)	
3	9 (6–14)	15 (8–26)	
4	8 (5–12)	9 (3–19)	
5	6 (3–10)	0	
6	5 (3–9)	0	
Steatosis >5% (*%*)[b]	18 (13–24)	20 (11–32)	.72
Biopsy length (*mm*)[a]	20 (7.8)	22 (9.2)	.35

[a]Mean (standard deviation).
[b]Percent (95% confidence interval).
[c]Median (IQR).