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Liver Fibrosis Progression After Acute Hepatitis C Virus Infection in HIV-Positive Individuals

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Fibrosis progression after acute hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)–infected patients with follow-up >9 months became similar to reported rates from studies in chronic HIV/HCV coinfection, as measured with transient elastometry. The duration of follow-up and serum alanine transaminase correlated with liver stiffness, and short follow-up resulted in high fibrosis progression rates.

An ongoing epidemic has been observed in Europe, and recently in the United States and Australia, of sexually transmitted acute hepatitis C (AHC) virus infections among human immunodeficiency virus (HIV)–infected men who have sex with men [1]. Little is known about the course of liver fibrosis development following AHC [2, 3]. With the recent availability of noninvasive tools for repeated liver fibrosis assessment, such as transient elastography (TE), studies on the natural course of fibrosis development following AHC have become possible in larger patient groups. TE is a noninvasive technique using mechanical waves sent into liver tissue that are analyzed by an ultrasound-based algorithm using the physical relationship between the velocity of the sound waves and the stiffness of the tissue. The procedure is validated for the assessment of liver fibrosis in the setting of chronic hepatitis C virus (HCV) infection in both human immunodeficiency virus (HIV)–negative and HIV-positive populations [4]. In the present study, we used TE to investigate the effect of AHC on hepatic fibrosis progression in men who have sex with men with HIV coinfection.

METHODS

HIV-infected men with AHC were asked to participate in a prospective study to evaluate the progression of liver fibrosis progression after AHC by means of TE (FibroScan, Echosens SA). For this analysis, only participants with a chronic course of AHC or those with available TE prior to anti-HCV therapy were included in the analysis. AHC was defined according to the current consensus recommendations for the diagnosis of AHC in HIV-infected individuals [1]. Retrospective enrollment of participants was possible provided data were completely available. Overall, 29 participants were retrospectively enrolled from 2005 to 2009, and 9 were prospectively enrolled from 2009 to 2011. Conservative cutoffs were chosen for the transformation of liver stiffness values to corresponding METAVIR fibrosis scores [5, 6]: kPa ≤6.0 was assigned METAVIR fibrosis score F1, kPa 6.1–9.0 was F2, kPa 9.1–12.0 was F3, and kPa > 12.1 was F4. Furthermore no Fibrosis (F0) was assumed for all patients before acute HCV infection. Prior AHC no fibrosis (F0) was assumed. The fibrosis progression rate is a mathematical model originally developed and validated in patients with chronic hepatitis C. The model implies that liver fibrosis is a linear process over time, with increasing liver fibrosis finally leading to liver cirrhosis [7]. A fibrosis progression rate of 1 implies that liver fibrosis advances by 1 stage per 1 year of follow-up; after 4 years of follow-up, such a patient would have advanced from no liver fibrosis (F0) to liver cirrhosis (F4). Fibrosis progression rates were calculated by dividing the difference in fibrosis units by the time of follow-up. Follow-up times were calculated from the estimated time point of AHC to the time of the last TE. The estimated time point of infection was determined as follows: (1) concrete date of transmission provided by the patient or (2) the mid–time point between the last normal liver transaminase level (alanine transaminase, ALT); the first elevated ALT was assumed to be the most likely date of infection. Box plots and subsequent nonparametric testing for dichotomous variables (Mann-Whitney test) were used to analyze parameters of possible influence on liver fibrosis progression rate (sex, age, alcohol abuse [men >50 g/day]), liver steatosis, diabetes, lipodystrophy

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Table 1. Patient Characteristics

	Patients (n = 38)
General characteristics and status of HIV-infection at the time of HCV infection	
Male sex	38 (100%)
Age, y	38 (35–42)
CDC stage A/B/C	31 (82%)/5 (13%)/2 (5%)
Use of ART	26 (68%)
CD4 count, cells/μL	447 (375–604)
HIV RNA[a] $\log_{10}$	4.3 (3.6–4.9)
Detectable HIV RNA[a]	6/25 (24%)
Risk factors for liver disease	
Alcohol abuse	2 (5%)
Drug abuse	11 (29%)
Diabetes	2 (5%)
Lipodystrophy	6 (16%)
Exposure to ART (mo)	32 (0–84)
ddI	4 (11%)
d4T	7 (18%)
AZT	13 (34%)
NVP	6 (16%)
HCV infection	
Acute HCV[b]	38 (100%)
Transmission risk factors	
MSM	26 (68%)
MSM + IVDA + NDA	1 (3%)
MSM + NDA	8 (21%)
NDA	2 (5%)
Unknown	1 (3%)
Maximum ALT IU/L	588 (255–1169)
Symptoms	14 (37%)
Jaundice	4 (11%)
HCV GT 1/4/6	30 (79%)/5 (13%)/1 (3%)
HCV RNA $\log_{10}$	6.0 (5.3–6.8)
Antiviral therapy[c]	31 (82%)
Follow-up and transient elastometry	
Follow-up (y)	0.4 (0.2–0.6)
ALT <2.5 × ULN	15 (40%)
Fibrosis assessment	
Stiffness (kPa)	6.1 (5.4–7.7)
Follow-up >1 y[d] (kPa)	5.4 (3.8–5.5)
METAVIR[e] F1/2/3/4	17 (45%)/15 (40%)/5 (13%)/1 (3%)
Follow-up >1 y[d]	4(80%)/1 (20%)/0 (0%)/0 (0%)
Fibrosis progression rate (units/year)	3.6 (1.8–6.8)
Follow-up >1 y[d] (units/year)	0.3 (0.2–0.4)

Data are no. of patients and percentage or median with interquartile range.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AZT, zidovudine; CDC A/B/C, Centers for Disease Control and Prevention AIDS Classification 1993; ddI, didanosine; d4T, stavudine; HCV, hepatitis C virus; HCV GT, HCV genotype; HIV, human immunodeficiency virus; IVDA, intravenous drug abuse; MSM, men who have sex with men; NDA, nasal drug abuse; NVP, nevirapine; ULN, upper limit of normal.

[a] Plasma HIV RNA level reported only for patients not on ART; no. (%) of patients with detectable HIV RNA reported only for patients on ART.

[b] Defined according to the European AIDS Treatment Network consensus statement [1].

[c] Interferon-based anti-HCV therapy.

[d] Subanalysis for 5 patients with a follow-up >1 year.

[e] Corresponding METAVIR fibrosis score as described in the Methods section.

syndrome, time on antiretroviral therapy, and exposure to didanosine, stavudine, zidovudine, or nevirapine [8–10]) as well as potential confounders (ALT at the time of TE [11], elapsed follow-up time after AHC). Continuous variables were analyzed by scatter plots and appropriate simple regression analysis. After factoring [12] and subsequent stratified analysis, factors of potential influence were incorporated into a multiple linear regression model to estimate the adjusted and marginal effects of potential variables on fibrosis progression rate. Statistical computing was performed using PASW Statistics 18 (IBM SPSS). The study was independently reviewed by the ethics committee of Bonn University and conducted according to the Declaration of Helsinki and subsequent revisions and good clinical practices.

RESULTS

Thirty-eight male participants were enrolled into the study (Table 1). The median follow-up was 0.4 years (interquartile range [IQR], 0.2–0.6). The median fibrosis progression rate was 3.6 METAVIR fibrosis units per year (IQR, 1.8–6.8). Both duration of follow-up and serum level of ALT at the time of TE had a relevant and significant impact on the fibrosis progression rates. The higher the ALT at the time of TE, the higher the calculated fibrosis progression rate. Likewise, the shorter the time of follow-up from the estimated time point of AHC infection to the TE examination, the higher the calculated fibrosis progression rate (Figure 1). The multiple linear regression model using the identified factors ALT and duration of follow-up as regressors was able to explain 92% of the observed variance in rates of fibrosis progression ($R^2 = 0.90$). The standardized regression coefficients revealed that duration of follow-up had the strongest impact on the fibrosis progression rate, which was greater than the level of ALT (−0.9 vs 0.1). The relationship between duration of follow-up and fibrosis progression rate was proportionally elastic. Prolonging the follow-up from 1 year to 10 years would translate to a reduction of the fibrosis progression rate to approximately one-tenth of the starting value. All other potential factors, such as duration of highly active antiretroviral

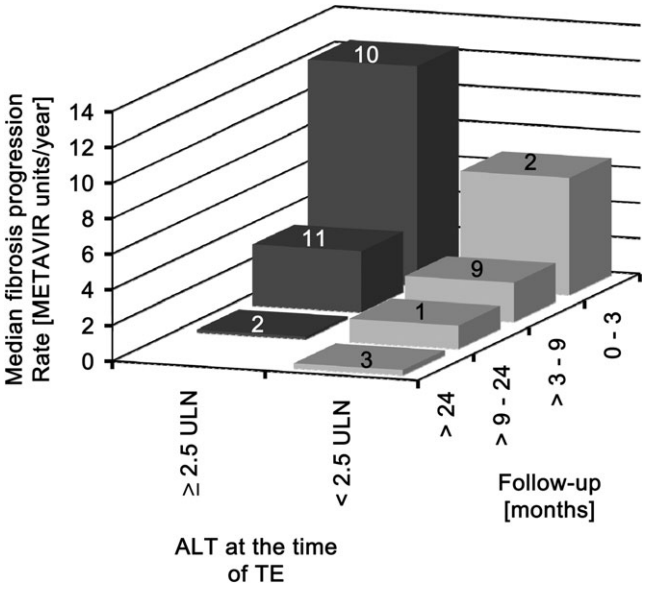

Figure 1. Median fibrosis progression rates are stratified according to length of follow-up and serum level of alanine aminotransferase (ALT) at the time of transient elastometry. The number of patients available for analysis in the respective stratum is given above each column. ULN, upper limit of normal.

therapy or use of any particular antiretroviral agent, were not associated with an increased rate of liver fibrosis progression.

DISCUSSION

Within our cohort of HIV-positive participants, we observed a strong influence of observation time on the fibrosis progression rate after AHC. Although the median fibrosis progression rate of our cohort (3.6 fibrosis units per year) was in line with previous reports on rapid liver fibrosis progression after AHC in HIV-infected participants [2, 3], it was markedly higher than that reported for participants with chronic HIV/HCV coinfection (0–0.8 fibrosis units per year) [13–15]. Similar fibrosis progression rates were observed when analysis was limited to patients with longer follow-up (0.8 units per year in participants with a follow-up >9 months).

The level of ALT at the time of TE, as has been reported previously [11], influenced fibrosis progression rates. Multivariate analysis of our study, however, revealed follow-up times to be more important than the level of ALT at the time of TE (Figure 1).

Most mathematical models for the prediction of progression of liver fibrosis rely on single time points to assess the extent of liver fibrosis and extrapolate fibrosis progression, assuming a constant rate of fibrosis progression between the time of infection with hepatitis C and the time of liver biopsy/TE. Applying such a linear model for the calculation of liver fibrosis progression cannot take into account the dynamics of inflammatory and remodeling changes occurring within the liver (eg, during acute hepatitis) [16]. More recent evidence also suggests that these models may be prone to underestimating the effect of liver fibrosis progression in certain subpopulations such as the aging patient, where liver fibrosis progression may accelerate with age [17]. Thus, a linear model to predict liver fibrosis most likely does not correctly reflect the biology of AHC. One may speculate that fibrogenesis accelerates during the early period of AHC with high liver transaminases. Once chronic HCV infection is established, fibrogenesis may continue at an individual set level. This would be far lower, however, than that observed during the weeks of acute hepatitis, because inflammation and thus fibrogenesis have declined [18]. In part, our observations may explain the high rate of liver fibrosis progression observed when using linear mathematical models to predict liver fibrosis progression in the setting of AHC. However, we were able to demonstrate the flaws of using a linear model of fibrosis progression during acute HCV infection; with a longer duration of follow-up, fibrosis progression rates converge toward those observed during chronic infection among HIV-infected participants. Thus, our findings have significant implications for patients and caregivers when discussing the urgency of treatment of AHC. Every HIV-infected patient should be advised to consider early treatment for acute HCV if spontaneous clearance does not occur [1]. However, there may be room for delaying treatment among those who prefer to wait for new HCV therapies without the risk of rapidly developing cirrhosis.

Our study does have limitations. We did not find a significant influence of other established risk factors for liver fibrosis such as alcohol abuse or diabetes, which may be explained in part by the small number of participants included with these risk factors. For ethical reasons, we used noninvasive markers to assess the degree of liver fibrosis. Even though we accounted for the level of ALT at the time of TE, we cannot exclude unknown factors within the setting of AHC that may have confounded our results. In order to overcome this, we made assumptions regarding the interpretation of TE results favoring rapid fibrosis progression, which should make our results robust against potential bias.

In conclusion, we did not find any evidence for continuing accelerated fibrosis progression rates after AHC in HIV-infected participants, which should reassure patients and caregivers regarding the risk of liver cirrhosis after AHC.

Notes

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Potential conflicts of interest. C. B. has received consultancy honoraria from Janssen-Cilag. J. C. W. has received grants from Abbott; payments for lectures including service on speakers' bureaus from BMS, Boehringer, Pfizer and Tibotec; and travel/accommodations/meeting expenses from Gilead. J. K. R. has received grants from Abbott, Merck, and Roche; fees for participation in data safety monitoring boards or scientific advisory boards from Merck, Pfizer, and Roche; advisory board memberships with Abbott, Bionor, BMS, Boehringer Ingelheim, Gilead, GSK, Merck, Novartis, Pfizer, Roche, Tibotec, and ViiV; consultancy fees from Abbott, Bionor, BMS, Boehringer Ingelheim, Gilead, GSK, Merck, Novartis, Pfizer, Roche, Tibotec, and ViiV; and payment for development of educational presentations from Abbott, Viral Ed, and Weber Shandwick. M. V. has been employed at Janssen-Cilag since June 2011. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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