Results of the Ritonavir Superboosting Study for TB/HIV presented at CROI 2017

LOPINAVIR/RITONAVIR 1:1 SUPER-BOOSTING OVERCOMES RIFAMPICIN INTERACTIONS IN CHILDREN

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Background: Lopinavir/ritonavir 4:1 (LPV/r) is important in 1st-line antiretroviral therapy for infants. In high-burden settings, rifampicin based co-treatment for tuberculosis (TB) is often needed, but causes significant drug interactions. Superboosting LPV/r with ritonavir for a 1:1 ratio is considered effective, based on pharmacokinetic (PK) studies in 15 children.

Methods: In an open-label, prospective study at 5 South African sites, we studied super-boosted LPV/r (1:1) during rifampicin co-treatment and LPV/r (4:1) thereafter in children weighing 3-15 kg. PK was studied on 3 occasions in each child with blood drawn at baseline and 1, 2, 4, 6 and 10 h post-dose: PK1 and PK2 after 2 and 5 months of rifampicin co-treatment (LPV/r 1:1); PK3 2-4 weeks after stopping TB therapy (LPV/r 4:1). Population PK modelling was used to interpret the data. PK1 data was used to develop a structural PK model for LPV, which was applied to PK2 and PK3 data to estimate all PK parameters. The uncertainty of PK parameters was obtained through a nonparametric bootstrap (n=500) and used for simulating 10 000 *in silico* patients, assuming a 30% decrease in clearance overnight to address known diurnal variation. The percentages of model-simulated (M-PK) C_0 below 1 mg/L at PK2 and PK3 were compared for non-inferiority using a 10% delta threshold.

Results: Eighty of 96 enrolled children, completed the study (Table 1: clinical data) 31% and 9% of children were <12 months at enrolment and PK 3 respectively. TB therapy was started first in 73% children. A 1-compartment PK model with 1st-order absorption and elimination, with allometric scaling to adjust for weight, best fitted the data. No age effect was identified. The percentage (95% CI) of M-PK C_0 levels below target was 7.6% (0.4% to 16.2%) for superboosting during rifampicin co-treatment, versus 8.8% (0.6% to 19.8%) without rifampicin. The median value of their difference -1.1% (95%CI -6.9% to 3.2%), confirmed the non-inferiority of LPV exposure during super-boosting with rifampicin to standard LPV/r without rifampicin. Three deaths were unrelated to study treatments. One case of jaundice and elevated liver enzymes occurred, treatment was interrupted but not considered associated with the medication. No electrocardiograph abnormalities occurred. 82% of children had a VL<log 2.6, with no major protease resistance mutation reported in those not virally suppressed.

Conclusion: Super-boosting is safe and effective for TB/HIV co-treated children.

Table 1: Patient characteristics and clinical data at enrolment and each pharmacokinetic (PK) visit

	At enrolment	PK1	PK2	PK3
Number on study	96	92	82	80
Number uncluded in PK analysis		92	81	80
Median age in months (IQR)	18.2 (9.6-26.8)	19.1 (10.4-27.6)	23.3 (15.2-34.4)	25.0 (16.7-34.3)
Number younger than 12 months (%)	30 (31%)	27 (29%)	15 (18%)	7 (9%)
Female	52 (54%)			
Median weight in kg (IQR)	8.4 (6.7-10.3)	8.8 (7.1-11.1)	9.8 (8.5-12.2)	10.1 (8.9-12.3)
Clinical stage 4	60 (62%)			
CD4 count (x10^6/L) (IQR)	924 (466 - 1,738)		1,337 (1,019 - 1,956)	
Median CD4 percentage (IQR)	19.5 (11.6 – 25.7)		27.3 (20.5 – 32.6)	
Median HIV RNA viral load (log10 copies/mL) (IQR)	5.7 (4.6 - 6.3)		2.1 (<1.6 - 2.3)	
Number with VL<log 2.6	6 (6%)		67 (82%)	