

PHARMACOKINETICS AND 24 WEEK EFFICACY/SAFETY OF SAQUINAVIR/LOPINAVIR/RITONAVIR IN RTI PRE-TREATED CHILDREN

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Introduction

For heavily reverse transcriptase inhibitor (RTI) experienced children, response to a second-line treatment containing a single boosted Protease Inhibitor (PI) may be sub-optimal since the nucleoside reverse transcriptase inhibitor (NRTI) component may contribute little to efficacy.

Both saquinavir and lopinavir have been evaluated in clinical trials of HIV-infected children^{1,2}

In adults, stable pharmacokinetics have been shown for the combination of saquinavir, lopinavir and ritonavir³ and this combination shows synergistic interactions *in vitro*⁴

Given the potential need for multiple PI treatment to overcome RTI resistant virus, a pilot study of saquinavir plus lopinavir/ritonavir at their approved dosages was conducted in 20 RTI pre-treated children.

Methods

Single-arm open-label, two center, prospective 24 week trial of 20 RTI pre-treated children (Baseline characteristics in Table 1).

Dosage of lopinavir/ritonavir was 230/57.5 mg/m² BID, provided primarily as adult capsules (lopinavir 133/ritonavir 33 mg) but supplemented with oral solution containing lopinavir/ritonavir 80/20 mg/ml where necessary.

Dosage for saquinavir was 50 mg/kg BID provided as 200mg hard-gel capsules.

Lamivudine was added in patients who had never taken it.

HIV RNA was summarised by visit week, using the Intent to treat missing equals failure method. Clinical and laboratory adverse events were graded by severity.

Pharmacokinetics.

For 12-hour pharmacokinetic assessments, intake of medication was with standardised meals and was observed. Plasma concentrations of lopinavir, saquinavir and ritonavir were measured in all available samples by means of a validated HPLC method.

Determination of pharmacokinetic parameters (AUC 0-12h, C_{max}, C_{trough}, T_{max}, t_{1/2}) of the PIs was made by non-compartmental methods.

Results

Efficacy

Body weight increased by a median 1.5kg during the trial (p=0.002) while height increased by a median 2 cm (Table 1).

The median CD4 count and % rose by 216 cells/ μ l (IQR 143-360) and 6% (IQR 3-9) at week 24 (p<0.001) with the total count and percent shown in Table 1.

HIV RNA levels fell from baseline by -2.5 log₁₀ copies/ml (IQR -2.9 to -1.9, p<0.001) with HIV RNA levels suppressed below 400 copies/ml for 16/20 children (80%), and below 50 copies/ml for 12/20 children (60%). Lamivudine use did not affect HIV RNA suppression (p =0.17).

HIV RNA levels above 400 copies/ml at week 24 (n=4) were associated with poor adherence (3/4) and ongoing *Mycobacterium tuberculosis* (1/4).

Pharmacokinetics

Table 2 and Figure 1 show the summary pharmacokinetic profiles for saquinavir, lopinavir and ritonavir for the 19 children.

One child with concurrent rifampicin treatment was excluded from analyses correlating plasma PI pharmacokinetics with efficacy and safety.

Safety

One child had a serious adverse event (Grade 3 diarrhoea, vomiting, back pain and convulsions), which was judged to the investigator to be at least possibly related to study medication.

During the 24 weeks of the trial, median triglyceride rose from 111 mg/dl to 161 mg/dl (p=0.014) with a rise in total cholesterol from 150mg/dl to 188 mg/dl (p=0.012). The proportion of patients with total cholesterol above 200mg/dl rose from 0% at baseline to 30% at week 24 (p=0.031), while the proportion with triglycerides above 150mg/dl rose from 25% at baseline to 60% at week 24 (p=0.031). SGPT showed a significant reduction during the trial, from 24 U/L at baseline to 14 U/L at week 2 (p<0.001).

Conclusions

1. In this pilot study of dual boosted lopinavir/saquinavir/ritonavir in NRTI pre-treated children, 16/20 (80%) patients showed reductions in HIV RNA to under 400 copies/ml after 24 weeks of treatment. In addition, significant improvements in CD4 percent, weight and height were observed.

2. Saquinavir plasma levels appear higher than for Caucasian adults, where the 1000/100 mg BID dosage with lopinavir led to a saquinavir AUC of 17 mg/L.hr³. However, there may be a racial effect on saquinavir levels. For 10 Thai adults treated with saquinavir/r 1000/100 mg BID, the median AUC₀₋₂₄ was 55.3 mg.h/L⁵, which is higher than for any trial in Caucasian patients.

3. Lopinavir AUC levels from this trial also appeared to be higher than from previous trials in Caucasian children. The median AUC level for lopinavir from this trial 118mg.hr/L (dosage 230/57.5 mg/m²), compares with a mean value of 72.6 mg.hr/L for 12 mainly Caucasian children given lopinavir/r at the 230/57.5 mg/m² dosage without nevirapine⁶, and 116.4 mg.hr/L for 15 children given lopinavir/r at 300/75 mg/m².

4. To save cost and to possibly minimize PI-related metabolic complication, our observations of higher PK profiles of both saquinavir and lopinavir compared to those in Caucasians should lead to further studies to investigate whether a dose reduction of boosted PI among Thai population will be cost-effective.

Table 1 Baseline characteristics and comparison of weight, height, CD4, HIV RNA, lipids between baseline and week 24

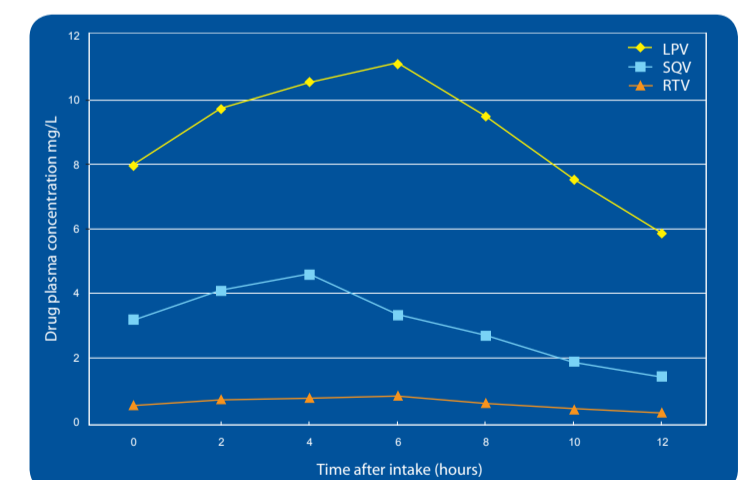
Characteristics	Baseline	Week 24	P value
Total sample size	20	20	
Gender			
Male	6 (30%)	-	-
Female	14 (70%)	-	-
Disease Stage			
A	1 (5%)		
B	17 (85%)		
C	2 (10%)		
Median age, years (IQR)	8.5 (6.9-9.9)	-	-
% with prior NRTI treatment	100%	-	-
Median duration, years (IQR)	3.4 (2.0-4.2)	-	-
% with prior NRTI treatment	35%	-	-
Median duration, years (IQR)	1.3 (0.5-2.3)	-	-
Median weight, kg (IQR)	19.5 (17.3-24.5)	20.5 (19-26)	0.002
Median height, cm (IQR)	116 (111-125)	117.5 (112.5-126.8)	< 0.001
Median HIV RNA, log (IQR range)	4.9 (4.5-5.4)	2.6 (1.7-2.6)	< 0.001
Median CD4, count, cells/ μ l (IQR)	129 (35-243)	378 (240-540)	< 0.001
Median CD4% (IQR)	6.5 (3.3 - 8.0)	11.5 (10-14.8)	< 0.001
Triglyceride (mg/dl)	111 (80.3-169.3)	161 (135.5-249.8)	0.014
Cholesterol (mg/dl)	150 (130.8-179.3)	188 (184.3-225.3)	0.012

Table 2 Summary statistics of lopinavir, saquinavir and ritonavir pharmacokinetics (n = 19)

Parameters (units)	Saquinavir	Lopinavir	Ritonavir
AUC ₁₂ (mg/L.hr)	39.4 (30.7-51.6)	118.1 (90.5-147.2)	6.9 (4.9-10.9)
T _{max} (hr)	4 (4-6)	2 (2-5)	4 (2-6)
C _{max} (mg/L)	4.9 (4.2-7.2)	11.8 (9.8-16.4)	0.9 (0.7-1.3)
C _{min} (mg/L)	1.4 (0.7-2.0)	5.9 (4.1-7.1)	0.3 (0.1-0.6)
T _{1/2} (hr)	3.2 (2.7-4.2)	6.0 (3.8-8.1)	4.8 (2.0-6.9)

Values are median (IQR)

Figure 1 12 hour profile of lopinavir, saquinavir and ritonavir levels during the trial



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