Impact of Treatment with Human Immunodeficiency Virus (HIV) Protease Inhibitors on Hepatitis C Viremia in Patients Coinfected with HIV

O. T. Rutschmann, F. Negro, B. Hirschel, A. Hadengue, D. Anwar, and L. H. Perrin

Division of Infectious Diseases and of Gastroenterology, and Laboratory of Virology, University Hospital, Geneva, Switzerland

The impact of human immunodeficiency virus (HIV) protease inhibitors on hepatitis C (HCV) viremia was assessed in 19 patients infected with both HIV and HCV. HIV and HCV RNA levels were measured before and during treatment with protease inhibitors. Before treatment, mean levels of HCV RNA were 5.3 log for HCV RNA and 5.0 log for HIV RNA. CD4 lymphocyte counts were 63/mm^3. After 6 weeks of treatment, a mean reduction of 2.1 log$_{10}$ in HIV RNA ($P < .001$) and a mean (±SE) increase of 73 (±21) CD4 and 296 (±70) CD8 cells were observed ($P < .05$). In contrast, both HCV viremia (+0.4 log ± 0.1) and alanine aminotransferase increased ($P < .04$). HCV RNA levels returned to baseline after 17 and 32 weeks of treatment. Thus, potent anti-HIV regimens with protease inhibitors may temporarily worsen HCV status despite improvement of HIV parameters.

Until recently, the prognosis of persons infected with the human immunodeficiency virus (HIV) was poor. New combinations of antiretroviral agents, including protease inhibitors, have resulted in decreased HIV RNA levels, increased CD4 cell counts, and fewer new opportunistic infections, resulting in prolonged survival [1].

Coinfection with hepatitis C virus (HCV) and HIV is frequent in injecting drug users and in transfused hemophiliacs [2]. If these persons survive longer because of better antiretroviral treatment, they may yet succumb to chronic liver disease caused by HCV. Treatments with HIV protease inhibitors may help to control HCV infection by improving immunity; in addition, HIV protease inhibitors might interact with the recently identified HCV protease [3]. However, the impact of therapeutic regimens containing HIV protease inhibitors on HCV infection is unknown. It was the aim of this trial to analyze changes in HCV viremia in HIV-infected persons treated with HIV protease inhibitors.

Patients and Methods

Patients. Patients coinfected with HCV and HIV-1 were included if they had detectable HCV viremia in plasma (Amplicor monitor kit; Roche, Basel, Switzerland) and indications for initiating HIV protease inhibitor therapy. They were prospectively followed at the outpatient AIDS clinic of the University Hospital of Geneva from May 1996 to April 1997, with clinical evaluation and blood sampling before the initiation of the protease inhibitor therapy, after 6 weeks of treatment, and every 3 to 4 months thereafter.

Immunologic and virologic parameters. CD4 and CD8 cell counts and HIV-1 RNA levels were determined at each clinical evaluation using the HIV-1 Amplicor monitor test with a lower detection limit of 200 HIV RNA copies/mm^3.

HCV viremia. Plasma samples were processed immediately after sampling at the time of HIV-1 RNA determination and kept frozen at −75°C. HCV was measured quantitatively in batches at the end of the study (HCV Amplicor monitor test; Roche).

Liver enzymes. Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured at each clinical evaluation.

Statistical analyses. Baseline values were compared with on-treatment values using Wilcoxon signed rank test (SPSS for Windows, version 5.0.1; SPSS, Chicago).

Results

Patient characteristics. Nineteen HIV-1– and HCV-seropositive patients (16 males, 3 females) were evaluated. Modes of transmission of HIV infection were intravenous drug use (16), transfusion (2), and sexual contact (1). Three patients had not received any antiretroviral agent. Sixteen patients had been pretreated for a mean of 143 weeks with one to five antiretroviral agents, including zidovudine (14), didanosine (11), zalcitabine (4), lamivudine (3), stavudine (8), and saquinavir (4).

Antiretroviral treatments. The choice of protease inhibitor therapy was determined by then-current guidelines [4], previous antiretroviral treatments, and potential interactions with concomitant medications. Nine patients were treated with ritonavir (600 mg, twice daily), 7 with indinavir (800 mg, three times per day), and 3 with a combination of saquinavir (600 mg, twice daily) and ritonavir (600 mg, twice daily). Seventeen patients received reverse transcriptase inhibitors, including zidovudine, lamivudine, or stavudine in combination with protease inhibitors.

Baseline characteristics. At inclusion, mean (±SE) HCV RNA levels were 5.27 log (±0.22), HIV RNA levels were 4.99

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Reprints or correspondence: Dr. Olivier T Rutschmann, Division of Infectious Diseases, University Hospital, 1211 Geneva 14, Switzerland (Rutschma@dminov1.hcuge.ch).

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Table 1. Evolution of HCV RNA, HIV RNA, CD4 and CD8 cell counts, and alanine (ALT) and aspartate (AST) aminotransferase levels in 19 HIV-1–infected patients treated with HIV protease inhibitors.

Parameter, mean ± SE	Baseline value	Changes at			*P**		
		Week 6	Week 17	Week 32	Week 6 vs. baseline	Week 32 vs. baseline	Week 32 vs. week 6
No. of patients	19	19	18	17			
Log HCV RNA (copies/mL)	5.27 ± 0.22	+0.37 ± 0.13	−0.16 ± 0.23	−0.14 ± 0.19	.01	.83	.02
ALT (IU/L)	57 ± 9	+17 ± 10	+23 ± 20	+19 ± 11	.04	.10	.72
AST (IU/L)	64 ± 9	+4 ± 9	+16 ± 20	−5 ± 7	.42	.38	.55
Log HIV RNA (copies/mL)	4.99 ± 0.14	−2.07 ± 0.11	−2.44 ± 0.19	−2.56 ± 0.19	<.001	<.001	.04
CD4 cells/mm^3	63 ± 13	+73 ± 21	+89 ± 18	+114 ± 28	.002	<.001	.02
CD8 cells/mm^3	456 ± 68	+296 ± 70	+244 ± 63	+197 ± 85	.001	.03	.12

* Wilcoxon matched paired test.

(±0.14) log, and CD4 and CD8 cell counts were 63 (±13) and 456 (±68) cells/mm^3, respectively. Mean ALT and AST values were 57 (±9) and 64 (±9) IU/L, respectively.

Evolution of HCV viremia. Six weeks after initiation of treatment with HIV protease inhibitor, a statistically significant mean (±SE) increase of 0.37 (±0.13) log was observed ($P = .01$; table 1). Thus, 9 patients showed an increase ⩾0.5 log, and 10 had a positive or negative variation <0.5 log in HCV RNA. After 4 months of treatment, HCV viremia returned to values slightly but not significantly ($P = .9$) below baseline with a mean decrease of 0.2 log (±0.2). After 8 months of treatment, HCV RNA values stabilized just below baseline, with a decrease of 0.1 (±0.2) log compared with baseline ($P = .8$). This pattern was observed in patients treated with indinavir or ritonavir, but the highest increases were observed in 2 patients treated with a combination of ritonavir plus saquinavir (increase in HCV RNA of 1.13 and 1.50 log, respectively, after 6 weeks of treatment).

Evolution of HIV viremia. A persistent decrease of HIV RNA was observed (mean ± SE): −2.1 (±0.1) log, −2.4 (±0.2) log, and −2.6 (±0.2) log after 6 weeks and 4 and 8 months, respectively ($P < .001$; table 1).

Evolution of CD4 and CD8 cell counts. An increase in CD4 cells was observed over time (mean ± SE): +73 cells (±21) after 6 weeks of treatment, +89 cells (±18) after 4 months, and +113 cells (±28) after 8 months of treatment ($P < .002$). The increase in CD8 cell counts was highest after 6 weeks of treatment but persisted during the follow-up period: +296 cells (±70) at week 6, +224 cells (±63) and +197 cells (±85) at months 4 and 8, respectively ($P < .03$; table 1).

Evolution of AST and ALT. No significant changes were observed in AST values over time (table 1). A statistically significant increase (17 IU/L ± 10) in ALT values was noticed at week 6. ALT values after 4 and 8 months of treatment were not statistically significantly different from baseline values.

Discussion

In this group of patients with advanced HIV infection (mean CD4 cell counts of 63/mm^3 at inclusion), with the majority (16/19) having been heavily pretreated, HIV protease inhibitors produced a major decrease in HIV RNA and an increase in CD4 and CD8 cell counts. Unexpectedly, the improvement in HIV virologic and immunologic parameters was initially associated with a significant increase in HCV RNA. HCV RNA levels remained stable over various time intervals in patients with chronic HCV infection who did not receive anti-HCV therapy [5]; thus, the initial increase observed in our patients was unexpected and most probably due to the recent modification of anti-HIV therapy.

Increase in HCV viremia was initially associated with a significant increase in ALT levels. Although our data cannot rule out a hepatotoxic effect of HIV protease inhibitors, they contrast with previously reported hepatic toxicity of protease inhibitors, which was only sporadic and usually included increases in both ALT and AST [6]. In contrast, an increase in ALT levels was also observed in HCV-infected patients who relapsed after treatment with interferon-α [7]. In these patients, elevation of ALT level was often preceded by an increase in HCV viremia and followed by a rise of the IgM anti-core antibody [7]. For the practicing physician, it is important to recognize this phenomenon, so the ALT increase in not attributed to drug toxicity, which might lead to erroneous interruption of treatment with protease inhibitors.

The initial increase in HCV RNA during the first weeks of an effective anti-HIV treatment may be linked to two pathophysiologic mechanisms. First, we observed a steep and rapid increase in CD8 cell counts, which was maximal during the first weeks of treatment with protease inhibitors in 16 of 19 patients. T cell response is crucial for the control of a number of viral infections, especially HCV [8]. Thus, an increase in the concentration of cytotoxic T lymphocytes might cause an immune-mediated lysis of HCV-infected cells, resulting in a release of HCV and increase in ALT level.

Second, endogenous interferon is known to play an important role in the control of HCV replication [9–11]. Cribier et al. [11] showed that high levels of HIV viremia were associated with high

interferon-α levels in patients coinfected with HCV and HIV. Thus, decreased HIV RNA levels could be associated with reduction in endogenous interferon-α, leading to a transient increase in HCV viremia.

Over the following months, low HIV RNA levels were maintained and CD4 cell counts continued to increase. This was associated with a return and stabilization of HCV viremia to values slightly below baseline. There is no agreement on the relation between CD4 cell counts and levels of HCV. In some studies, HCV viremia was not linked to the degree of immunosuppression induced by HIV [12, 13], whereas others clearly demonstrated an increase in HCV viremia associated with progression of immunosuppression [14, 15]. In our patients, the pattern of HCV RNA levels during the second phase of treatment suggests that the constant and persistent increase in CD4 cell counts contributed to the stabilization of HCV viremia despite the initial increase.

In conclusion, in this group of HCV- and HIV-infected patients with advanced immunosuppression, effective anti-HIV treatments resulted in an initial increase in HCV viremia that then returned to baseline values. This suggests that improvement in HIV status may temporarily worsen HCV status, either by an increased destruction of hepatocytes through cytotoxic T cells or decreased endogenous interferon. This also emphasizes that HIV protease inhibitors have certainly no direct anti-HCV activity and that improvement of immunologic parameters is not sufficient to control HCV infection. Further studies are warranted to better explore the relationship between restoration of immune function and HCV infection, and major efforts are required to develop specific anti-HCV protease inhibitors.

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