

6-Month Follow-up of Once-daily Lopinavir/ritonavir in HIV-infected Children

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Background

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r). The paediatric approved dose is 230/57.5 mg/m² twice daily. In HIV-infected children a once-daily (QD) dosing schedule may offer an advantage in terms of convenience and adherence. We studied the pharmacokinetics, tolerability and efficacy of lopinavir/ritonavir (LPV/r) QD in HIV-1 infected children in the RONDO study

Methods

20 HIV-1 infected children on stable antiretroviral therapy (ART) with a viral load <50 copies/mL for at least 6 months could enroll into the RONDO study. They received LPV/r 460/115 mg/m² QD with zidovudine and lamivudine BID. LPV/r was taken with food in the morning. Blood samples for pharmacokinetic measurements of LPV were collected at 0, 2, 4, 6, 8, 12, 18 and 24 hours after observed intake during steady state at day 14. Target for C_{min} was 1.0 mg/L. After day 14, time of intake could be changed to the evening. Single sample plasma levels of LPV/r were collected at day 28 and months 2, 3 and 6. Clinical assessment included plasma RNA levels, lymphocyte counts, chemistry, hematology, and adverse events monitoring.

Results

These are preliminary results of the first 14 patients completing 6 months of follow-up

Patients

All 14 children were treated with protease inhibitor based HAART for a median of 28.5 months. They never had to change their treatment for virological failure, and had an undetectable viral load <50 copies/mL for at least 6 months and at the screening visit.

Table 1. Patient characteristics at baseline

Characteristics	Median (IQR)
N=14, 7 boys/7 girls	
Age (years)	4.5 (3.3-9.5)
Height (cm)	109.6 (95.1-137.6)
Weight (kg)	19.9 (14.6-33.5)
Surface Area (m ²)	0.77 (0.62-1.11)
Initial lopinavir dose (mg/m ²)	456 (444-479)
Initial lopinavir dose absolute (mg)	400 (276-533)
Antiretroviral treatment	
Months on HAART, median (range)	28.5 (12-81)
LPV/r BID + AZT + 3TC	n=10
Indinavir/r + AZT + 3TC	n=3
Nelfinavir + AZT+ 3TC	n=1
Previous NRTI monotherapy	n=1 (20 months, AZT)

Pharmacokinetics

Steady state AUC (0-24h), C_{max}, T_{max} and C_{min}(24 h) of lopinavir were similar to LPV/r 800/200 mg QD in adults. C_{min}(24h) was lower than target (<1.0 mg/L) in 3/14 patients. Two of these 3 patients were 3 years and younger.

Figure 1.

Population pharmacokinetics of lopinavir 460 mg/m² in children

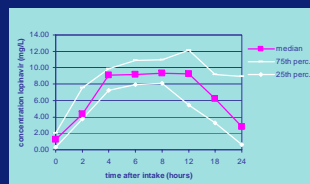


Table 2. Pharmacokinetics of lopinavir in children vs. Adult data

parameter	460 mg/m ² QD in children Median (IQR)	800 mg QD in adults Mean (± SD)
AUC (0-24 h)	158.6 (130-238.50)	164.9 (67.5)
C _{max}	11.64 (9.71-13.40)	10.9 (2.8)
T _{max}	7.25 (4.33-12.50)	6.6 (2.8)
C _{min} (24h)	2.74 (0.65-9.00)	3.62 (3.38)

Bertz et al. 9th CROI, 2002

Dose adjustment and intake with food

At day 14, C_{min} (24h) was lower than target (<1.0 mg/L) in 5 patients. On day 28, the (estimated) C_{min} (24h) of lopinavir was sufficient in 2 of these patients after time of intake changed to the evening meal (Figures 2 and 3).

In three patients, dose adjustment to 600 mg/m² (n=2) or 798 mg/m² (n=1) was necessary. However, intake with the evening meal was necessary to reach adequate plasma levels in these patients too.

In the 11 children who chose to take LPV/r with their evening meal after day 14, 44% (17/39) of available LPV plasma levels at day 28, month 2, 3 and 6 were higher than during the 24-hour curve in these children.

2 of 3 children taking LPV/r with breakfast had insufficient single plasma levels at day 28, month 2, 3 and 6.

Figure 2. LPV PK from patient 1, effect of intake with evening meal

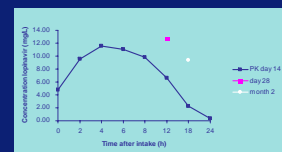
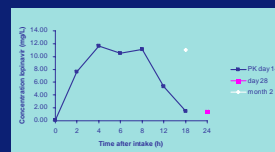


Figure 3. LPV PK from patient 3, effect of intake with evening meal



Viral load

All 14 patients had HIV-1-RNA <50 copies/mL at month 6. Three patients experienced a small blip (52-136 copies/mL) during the study period.

CD4

CD4 count remained stable over 6 months of treatment with once-daily LPV/r. At baseline, median CD4 count was 1280 *10⁶/L (= 101% of normal corrected for age) and after 6 months 1080 *10⁶/L (= 89.5% of normal), P=0.152

Adverse events

6/14 children suffered from transient mild gastrointestinal side effects. 4 patients experienced grade 1, 2 or 3 nausea and vomiting shortly after intake of LPV/r. 3 patients had mild abdominal pain and 1 patient suffered from grade 1 diarrhea. All adverse events were resolved by month 2.

Lipids

Cholesterol and triglycerides remained stable during 6 months of follow-up in patients who used LPV/r before baseline. In patients who used another protease inhibitor before the study, total cholesterol often decreased significantly (p=0.034) from 5.50 to 4.85 mmol/L (209 to 184 mg/dL). Triglycerides were also stable in the last group of patients.

Figure 4. Change in total cholesterol for LPV/r or other PI pre-study treatment

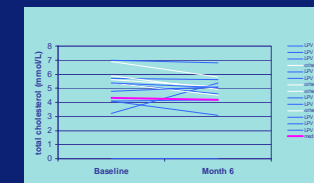
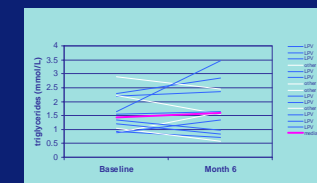


Figure 5. Change in triglycerides for LPV/r or other PI pre-study treatment



Conclusions

- Lopinavir/ritonavir 460/115 mg/m² QD in children led to the expected plasma levels compared to adult data.
- In only 3/14 patients dosage increase to 600 mg/m² or 798 mg/m² was necessary because of C_{min}(24h) below target.
- Intake with a reasonable amount of food, like dinner, is important to obtain adequate plasma levels when LPV/r is dosed once-daily in children.
- Because of high interindividual variability in plasma levels, therapeutic drug monitoring (TDM) may be useful to determine the correct dose for each child.
- LPV/r QD + 2 NRTIs provides continued viral suppression.
- Once-daily administration of LPV/r was well tolerated. Only mild transient gastrointestinal side effects were seen.
- Lipids remained stable.

Acknowledgements

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