Poster H-570

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Virologic Response to a Once-Daily Lopinavir/ritonavir (LPV/r) Based Regimen in ARV-Naïve Patients Is Not Associated with Trough Lopinavir Concentrations or Baseline HIV RNA and CD4 Count

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r), which functions as a pharmacokinetic enhancer. LPV/r is marketed as Kaletra®. The approved adult dose of LPV/r is 400/100 mg twice-daily (BID). In a phase 2 study of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral (ARV)-naïve patients (Study 720), by intent-to-treat analysis, 67% of patients maintained HIV RNA <400 copies/mL through 5 years.[1] Once-daily (QD) dosing regimens may offer an advantage over BID regimens with regard to convenience. However, they must be carefully studied to ensure that a potential gain in convenience is not offset by a loss of antiviral potency or resistance development.

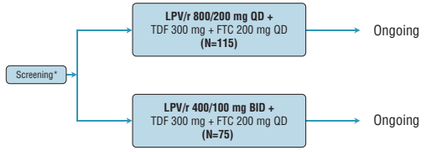
Study 418 is the first study of an entirely QD LPV/r-based regimen in ARV-naïve patients. Through 48 weeks, a regimen of LPV/r dosed at 800/200 mg plus tenofovir DF (TDF) 300 mg and emtricitabine (FTC) 200 mg QD was demonstrated to have non-inferior efficacy to the same regimen with LPV/r dosed BID, despite trough concentrations more than 60% lower with QD compared to BID dosing. The proportion of patients with HIV RNA <50 copies/mL by intent-to-treat, noncompleter=failure analysis was 70% for the QD arm and 64% for the BID arm (95% confidence interval for the difference, –7% to 20%).[2]

The current analysis was conducted to investigate whether the overall similarity of results between the two arms was also observed in specific subgroups, such as patients with more advanced HIV disease (lower baseline CD4 count, higher baseline HIV RNA) or patients with lower trough (pre-dose) LPV concentrations.

METHODS

- Randomized, open-label, multi-center, international study (Figure 1).
- Patients were ARV-naïve, with HIV RNA >1,000 copies/mL and any CD4 count.
- 190 patients were randomized 3:2 to LPV/r 800/200 mg QD (n=115) or 400/100 mg BID (n=75).
- All patients also received TDF 300 mg and FTC 200 mg QD.
- Pre-dose (trough) concentrations were obtained at Weeks 4, 8, 16, 24, and 48.

Figure 1. Study 418 Schematic



* Patients were randomized in a 3:2 ratio to one of two study arms; baseline adherence was assessed over a 5-7 day placebo lead-in period.

- Antiviral activity was assessed by the proportion of patients with HIV RNA <50 copies/mL at Week 48, by intent-to-treat, noncompleter=failure analysis.
- Immunologic response was assessed by the change from baseline to Week 48 in CD4 cell count.
- All patients with HIV RNA >500 copies/mL after Week 12 had samples submitted for resistance testing. Confirmed LPV resistance was defined as the emergence of any primary or active site mutation in protease (positions 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, 90) with corresponding reduction in LPV phenotypic susceptibility of at least 2.5-fold vs. wild-type. TDF resistance was defined as the emergence of the K65R mutation or any thymidine analog mutation (TAM, positions 41, 67, 70, 210, 215, 219) in reverse transcriptase. FTC resistance was defined by the emergence of the M184V/I mutation in reverse transcriptase.
- Associations between virologic response and LPV trough concentrations or baseline HIV RNA and CD4 cell count were assessed using logistic regression or Fisher's exact test.
- Associations between CD4 count increases and LPV trough concentrations and baseline HIV RNA or CD4 cell count were assessed by linear regression.
- LPV trough concentration for each patient was defined as the median concentration obtained from 1-5 measurements between Weeks 4-48.

RESULTS

Demographics

- Demographics and baseline characteristics were similar between treatment groups.
- Overall, 22% were female and 46% were non-white.
- The patient population had relatively advanced HIV disease, as approximately 45% of patients had baseline CD4 count below 200 cells/mm^3 and 38% had baseline HIV RNA above 100,000 copies/mL.
- Mean (range) baseline HIV RNA and CD4 cell count were 4.8 (2.6-6.4) $\log_{10}$ copies/mL and 260 (3-1006) cells/mm^3, respectively.

Efficacy

- By intent-to-treat, noncompleter=failure analysis, 70% (QD) and 64% (BID) of patients demonstrated HIV RNA <50 copies/mL at Week 48 (Figure 2), 95% CI for the difference (–7% to 20%) as shown in Figure 2.
- CD4 cell count mean increases from baseline were comparable between treatment groups as shown in Figure 3.

Figure 2. Study 418: HIV RNA <50 copies/mL (ITT NC=F)

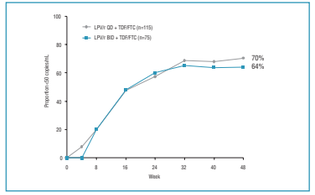
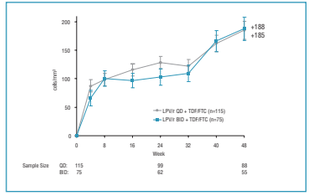


Figure 3. Study 418: CD4 Cell Count Mean (±SE) Change from Baseline



- Resistance testing was successful in 15 (8 QD, 7 BID) of 22 patients eligible for testing. Testing failed in several subjects due to low HIV RNA levels (500-1000 copies/mL). No patient had virus with LPV or TDF resistance, whereas only 3 patients (2 QD, 1 BID) had virus with FTC resistance (Table 1).

Table 1. Incidence of Confirmed Drug Resistance

Drug	QD	BID
Lopinavir	0/8 (0%)	0/7 (0%)
Tenofovir DF	0/8 (0%)	0/7 (0%)
Emtricitabine	2/8 (25%)	1/7 (14%)

Association of Response with Baseline Characteristics or Pharmacokinetics

- By logistic regression, Week 48 virologic response was not associated (p=0.72) with lopinavir trough concentration (Figure 4).
- Similarly, Week 48 virologic response was not associated with baseline HIV RNA (Figure 5) or baseline CD4 cell count (Figure 6).

Figure 4. No Association Between LPV Trough Concentration and Virologic Response

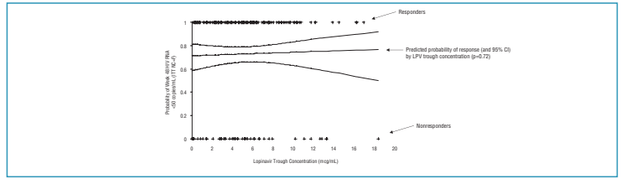


Figure 5. No Association Between Baseline HIV RNA Level and Virologic Response

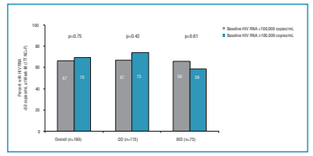
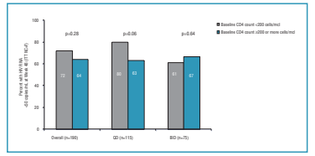


Figure 6. No Association Between Baseline CD4 Count and Virologic Response



- Correlations between CD4 count change from baseline and either LPV trough concentrations or baseline HIV RNA level were statistically significant or marginally statistically significant (Figures 7-8). However, the correlations are not likely to be clinically significant, since the slope of the relationship is relatively flat, and more importantly, because CD4 increases were larger in patients with lower LPV trough concentrations and those with higher baseline HIV RNA levels.
- There was no significant correlation between CD4 count change from baseline and baseline CD4 cell count (Figure 9).

Figure 7. LPV Trough Concentration vs. CD4 Count Change from Baseline

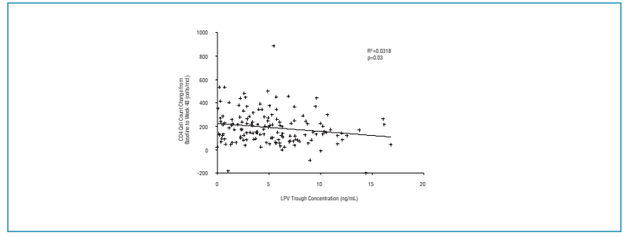


Figure 8. Baseline HIV RNA Level vs. CD4 Count Change from Baseline

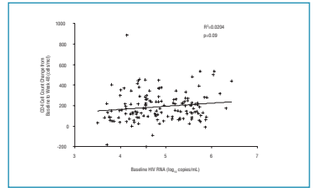
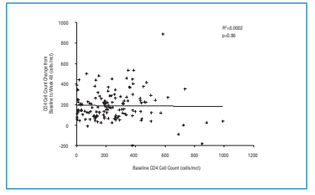


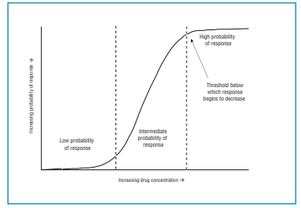
Figure 9. Baseline CD4 Count vs. CD4 Count Change from Baseline



DISCUSSION

We observed no significant association between trough LPV concentrations and virologic response in this study. The putative shape of a concentration-response curve is sigmoidal; a simple model of such a curve is illustrated in Figure 10. As drug concentration increases, the probability of response also increases, effectively reaching a maximum at a certain threshold. Results of this analysis suggest that, while the trough concentrations obtained with QD dosing of LPV/r are lower than those with BID dosing, they remain above the threshold required for optimal activity in ARV-naïve patients. For previously-treated patients with drug resistant virus, the concentration-response curve would be shifted to the right; thus, results might be different for ARV-experienced patients.

Figure 10. Concentration-Response Curve



Even though overall response was not affected by trough concentrations, we wanted to evaluate whether patients with more advanced HIV (higher baseline HIV RNA levels or lower baseline CD4 counts) might have a different rate of response with the QD regimen. No evidence of reduced response was observed.

CONCLUSIONS

- Overall through 48 weeks, a QD regimen of LPV/r plus TDF/FTC demonstrated noninferior antiviral activity to the same regimen with LPV/r dosed BID in ARV-naïve patients. No primary protease inhibitor or TDF resistance was observed in either treatment group.
- Lower LPV trough concentrations were not associated with reduced virologic or immunologic responses in this study. These data suggest that in ARV-naïve patients, the LPV concentration range achieved with QD dosing appears to remain above the dose-response threshold required for optimal antiviral activity.
- Virologic response to QD or BID LPV/r was independent of baseline HIV RNA level or CD4 cell count in this population.
- Immunologic response to QD or BID LPV/r was independent of baseline HIV RNA level or CD4 cell count in this population.

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1. Eron J, da Silva B, King M, et al. Lopinavir/ritonavir in Antiretroviral-Naïve HIV-Infected Patients: 5-Year Follow-Up. 43rd ICAAC, Chicago, IL, 2003 (poster # H-844).
2. Gathe J, Podzamczer D, Johnson M, et al. Once-Daily vs. Twice-Daily lopinavir/ritonavir in Antiretroviral-Naive Patients: 48-Week Results. 11th CROI, San Francisco, CA, February 8-12, 2004. Abstract 570.