

Pharmacokinetics (PK) and 24-week Efficacy and Safety of Lopinavir/Ritonavir (LPV/r) in HIV-1-Infected Infants <6 weeks of Age.

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Abstract

Background: LPV/r has been proposed as primary therapy for infants, but there are no published data on PK and efficacy in infants <6 wks of age. We hypothesized young infants require higher doses of LPV/r than older children to achieve the target exposure, similar to that observed in other protease inhibitors.

Methods: A prospective, Phase I/II, open-label, dose-finding trial evaluated LPV/r at a dose of 300/75 mg/m² twice daily plus 2 nucleoside analogs (NRTI) in HIV-1 infected infants ≥14 days and <6 wks of age. Patients had a 12 hour PK evaluation performed after 2 weeks of LPV/r therapy. LPV and RTV concentrations were measured by HPLC. Both compartmental (ADAPT-II) and non-compartmental PK analyses were performed. Doses were modified to maintain LPV pre-dose (Cpre) >1mcg/mL and AUC <170 mcg*hr/mL. A virologic endpoint (VE) was reached if plasma HIV-1 RNA was >400 cps/ml at wk 16 or >4000 cps/ml thereafter. All evaluations were performed as an intent-to-treat analysis.

Results: Eight infants were enrolled at a median (range) age of 5.6 (3.6-5.9) wks and all have completed ≥24 weeks of follow up. At entry, median (range) HIV-1 RNA was 5.9 (4.7-6.5) log₁₀ cps/ml and CD4% was 45 (29-59) % One infant had unevaluable PK due to non-adherence to medications and the remaining 7 infants completed the PK evaluation at a median (range) age of 7.2 (5.5-8.0) wks at a LPV dose of 279 (246-305) mg/m² q12h. The median (range) parameters were: AUC=33.0 (27.9 - 42.0) mcg*hr/mL, C_{pre}=2.6 (1.1 - 4.9) mcg/mL, C_{max}=3.8 (2.8 - 7.2) mcg/mL, and CL/F (L/hr/m²)=9.4 (3.2 - 12.8). There were no ≥ grade 3 adverse events considered definitely related to study treatment, but 2/8 infants (25%) had grade 3 neutropenia at wk8, considered possibly related to NRTIs. None of the 8 infants reached a VE at wk 16 but 1/8 (12%) reached a VE at wk 24 due to medication non-adherence. There were no significant changes in CD4 percentage from baseline to wk24 in 4/4 infants with data available.

Conclusions: Although the LPV AUC in this population was significantly lower than seen in an older cohort ages 6 wks-6 months [median [range] AUC=67.5 [23.7 - 164.0] mcg*hr/mL, p=0.032], LPV/r-based HAART at a dose of 300/75 mg/m² BID was well tolerated and resulted in good virologic suppression with only 1/8 infants meeting a protocol-defined virologic endpoint at 24 weeks. Additional investigation is needed to understand the long term implications of the lower LPV exposure in this age group.

Background

LPV/r has been proposed as primary therapy for infants, but there are no published data on PK and efficacy in infants <6 wks of age. We hypothesized young infants require higher doses of LPV/r than older children to achieve the target exposure, similar to that observed in other protease inhibitors.

Primary Objectives

PACTG P1030

- To evaluate lopinavir/ritonavir (LPV/r) dose requirements for HIV-infected infants <6 months of age that provide systemic exposure similar to that which has been shown to be safe and effective in older children and adults.
- To determine the short-term and long-term safety and tolerance of LPV/r initiated in HIV-infected infants <6 months of age as part of a combination regimen including nucleoside analogs.

Methods

Study Design

- Prospective Phase I/II, open label, dose finding study
- Sample size: 8 evaluable infants
- Population: HIV-infected infants ≥14 days to <6 weeks of age
- Regimen: Lopinavir 300 mg/m²/Ritonavir 75 mg/m²/BID and 2 NRTIs chosen by site investigator

Pharmacokinetics

- Week 2: 12 hour LPV PK (Pre 2, 4, 8 & 12hr)
 - Infants not reaching target (Cpre >1 mcg/mL and AUC<170mcg*hr/mL) have dose increased by 50%; repeat PK performed 2 weeks later
 - Infants who do not reach target after dose adjustment discontinue treatment
- Pre-dose levels drawn every 4-12 weeks

Virologic endpoints

- HIV-1 RNA>400 copies/ml by week 16 or,
- HIV-1 RNA>4000 copies/ml after week 16

Results

Baseline Values n=8	
Median Age (Range)	5.6 wks (3.6 - 5.9)
CDC Category	6 N
	2 A
Median Viral Load (log ₁₀ copies/ml) (Range)	5.9 (4.7 - 6.5)
Median CD4% (Range)	45 (29 - 59)
Median CD8% (Range)	23 (15 - 37)

Adverse Events

- There were no Grade 3 or higher adverse events definitely related to study treatment
- Two infants had reversible Grade 3 neutropenia at week 8, possibly related to nucleoside therapy

Pharmacokinetic Parameters n=7 evaluable infants

Median (Range)	
Age at PK (wk)	7.2 (5.5 - 8.0)
Weight (kg)	4.7 (3.6-6.1)
BSA (m ²)	0.27 (0.21 - 0.33)
Dose (mg)	80 (64 - 87)
Dose (mg/m ²)	279 (246 - 305)

Median (Range)	
AUC (mcg*hr/mL)	33.0 (27.9 - 62.0)
Cpre (mcg/mL)	2.6 (1.1 - 4.9)
Cmax (mcg/mL)	3.8 (2.8 - 7.2)
CL/F (L/hr/m ²)	9.4 (3.2 - 12.8)

Results (Cont.)

Figure 1. Week 2 Lopinavir Non-Compartmental AUC in evaluable study participants compared with means from older infants (Ref 1) and adults (Ref 3).

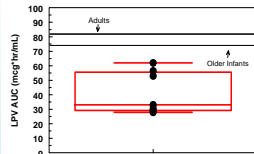
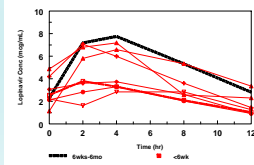
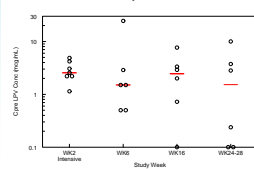


Figure 2. Week 2 Lopinavir concentrations in evaluable study participants



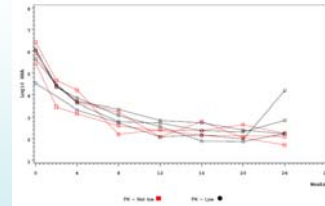
Four infants had "low" concentrations and three had "not low" concentrations, shown in reference to median concentrations for infants 6 wks-6 months (in black)¹

Figure 3. Individual and median Cpre concentrations in evaluable infants over time. All infants' Cpre were above 1.0 at WK2



Results (Cont.)

Figure 4. Log HIV-1 RNA (Log₁₀ copies/ml) over time by WK2 PK (Cmax) results (n=7)



See Figure 2 for "low" vs. "not low" definitions

Conclusions

- LPV/r-based HAART at a dose of 300/75 mg/m² BID was well tolerated
- The LPV AUC (med AUC=33 mcg*hr/mL) in this age group was significantly lower than seen in older cohorts ages 6 wks-6 months (med AUC=67.5 mcg*hr/mL) and 6 months-12 years (med AUC=76.9 mcg*hr/mL)^{1,2}
- Individual LPV pre-dose concentrations were variable, but median values were stable over time
- Virologic response did not correlate with week 2 PK results
- Despite the lower LPV exposure, viral suppression (HIV-RNA <400 copies/mL) was achieved by 7/8 infants (87%) at 24 weeks.
- Longer follow-up will help elucidate the impact of the lower LPV exposure on virologic efficacy in very young infants.

References

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