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Response of HIV positive patients to the long-term salvage therapy by lopinavir/ritonavir

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Abstract

Background: The cohort of 19 patients on LPV/r salvage regimen was followed for the period of up to 37.5 months. Patient's virologic response was evaluated with regard to the various baseline characteristics.
Results: A 73.7% of patients (14 out of 19) achieved viral suppression during the first three months of treatment, either complete (47.4%) or partial (26.3%). This effect was only transient in five cases (virologic rebound emerged after 9 months of treatment on average) and in nine cases the treatment was successful in the long-term analysis (HIV RNA plasma level still undetectable at 31st month of the therapy on average with maximum of 36 months).

We analyzed the link between the virologic response and possible predictive factors of treatment efficiency, such as lopinavir mutation score, various individual mutations, previous PI exposure, etc. We also describe changes in the PR sequence associated with poor response to the salvage therapy to LPV/r.
Conclusions: The results of LPV/r salvage therapy were encouraging. About 47% of patients from our study achieved stable suppression of viral replication for 31 months on average. LPV/r proved to be potent inhibitor despite unfavourable prognosis.

Keywords: HIV-1; Drug resistance; HAART; Protease inhibitors; Lopinavir; Salvage therapy

1. Introduction

Inhibitors of HIV protease (PR) represent very powerful virostatics that as a part of highly active antiretroviral therapy (HAART) revolutionized the treatment of HIV infection. However, resistance development remains main obstacle in the long-term anti-HIV treatment. Salvage therapy is designed to suppress HIV replication and improve surrogate markers of a patient who experienced numerous previous treatment regimens (Loutfy and Walmsley, 2002). Combined usage of LPV/r in this setting was described in several studies (Bongiovanni et al., 2003; de Mendoza et al., 2002).

A specific primary mutation selected by LPV/r, which would correlate with resistance phenotype (as it is the case, for example, for mutation D30N and nelfinavir) has not been determined. Instead, the set of mutations that correlates with decreased susceptibility to LPV has been characterized in samples retrieved from PI-experienced patients (Kempf et al., 2001). Cumulative number of

Abbreviations: 3TC, lamivudin; ABC, abacavir; AZT, azidothymidin (zidovudin); d4Tstavudin; ddC, dideoxycytidin (zalcitabin); ddI, dideoxyinosin (didanosin); EFV, efavirenz; HAART, highly active antiretroviral therapy; IDV, indinavir; LPV, lopinavir; LPV/r, combination of lopinavir and ritonavir (Kaletra™); NFV, nelfinavir; NVP, nevirapin; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; PR, protease; RT, reverse transcriptase; RT-PCR, reverse transcriptase polymerase chain reaction; RTI, inhibitor of reverse transcriptase; RTV, ritonavir; SQV, saquinavir

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these amino acid exchanges (L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M) is regarded as a measure of potential resistance to lopinavir treatment (lopinavir mutation score) (de Mendoza et al., 2002; Kempf et al., 2002; Masquelier et al., 2002).

Beside lopinavir mutation score, other genotypic patterns were suggested as a predictors of LPV susceptibility, such as overall number of mutations or presence of specific mutations at baseline (changes at positions 10, 54, 71, 82 as a negative and D30N, V77I, N88D as positive factors) (Bongiovanni et al., 2003; de Mendoza et al., 2002; Kempf et al., 2002; Masquelier et al., 2002).

Masquelier et al. (2002) identified several LPV susceptibility predictors not related to the protease sequence. Higher incidence of virologic failure correlated with high number of previous PIs, prior therapy with ritonavir or indinavir and low lopinavir plasma concentration, whereas better response was associated with co-prescription with efavirenz and, surprisingly, female gender and older age.

Reliable prediction of the treatment outcome based on the factors that are easily determined for individual patients (treatment history, genotypic analysis, etc.) would be advantageous for selecting suitable salvage regimen.

2. Materials and methods

Within this observational study, 19 HIV positive patients from the Clinic of Infectious Diseases, Faculty Hospital Bulovka, Prague, have been on LPV/r salvage regimen during the years 2000–2003. Patients' HIV-1 RNA plasma level was determined by a quantitative RT-PCR (Amplicor HIV-1 Monitor Version 1.5) as described previously (Reinis et al., 2001). The protease-coding region was isolated from the patient's peripheral blood mononuclear cells (PBMC) or plasma, amplified and sequenced as previously reported (Soriano, 2001; Václavíková et al., in press; Weber et al., 2002). Lopinavir mutation score was determined as a cumulative number of present mutations as follows: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M.

3. Results and discussion

3.1. Patients and treatment

Nineteen patients were undergoing LPV/r salvage regimen during 2000–2003. All subjects in the study experienced previous antiretroviral therapy; the mean number of used RTIs and PIs was 6 and 3, respectively. Baseline genotype was determined at the onset of the therapy for 16 patients. Increased frequency of resistance-associated mutations reflects prior exposure to PIs (Fig. 1). Additional characteristics are summarized in Table 1.

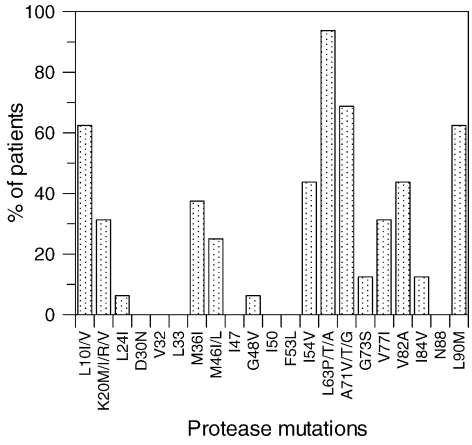

Fig. 1. Prevalence of resistance-associated mutations.

Table 1
Baseline characteristics of the patient population

Year of birth—median (range)	1960	(1939–1975)
Gender—*n* (%)		
Female	1	(5.3)
Male	18	(94.7)
Year of first HIV-registration—median (range)	1991	(1985–1998)
Other than B-subtype of HIV—*n* (%)		
C-subtype	1	(5.3)
Mode of transmission—*n* (%)		
Homo/bisexual	14	(73.7)
Heterosexual	2	(10.5)
Injecting drug use	0	(0)
Transfusion	2	(10.5)
CD4 cell count		
Median (range) [$\times 10^{-6}$ l^{-1}]	265	(7–839)
Plasma HIV RNA level		
Median (range) [$\log_{10}$ copies/ml]	5	(2.6–6.4)
HIV stage (CDC)—*n* (%)		
A	2	(10.5)
B	10	(52.6)
C	7	(36.8)
Previous exposure to antiretrovirotics in months—median (range)		
Protease inhibitors	48.5	(8.5–55)
Reverse transcriptase inhibitors	94.5	(23.5–135)
The use of individual PR inhibitors—number of experienced patients (%)		
IDV	16	(84.2)
NFV	11	(57.9)
RTV	12	(63.2)
SQV	15	(78.9)
The use of individual RT inhibitors—number of experienced patients		
3TC	19	(100)
ABC	9	(47.4)
AZT	19	(100)
d4T	16	(84.2)
ddC	18	(94.7)
ddI	7	(36.8)
EFV	10	(52.6)
NVP	8	(42.1)