Letter

Evolution of protease and reverse transcriptase inhibitor resistance-associated mutations in HIV-1-infected protease inhibitor-treated patients with persistent low viraemia

Xavier Duval1,2, Diane Descamps2, Guillaume Breton1, Sophie Darmon3, Jean-Luc Ecobichon1, Séverine Delarue3, Gilles Peytavin6, Catherine Leport1, Jean-Louis Vildé1 and Françoise Brun-Vézinet3

1Service des Maladies Infectieuses, 2INSERM E 0357, 3Service de Virologie and 4Service de Pharmacologie Clinique, Hôpital Bichat Claude Bernard, Paris, France

*Corresponding authors: Tel: +33 1 4025 7803; Fax: +33 1 4025 8860; E-mail: xavier.duval@bch.ap-hop-paris.fr; francoise.brun-vezinet@bch.ap-hop.paris.fr

Introduction

In patients with sustained low level viraemia after having achieved undetectability, the unresolved question of changing therapy arises [1–3]. We retrospectively evaluated the selection of additional protease inhibitor (PI) and reverse transcriptase (RT) inhibitor resistance-associated mutations in PI-treated patients with persistent low viraemia.

Design

Thirteen patients receiving stavudine/lamivudine/indinavir (n=8), stavudine/didanosine/indinavir (n=1), lamivudine/indinavir (n=1), stavudine/lamivudine/nelfinavir (n=3) were selected if they presented persistent viraemia of <7500 copies/ml for at least 6 months. The period of analysis comprised the time interval between the first specimen with detectable low viral load and the last specimen. Viral load and genotyping were performed three to four times per year. Mutations were listed according to the IAS 2002 expert panel list (www.iasusa.org). Therapeutic options were determined at the time of the first rebound and at the end of the follow-up (ANRS AC-11 algorithm 2002). PI minimal concentrations (Cmin) were measured throughout the study period.

Results

At the time of the first low viraemia, median duration of HAART was 10 months (range 6–46). Median CD4 nadir and HIV viral load zenith were 192/mm³ and 88 000 copies/ml respectively.

At the end of the study period (median duration 17 months), no additional PI resistance-associated mutations were detected in six (46%) patients; additional major PI resistance-associated mutations were found in four (30%), combined with minor PI resistance-associated mutations in one patient; additional minor PI resistance-associated mutations were found in the other three patients (Table 1). At the time of the first low viraemia, nine patients carried viruses with thymidine-associated mutations, including T215Y/F in eight patients. During the study period, selection of reverse transcriptase-associated mutations occurred in patients 3 and 10. Overall, no major impact on further therapeutic options was noted in 10 (76%) patients according to the genotypic interpretation.

All indinavir receiving patients had Cmin between 30 and 450 ng/ml. Two out of the three nelfinavir-receiving patients had Cmin above 700 ng/ml.

Discussion

This study shows that accumulation of major PI resistance-associated mutations was observed in less than one-third of study patients, and had a limited impact on future drug options, arguing that complete viral suppression may not always be a prerequisite for midterm immunological and clinical benefit [3–5]. This lack of mutation selection in six patients was particularly striking in the case of the four patients receiving indinavir who had mutations neither at the time of the first low viraemia nor at the end of the follow-up, despite a mean time interval of 30 ±13 months. This
viral evolution can probably be explained to a certain extent by the pharmacovirological relationship (indinavir $C_{\text{min}} > 100$ ng/ml in the four patients remaining sensitive but <100 ng/ml in the two patients who selected mutations).

No predictive factors of resistance mutation selection could be identified. Even though maximal viral suppression should be the goal of therapy, in certain situations – especially for patients for whom treatment is both well-tolerated and well-integrated into daily life and who have CD4 cell counts above the at-risk threshold for most opportunistic infections – careful observation without treatment modification may be the preferred choice.

Presented in part at the 10th Conference on Retroviruses & Opportunistic Infections, 10–13 February 2003, Boston, MA, USA. Abstract 609.

The authors do not have commercial or other associations that might pose a conflict of interest.
References


