Abstract R-180

Recommended Dose of Lopinavir/ritonavir May Be Sub-Optimal in Protease Inhibitor-Experienced Children

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ABSTRACT

BACKGROUND: Lopinavir/ritonavir (LPV/rtv, Kaletra®), the only co-formulated protease inhibitor (PI), is approved for use in children ≥6 months of age at a dose of 230 mg/m2 twice daily, with a maximum of 400 mg/dose. In adult PI-experienced patients, a target trough LPV concentration of <5.7 mg/L has been associated with lower likelihood of viral suppression. The aim of this study was to determine whether this target is relevant in children and achievable at the recommended pediatric dose.

METHODS: Prospective (52 weeks) data were collected from HIV-infected PI-experienced children (4-18y) receiving single PI-based therapy that included LPV/rtv. Baseline drug susceptibility was measured (PhenoSense®). HIV RNA viral load (VL) (Roche Amplicor) and adherence (self/family report through interactive interview) were measured at each study visit. The 12 hours pharmacokinetic (PK) study for LPV was performed within 8 weeks of resistance testing. LPV concentrations were measured by a published, validated tandem-mass spectrometric method. By multiple logistic regression, trough LPV concentration, adherence and resistance were modeled as predictors of virologic outcome (SAS). PK data were fitted to candidate PK models (USC*PACK software), and the model with the highest log-likelihood was used to simulate 1000 children (ADAPT 5 software) to determine the percentage with trough LPV concentration <5.7 mg/L after standard dosing.

RESULTS: Forty seven PI-experienced pediatric and adolescent patients on cART with boosted LPV as a single PI completed 52 weeks of study follow up. Only 51% achieved virologic suppression below 400 copies/mL. Out of 47 children 38 (80 %) had no documented resistance to the LPV and 9 (19 %) had >55 fold increase in IC50. LPV resistance (p=0.005) and trough concentration <5.7 mg/L (p=0.05) were significant independent predictors of never achieving VL <400 copies/ml during the study period. Self-reported adherence was not a significant predictor of virologic outcome. The data from 33 patients chosen at random were used to build the LPV model. The regression line of observed vs. predicted LPV had an R2 of 0.99, and a slope of 0.99. Of the remaining 14 patients, 2 had repeat PK sampling after a dose adjustment, and the data from these 16 person-events were used to validate the model. The regression line in the remaining 16 patients had a similar slope of 0.90, with increased scatter (R2 = 0.73). Visual predictive checks against all available measured concentrations showed good predictive ability of the model. LPV trough was <5.7 in 49.3% of the 1000 children simulated from this model given the standard dose of 230 mg/m2 twice daily.

CONCLUSIONS: For PI-experienced children, an LPV trough of <5.7 mg/L was statistically significantly associated with sub-optimal virologic response, independent of viral resistance and patient adherence. Furthermore, in this validated pediatric population PK model of LPV/rtv, the currently recommended dose of LPV will fail to consistently achieve this target half the time.

BACKGROUND

Lopinavir/ritonavir (LPV/rtv, Kaletra®) is the first and only co-formulated ritonavir-boosted protease inhibitor (PI) approved for use in children ≥6 months of age. The recommended doses for children who weigh more than 15 kg are 10 mg/kg or 230 mg/m2 twice daily, with a maximum of 400 mg per dose.[1,2] LPV/rtv has been shown to be effective in treating HIV infection in children including those with advanced HIV infection. Sustained undetectable viral suppression is observed in 90% to 100% of PI-naïve children, while in approximately half of PI-experienced children viral replication is not controlled. [3,4] There is also an equally important relationship between drug exposure and virologic outcome. In adult PI-experienced patients, a trough plasma LPV concentration (C_{trough}) of <5.7 mg/L measured just prior a dose has been associated with lower likelihood of viral suppression.[5] The study by Saez-llorens X, et al. has shown that the average C_{trough} in children given the currently recommended pediatric dose of LPV is 67% lower than in adults.[3] Recently published data from a Dutch study in 23 children reported a mean LPV C_{trough} in overall study cohort of 3.68 ± 2.48mg/L.[6] The purpose of our study was to determine whether the recommended LPV pediatric doses are likely to achieve a minimum target trough concentration of 5.7 mg/L, as well as to determine if this target appears relevant in children.

METHODS

This study is a subgroup analysis of a larger study on optimization of combination ART (cART) designed to assess the relationship between plasma concentrations of PIs and virologic suppression of HIV replication in HIV-infected pediatric and adolescent patients. Prospective (52 weeks) data were collected from HIV-infected PI-experienced children (4-18y) receiving single PI-based therapy that included LPV/rtv. All subjects in this study were on uninterrupted, unchanged, twice-daily dosed LPV/rtv-based cART for at least 4 weeks prior to study entry. The backbone regimen was optimized according to historic resistance data. LPV resistance was determined by the Phenosense® assay within 8 weeks of enrollment. Based on the Phenosense® results LPV resistance was defined as >55-fold increase in the IC50 of each patient's dominant HIV strain relative to that of the reference wild type strain.

METHODS

Every 3 months, HIV RNA viral load (VL) (Roche Amplicor) was measured and patient medication adherence was assessed by interview of the caregivers as well as those children older than 10 years of age and able to self-report drug intake at each study visit. Participants reported the number of missed doses in the previous 3 days. Adherence was calculated as the fraction of taken over prescribed doses. The 12 hours pharmacokinetic (PK) study for LPV was performed within 8 weeks of resistance testing. LPV concentrations were measured by a published, validated tandem-mass spectrometric method. By multiple logistic regression, trough LPV concentration, adherence and resistance were modeled as predictors of virologic outcome (SAS). PK data were fitted to candidate PK models (USC*PACK software), and the model with the highest log-likelihood was used to simulate 1000 children (ADAPT 5 software) to determine the percentage with trough LPV concentration <5.7 mg/L after standard dosing.

RESULTS

- 47 pediatric patients completed 52 weeks of study follow up. The median age was 11.0 (5.3-17.5yo). The female to male ratio was 0.96, and the majority of the children were African American (39).
- The mean self-reported adherence during the 3 days prior to the PK study visit was 92%, with 38 (77.6%) reporting 100% adherence.
- 38 (80 %) had no resistance to the LPV and 9 (19 %) had >55 fold increase in IC50. The children with documented LPV resistance had no alternative option for NNRTI or another PI due to resistance profile or inability to tolerate tablets or capsules.
- Median LPV dose was 264 mg/m2 (interquartile range 246-287 mg/m2). Patients on NNRTI (NVP, EFV) had their LPV/rtv dose increased to median 312 (286-333 mg/m2).
- 2 patients (both with LPV resistance >55 IC50 by Phenosense®) had LPV doses increased by 50% (345 mg/m2) as a part of IQ adjustment.

Prediction of Virologic Outcome

- Only 51% achieved virologic suppression below 400 copies/mL.
- By multiple logistic regression, LPV trough < 5.7 mg/L was independently statistically significantly associated with failure to achieve a plasma viral load <400 copies/mL (P=0.05), as was baseline LPV resistance (P=0.005).
- Self-reported adherence was not statistically significantly associated with virologic outcome (P=0.16).

Pharmacokinetic Modeling and Simulation

- The mean ± SD measured plasma trough LPV was 6.4 ± 3.3 mg/L; the maximum peak was 28.1 mg/L and the maximum trough was 16.8 mg/L. The data from 33 patients chosen at random were used to build the LPV model. Of the remaining 14 patients, 2 had repeat PK sampling after a dose adjustment, and the data from these 16 person-events were used to test the model.
- The final model consisted of linear absorption after a delay into a single compartment with a BSA-dependent volume and age-dependent linear elimination. Sex was not significantly related to any PK parameter estimate. The median and interquartile ranges of the Bayesian-posterior parameter estimates, using the population parameter estimates as Bayesian priors, are reported in Table 1.

Table 1. Estimated and Calculated Pharmacokinetic Parameters

Estimated Parameter (Units)	Median (Interquartile range)
Tlag (h)	0.89 (0.75, 0.93)
Ka (h^{-1})	4.37 (0.93, 6.43)
V = α + β*BSA	53.39 (25.92, 73.30)
A (L)	45.58 (22.86, 70.49)
B (L/m^2)	5.80 (0.01, 6.49)
Kel = α - β*Age	0.06 (0.05, 0.08)
α (h^{-1})	0.08 (0.06, 0.28)
β ($Y^{-1}h^{-1}$)	0.001 (0.000, 0.015)
$AUC_{0-\infty}$ (mg*h/L)	188.55 (119.78, 299.72)
Calculated Parameter (Units)	Median (Interquartile range)
CL (L/kg/h)	0.05 (0.02, 0.07)
T ½ (h)	11.83 (9.12, 14.08)

Figure 1A. Model Building Population (n=33)

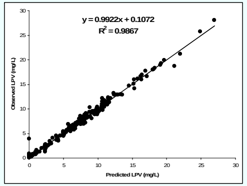

Figure 1B. Validation Population (n=16)

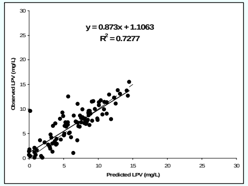

Figure 1. Linear Regression of Individual Observed on Individual Bayesian-Posterior Predicted LPV Concentrations.
Solid lines are fitted regression lines with equations displayed.
Dashed lines are the unity lines (fully superimposed on regression line in A)

RESULTS (continued)

- The quality of the fit for the model population, as measured by linear regression of observed vs. predicted LPV concentrations, was excellent (Figure 1A).
- There was more scatter when the model was fitted to the validation subset (Figure 1B) although the slope of the regression line was still close to one and the explained variability in LPV PK was high (R2=0.73).
- The visual predictive check showed that the model described the population well (Figure 2), with a slight bias towards higher trough concentrations in the upper quartile than those observed in the children.
- Of the 1000 simulated patients, 43.6% given the median dose of 264 mg/m² had a 12-hour post-dose trough of <5.7 mg/L, which was in excellent agreement with 19 (40.4%) of 48 patient visits with measured troughs.
- Using the same simulated population, 49.3% of children given the standard dose of 230 mg/m2 would fail to reach the target trough.

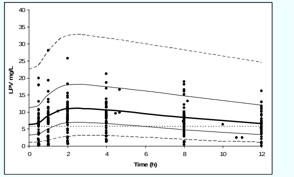

Figure 2. Visual Predictive Check of Concentration Percentiles from Model-Simulated Data (lines) Superimposed on Measured Patient Concentrations from the Entire Population of 49 patients (dots). Target trough is shown as a horizontal dotted line at 5.7 mg/L.

CONCLUSIONS

Our study has shown that for PI-experienced children, an LPV trough of <5.7 mg/L was statistically significantly associated with sub-optimal virologic response, independent of viral resistance and patient adherence. Furthermore, in this validated pediatric population PK model of LPV/rtv, the currently recommended dose of LPV will fail to consistently achieve this target in half of children. In PI-pretreated children, LPV plasma levels should be optimized in order to achieve maximal virologic suppression.

Acknowledgements

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