Abstract #827

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Virological and Pharmacological Parameters Predicting the Response to Lopinavir/ritonavir

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BACKGROUND

Lopinavir/ritonavir (LPV/r, Kaletra) has demonstrated antiviral activity for up to four years in a variety of HIV-infected patient populations.[1-4] In an observational cohort of 792 highly ARV-experienced patients, mutations at 10 positions in protease (10, 20, 24, 33, 36, 47, 48, 54, 82, and 84), designated the ATU mutation set, were found to be associated with lowered rates of virologic response. The total number of mutations in protease appeared to predict virologic response better than any individual mutation.[5]

In a separate cohort of protease inhibitor (PI)-experienced patients treated with a ritonavir/amprenavir-based regimen, the genotypic inhibitory quotient (GIQ, ratio of trough amprenavir levels to number of baseline PI mutations) was shown to be associated with virologic response.[6]

OBJECTIVE

The purpose of this study was to analyze the relationship between virological/pharmacological parameters, including the GIQ, and the response to LPV/r in PI-experienced patients.

METHODS

Patients

116 PI-experienced patients treated in the Kaletra ATU ("Authorisation Temporaire d'Utilisation," Provisional Authorization of Use) program with baseline genotype data and during-study viral load and pharmacokinetic data available for analysis.

Statistical Methods

The efficacy variable was HIV RNA change from baseline to Month 3-6. If a patient had multiple values in Months 3 to 6, the value closest to Month 6 was used.

The effects of the number of baseline PI mutations from among positions 10, 20, 24, 33, 36, 47, 48, 54, 82, 84 in protease, lopinavir trough concentration (LPV C_{min}), and lopinavir genotypic inhibitory quotient (LPV GIQ) were assessed by linear regression. LPV GIQ was defined as the ratio of the LPV C_{min} to the number of baseline PI mutations, as previously described for amprenavir.[6] Only patients with at least one of the above PI mutations at baseline were included in GIQ calculations. For patients with multiple LPV trough concentrations, the median trough LPV concentration was used.

Analyses were conducted among all patients and among the subset of patients with at least 3 baseline PI mutations.

Baseline Characteristics

- 116 patients had at least one C_{min} value and had an HIV RNA value at Month 3-6 and were included in the analyses.
- Mean baseline HIV RNA was 4.9 $\log_{10}$ copies/mL
- Mean number of prior PIs was 3.2
- Mean number of baseline PI mutations was 2.9
- Overall decrease in HIV RNA to month 6 was –1.55 $\log_{10}$ copies/mL

All Patients

- Among all patients, number of mutations was positively correlated with HIV RNA change from baseline ($p<0.001$, Figure 1).
- LPV C_{min} ($p=0.53$, Figure 2), and LPV GIQ score ($p=0.25$, Figure 3) were not significantly associated with HIV RNA response.

Figure 1. Virologic Response by Number of Baseline Mutations

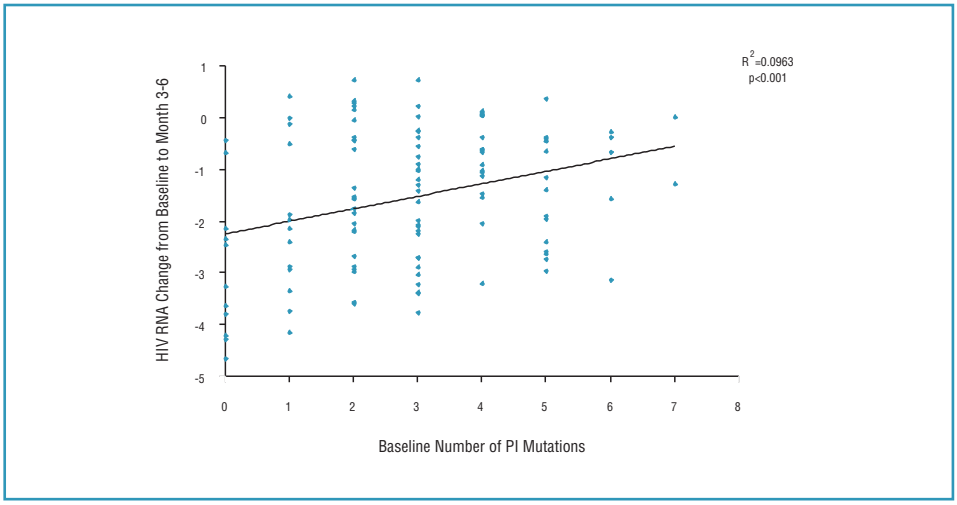


Figure 2. Virologic Response by LPV Concentration

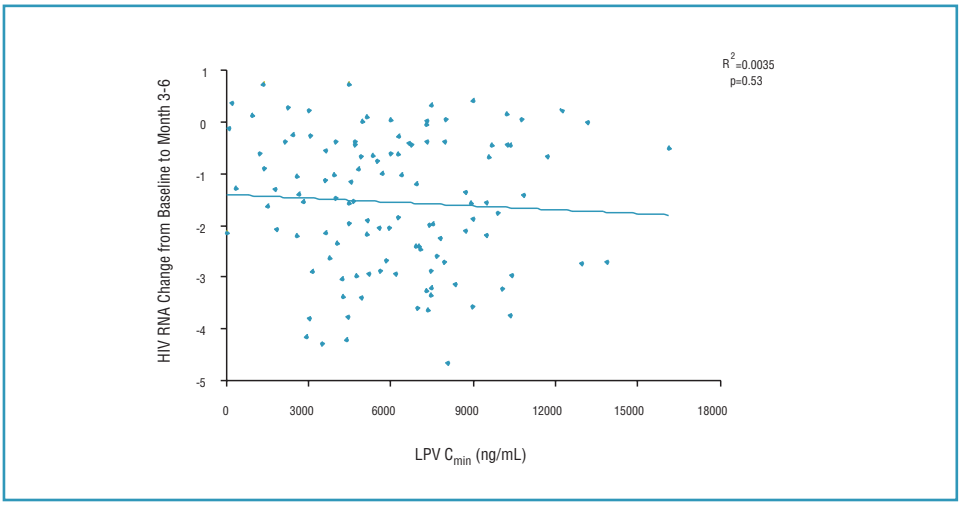
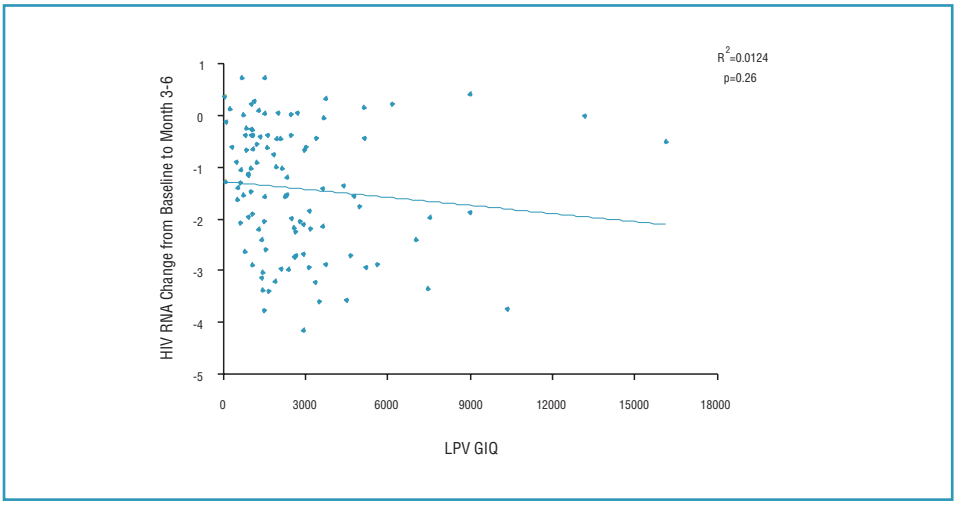


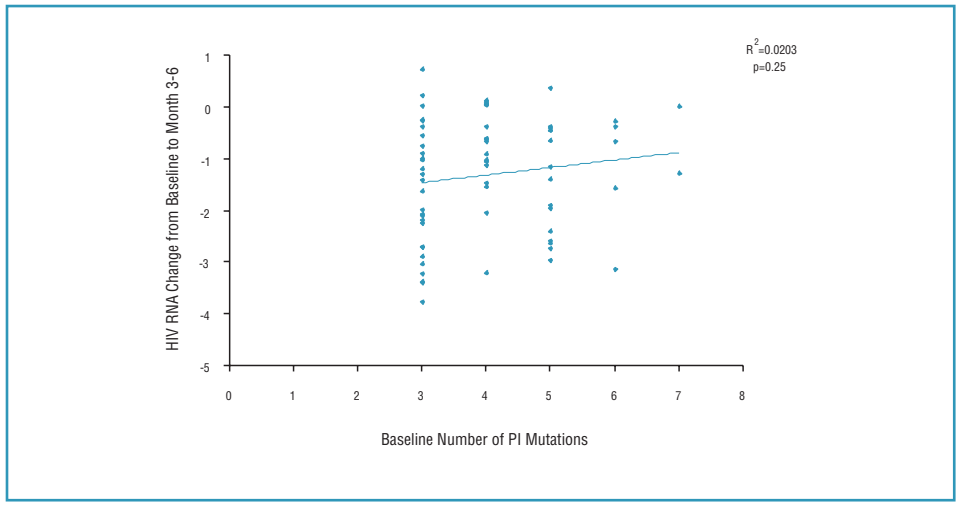
Figure 3. Virologic Response by LPV GIQ



Patients with 3 or More Mutations

- Among 67 patients with 3 or more baseline PI mutations, number of mutations was no longer a statistically significantly associated with HIV RNA change from baseline (p=0.25, Figure 4).
- LPV C_{min} was marginally significantly associated with HIV RNA response (p=0.06, Figure 5).
- However, among these patients, LPV GIQ was statistically significantly associated with HIV RNA response (p=0.025, Figure 6).
- In a stepwise selection linear regression model, LPV GIQ, but not LPV C_{min} or number of baseline PI mutations, remained a statistically significant predictor of virologic response.

Figure 4. Virologic Response by Number of Baseline PI Mutations: Patients with 3 or More Baseline PI Mutations



RESULTS *continued*

Figure 5. Virologic Response by LPV Concentration: Patients with 3 or More Baseline PI Mutations

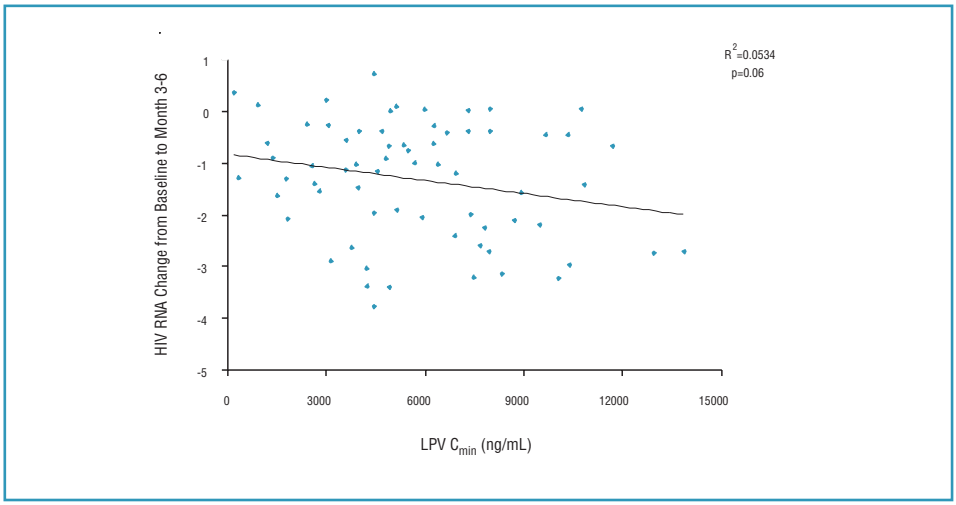
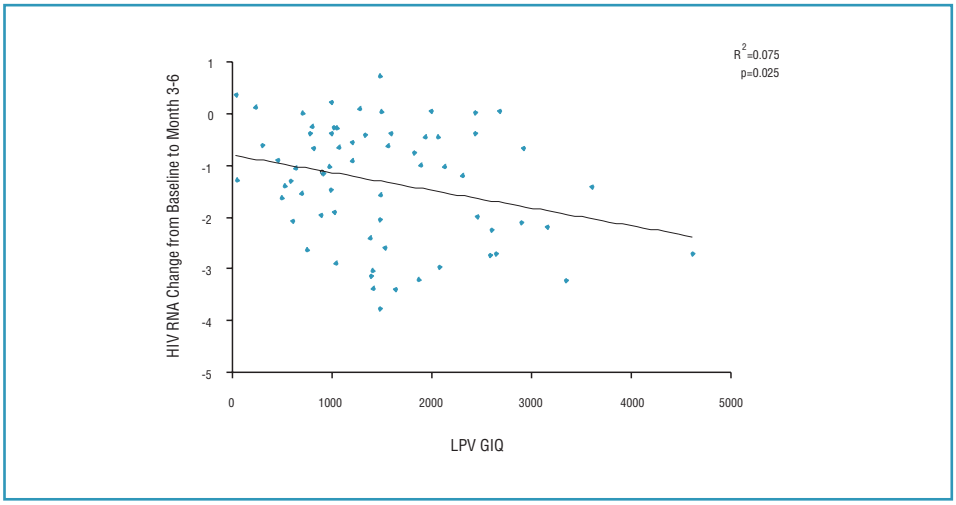


Figure 6. Virologic Response by LPV GIQ: Patients with 3 or More Baseline PI Mutations



CONCLUSIONS

- In patients with fewer baseline PI mutations, virologic response was independent of LPV drug levels.
- Among patients with more baseline PI mutations, the genotypic inhibitory quotient was a better predictor of response than baseline genotype or pharmacokinetic measures alone.
- The influence of LPV pharmacokinetic variability on response to LPV/r-based regimens is likely to be most important when significant resistance is present at baseline.

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