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Hepatitis B or Hepatitis C Virus Infection Is a Risk Factor for Severe Hepatic Cytolysis after Initiation of a Protease Inhibitor-Containing Antiretroviral Regimen in Human Immunodeficiency Virus-Infected Patients

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In a cohort of 1,047 human immunodeficiency virus type 1-infected patients started on protease inhibitors (PIs), the incidence of severe hepatic cytolysis (alanine aminotransferase concentration five times or more above the upper limit of the normal level ≥ 5N) was 5% patient-years after a mean follow-up of 5 months. Only positivity for hepatitis C virus antibodies (hazard ratio [HR], 7.95; $P < 10^{-3}$) or hepatitis B virus surface antigen (HR, 6.67; $P < 10^{-3}$) was associated with severe cytolysis. Before starting patients on PIs, assessment of liver enzyme levels and viral coinfections is necessary.

Several cases of acute hepatitis have been reported after exposure to protease inhibitor (PI)-containing regimens (2, 10, 11, 13, 19). At least two mechanisms may be involved in drug-related hepatitis: either a toxic effect of the PIs or other antiretroviral drugs or an enhanced inflammatory response against hepatitis B virus (HBV) or hepatitis C virus (HCV) induced by an immune reconstitution (4, 18). Our report aims at estimating the incidence of severe hepatic cytolysis among patients exposed to PIs in a multicenter cohort study of human immunodeficiency virus (HIV) type 1 (HIV-1)-infected patients started on PIs, the anti-proteases cohort, named APROCO (ANRS EP11), and assessing the determinants of the occurrence of severe cytolysis.

APROCO was set up to study the clinical and immunovirological evolution in HIV-1-infected patients started on PI-containing regimens. Patients were enrolled at the initiation of PI therapy from May 1997 to July 1998 and were monitored at month 1 (M1), M4, and then every 4 months in 47 French AIDS centers. Patients eligible for this analysis were those who had a serum alanine aminotransferase (ALT) concentration under fivefold the upper limit of the normal value (<5N) at the baseline. The HBV and HCV infection statuses at the time of inclusion in the study were retrospectively recorded. Clinicians were asked to report the most recent results. For HCV and HBV surface (HBs) antigen, this was part of routine care, but this might have been performed more often if the patient had a potential risk of contamination.

Severe adverse events (i.e., events graded 3 or 4 according to the grading scheme of the AIDS Clinical Trials Group [6]), had to be reported to the sponsor within 48 h after recognition. In this classification, a case of severe cytolysis was defined as an increase in the ALT level to ≥5N. A validation committee reviewed the cases and classified them as "not related" or "related" to PIs (12). Cox regression models were used for the analysis of potential determinants of severe hepatic cytolysis.

Among the initial cohort of 1,080 patients, 1,047 (96.9 %) had a baseline ALT of <5N (median age, 35 years; proportion of men, 77%). The main HIV transmission route categories were homosexuality (39%), heterosexuality (34%), and intravenous drug use (17%). The serological status for hepatitis viruses was known for 613 patients: 26% ($n = 159$) were HCV seropositive and 4% ($n = 45$) had HBs antigen. After a mean follow-up of 5 months, severe cytolysis developed in 23 patients, yielding an incidence of 5 per 100 patient-years (95% confidence interval, 3.2 to 7.6). The median time from cohort entry to an ALT of ≥5N was 95 days (interquartile range, 34 to 121 days). Median (minimum to maximum) ALT and aspartate aminotransferase (AST) concentration (fold N) were 1.1 (0.5 to 4.8) and 1.1 (0.4 to 5.1) at the initiation of PI, 3.4 (0.6 to 85.6) and 1.8 (0.6 to 55.7) at M1, 5.3 (0.4 to 17.8) and 3.8 (0.7 to 7.7) at M4, 1.3 (0.4 to 7.8) and 1.2 (0.5 to 5.5) at M8, 2.0 (0.4 to 5.8) and 2.0 (0.5 to 4.9) at M12, 2.9 (0.7 to 7.7) and 2.6 (0.7 to 4.7) at M16, 1.2 (0.4 to 3.9) and 1.2 (0.7 to 4.1) at M20, and 1.6 (0.3 to 7.4) and 1.1 (0.6 to 3.3) at M24. It was associated with at least one clinical manifestation, mainly jaundice ($n = 6$) and abdominal pain ($n = 5$), in 11 patients (48%).

Among the 23 patients with severe cytolysis, intravenous drug use was the most frequent HIV transmission route cate-

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TABLE 1. Baseline characteristics and immunological and virological responses in 1,047 HIV-infected patients started on a PI-containing antiretroviral regimen according to occurrence of severe hepatic cytolysis during follow-up, APROCO, 1997 to 1999[a]

Characteristic or response	Severe hepatic cytolysis	
	Yes (n = 23)	No (n = 1,024)
Baseline characteristics		
Median age (yr [IQR[b]])	35 (33–39)	36 (32–43)
% Men	69.6	76.8
% Patients in the following HIV transmission route category:		
Homosexuality	4.3	39.6
Injection drug use	52.2	16.2
Other	43.5	44.2
% Patients with AIDS	30.4	18.1
Median $CD4^+$-cell count (10^6/liter [IQR])	295 (128–444)	290 (141–437)
Median $CD8^+$-cell count (10^6/liter [IQR])	1,015 (615–1,170)	838 (584–1189)
Median HIV RNA level ($\log_{10}$ copies/ml [IQR])	4.41 (3.64–5.04)	4.36 (3.63–5.07)
% Patients with ALT level, greater than upper limit of normal values	43.5	25.3
% Patients with the following duration of previous antiretroviral treatment (mo):		
0	29.0	41.0
1–12	21.0	23.0
12–24	17.0	15.0
≥24	33.0	21.0
% Patients exposed to a nucleoside analogue prior to initiation of PI		
Zidovudine	63.0	56.0
Didanosine	33.0	33.0
Zalcitabine	42.0	21.0
Lamivudine	42.0	37.0
Stavudine	29.0	24.0
% Patients prescribed a PI		
SQV	8.7	11.2
RTV	21.7	14.8
IDV	34.8	44.7
NFV	30.4	24.1
Other	4.4	5.2
% Patients receiving co-trimoxazole	30.0	34.0
% Patients HCV antibody positive	69.6[c]	24.3[c]
% Patients HBs antigen positive	21.7[c]	4.1[c]
Immunological and virological responses (M1 to M0)		
Median change in $CD4^+$-cell count (10^6/liter [IQR])	+72 (+2 to +195)	+52 (−4 to +121)
Median change in $CD8^+$-cell count (10^6/liter [IQR])	+7 (−84 to +115)	+31 (−138 to +224)
Median change in HIV RNA level ($\log_{10}$ copies/ml [IQR])	−1.84 (−2.23 to −0.86)	−1.52 (−2.09 to −0.74)

[a] Unless indicated otherwise, denominators were 23 for cases and 1,024 for patients without severe cytolysis.
[b] IQR, interquartile range.
[c] Denominators were 23 for patients with severe cytolysis and 590 for patients without severe cytolysis.

gory (52%); 16 (70%) were positive for HCV antibodies and 5 (22%) were positive for HBs antigen (Table 1). The median change between M0 and M1 was 72×10^6/liter for the $CD4^+$ cell count and -1.84 $\log_{10}$ copies/ml for the HIV RNA level. At the onset of severe cytolysis, two patients were receiving saquinavir (SQV), five patients were receiving ritonavir (RTV), seven patients were receiving indinavir (IDV), five patients were receiving nelfinavir (NFV), one patient was receiving SQV and RTV, one patient was receiving IDV and NFV, and one patient was receiving RTV and NFV. NFV had been discontinued 17 days before severe cytolysis in one patient, and no other PI was used at the onset of severe cytolysis. The initially prescribed PIs were stopped after the occurrence of severe cytolysis in 17 other patients, among whom 6 were switched to another PI and 1 was switched to nevirapine. Among these 17 patients, the ALT concentration decreased to <5N in the 13 patients for whom follow-up data were available. Death occurred in one patient with HCV-related cirrhosis, despite withdrawal of PI, 150 days after the initiation of PI therapy and 3 days after the onset of severe cytolysis. Among the five patients who continued to take PIs, the ALT concentration decreased to <5N in two patients and the ALT concentration remained at ≥5N in three patients. Complete data for variables entered in the multivariate analysis were available for 570 patients (Table 2). The patients not included were comparable for HIV transmission route category ($P = 0.99$) and baseline level of ALT ($P = 0.58$). Positivity for HCV antibodies (hazard ratio [HR], 7.95; $P < 10^{-3}$) and positivity for HBs antigen (HR, 6.67; $P < 10^{-3}$) were identified as the only risk factors for severe cytolysis. After adjustment for hepatitis virus status, we found no association between severe cytolysis and the type of PI or the response at M1 in terms of $CD4^+$ cell count and

TABLE 2. Effect of baseline characteristics and immunological and virological responses on the risk of severe cytolysis in 570 HIV-infected patients started on a PI-containing antiretroviral regimen, APROCO, 1997 to 1999

Characteristic or response	Univariate analysis		Multivariate analysis, final model[a]		
	HR	*P*	HR	95% CI[b]	*P*
Baseline characteristics					
Homosexuality vs other	0.11	0.03			
Injection drug use vs other	3.30	0.01			
AIDS vs no AIDS	1.92	0.15			
$CD4^+$-cell count (per 50×10^6/liter higher)	0.99	0.91			
$CD8^+$-cell count (per 50×10^6/liter higher)	1.01	0.53			
HIV RNA level (per l $\log_{10}$ copy/ml higher)	1.09	0.70			
ALT level > ULN vs ALT level ≤ ULN[c]	2.28	0.05			
Antiretroviral naive vs nonnaive	0.77	0.57			
Exposure to a nucleoside analogue prior to initiation of PI					
Zidovudine vs no zidovudine	1.24	0.62			
Didanosine vs no didanosine	0.93	0.87			
Zalcitabine vs no zalcitabine	2.77	0.02			
Lamivudine vs no lamivudine	1.10	0.82			
Stavudine vs no stavudine	1.24	0.63			
PI therapy					
RTV vs SQV	4.29	0.18			
IDV vs SQV	2.37	0.42			
NFV vs SQV	6.96	0.07			
Other vs SQV	5.72	0.15			
Co-trimoxazole vs no co-trimoxazole	0.79	0.60			
HCV antibody positive vs HCV antibody negative	7.35	$<10^{-3}$	7.95[d]	3.05–20.70	$<10^{-3}$
HBs antigen positive vs HBs antigen negative	6.33	$<10^{-3}$	6.67[d]	2.42–18.45	$<10^{-3}$
Immunological and virological responses					
CD4 at M1 − CD4 at M0 (per 50×10^6/liter higher	1.11	0.24			
CD8 at M1 − CD8 at M0 (per 50×10^6/liter higher)	0.98	0.42			
HIV RNA level at M1–HIV RNA level at M0 (per 1 $\log_{10}$ copy/ml higher)	0.87	0.57			

[a] The first model contained all variables with a *P* value of <0.25 in univariate analysis; only the HIV transmission route category was not included in the model due to high collinearity between this variable and HCV status. The final model was obtained from the first model after a stepwise procedure for deletion of variables (Wald test, $p > 0.05$).
[b] CI, confidence interval.
[c] ULN, upper limit of normal values.
[d] Only variable remaining in the final model after the procedure of deletion defined in footnote *a*.

plasma HIV RNA level. The interaction between HCV and HBV status was not significant.

Among the present cohort of HIV-infected patients treated with PI-containing regimens, a higher incidence of severe hepatic cytolysis was detected in patients positive for HCV antibodies or HBs antigen. In large phase III trials assessing the efficacies of PI-containing regimens (3, 5, 7–9, 15), when reported, the incidences of severe hepatic cytolysis were 2 and 3% in the groups receiving IDV (7, 15) and 9% in the group receiving RTV (3). The prevalence of HBV or HCV coinfection was never mentioned, but abnormal liver enzyme levels were a common exclusion criterion. Therefore, it is likely that coinfected patients have most frequently been excluded, and this may have precluded the detection of this adverse event and its risk factors in some of these trials. Monitoring of severe adverse events after expanded use of PIs therefore seems mandatory to confirm or assess their incidence and identify risk factors in unselected population samples.

Although an increase in the ALT concentration greater than 5N may not be considered severe from a hepatologist's point of view, it seems to be a reasonable threshold considering that it provides an assessment of hepatocellular necrosis and seems to be a reasonable threshold in the context of adverse events surveillance from international standardized toxicity tables (6).

Severe cytolysis in HIV-infected patients may be related to several causes such as drug treatment regimens that include PIs and other antiretroviral drugs, concomitant infections or neoplasms, and immune restoration, which may interact with each other. Drug-related hepatitis may be suggested by a decrease in ALT levels after withdrawal of PI treatment, a positive response upon rechallenge, and the presence of an hepatic eosinophilic infiltrate (1, 2, 10). In the present study, ALT levels decreased to normal after the withdrawal of PI treatment in some patients; however, the observation of a return of ALT levels to normal levels in other patients who continued PI treatment suggests that the drug may not have been the only cause of cytolysis.

The first cases of severe cytolysis were described in patients receiving IDV only (2, 10, 13, 19). We did not confirm these results in our study, and we suggest that a selection bias might have occurred in previous studies, related to clinical habits for prescription. Through its wide composition, APROCO may be considered fairly representative of the French population of HIV-infected patients routinely started on a PI-containing regimen and is a particular contributor to the surveillance for these adverse events. However, all patients in APROCO were started on a PI, and it was therefore not possible to compare them to patients not receiving a PI. Moreover, as patients were

not randomized to receive each PI, confounding by indication may exist, so comparisons were adjusted for other potential risk factors to avoid confounding as much as possible.

Another limitation was that only those patients with a known serologic status could be included in the multivariate analysis and a potential selection bias could tend to overestimate the excess risk associated with hepatitis status. In fact, the proportion of patients with known serologic HCV status on entry into the study was the same (both 61%) for the group of patients with AST or ALT levels of at least >1N ($n = 305$) and the group with normal liver enzyme levels ($n = 742$). It is therefore unlikely that only patients with abnormal liver enzyme levels underwent HCV antibody testing. Moreover, we performed a robustness analysis in which patients with unknown serologic status were considered HCV positive: the HR for HCV antibody-positive patients versus HCV antibody-negative patients was 2.1, which could be considered the minimal HR for severe cytolysis associated with the presence of HCV. Thus, our results clearly confirm the relationship between severe cytolysis in patients started on a PI-containing regimen and HBV or HCV infection (2, 4, 11, 18).

It was an hypothesis that restoration of immune status in patients coinfected with HIV and HCV or HIV and HBV may lead to an enhanced inflammatory response against hepatitis viruses mediated by $CD8^+$ and $CD4^+$ cells (4, 14, 18). Our data do not support the hypothesis that in patients positive for HBs antigen or HCV antibodies the likelihood of severe hepatic cytolysis is related to the intensity of the immunological response to highly active antiretroviral therapy (HAART). Nevertheless, our study had several limitations. First, a 1-month delay may be too short to assess the immunological response, and markers other than the peripheral $CD4^+$ cell count might be more relevant for study of the HCV-specific immune response (20). Second, HCV or HBV status was assessed only by serology and did not take the plasma HCV RNA or HBV DNA concentration into consideration, the latter of which is not determined as part of routine care. Nevertheless, several studies have shown that HAART does not significantly modify HCV replication (16, 21). Third, without assessment of histopathological lesions by liver biopsy, the discussion of the underlying pathologic mechanism remains speculative.

In conclusion, because nearly 90% of HCV-infected patients did not develop severe hepatic cytolysis, our data do not question the recommendation that patients coinfected with HIV and HCV be treated with HAART, according to recent guidelines on the management of HIV-infected patients (17). However, before starting these patients on a PI, assessment for liver enzyme levels and viral coinfections is necessary. In patients with HIV and HBV or HCV coinfection, careful monitoring of liver enzyme levels is suggested during the first months after the initation of such treatments. It may be hypothesized that other markers, such as HCV RNA or HBV DNA levels, might be useful to provide a better understanding of the pathophysiology of acute cytolysis in antiretroviral-treated patients coinfected with HIV and HBV or HIV and HCV.

APPENDIX

Members of the APROCO Study Group are as follows:

Scientific Committee: Steering Committee, *principal investigators* C. Leport and F. Raffi; *methodology*, G. Chêne and R. Salamon; *social sciences*, J.-P. Moatti and J. Pierret; *virology*, F. Brun-Vézinet and H. Fleury; *pharmacy*, G. Peytavin; Other members of the Scientific Committee, D. Costagliola, P. Dellamonica, C. Katlama, L. Meyer, M. Morin, D. Sicard, A. Sobel, and F. Vincent-Ballereau; Events Validation Committee of the Scientific Committee, M. Dupon, V. Le Moing, B. Marchou, T. May, P. Morlat, A. Waldner-Combernoux; *observers* to the Scientific Committee, F. Agid, F. Bourdillon, J.-F. Delfraissy, J. Dormont, J.-Y. Lacut, Y. Souteyrand, and J.-L. Vildé. Monitoring and statistical analysis were conducted by V. Cailleton, D. Carricaburu, C. Deveaud, G. Dupouy, S. Dutoit, J.-L. Ecobichon, C. Egouy, C. Jadand, P. Joly, V. Journot, S. Lawson-Ayayi, C. Lewden, B. Masquelier, W. Nouioua, G. Palmer, M. Savès, and M. Souville. Promotion was done by the Agence Nationale de Recherches sur le Sida (ANRS, Action Coordonnée no. 7). Other support was provided by the Association des Professeurs de Pathologie Infectieuse et Tropicale and associated pharmaceutical companies: J. P. Chauvin (Abbott), D. Delavelle (Boerhinger-Ingelheim), E. Dohin (Roche), B. Gallet (Bristol-Myers Squib), M.-C. Gervais (Merck Dohm Chibret), and D. Lapierre (Glaxo-Wellcome).

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