Simulation and Exposure-Based Assessment of Pediatric Lopinavir Fixed-Dose Combination Product

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ABSTRACT

Background: The development of low-cost, solid fixed-dose combinations of LPV/r to nucleoside reverse transcriptase inhibitor (NRTI) backbones in modular unit forms (LPV/r/ABC/3TC) is greatly needed to improve both management and adherence of children especially in resource-limited settings.

Methods: The pharmacokinetic (PK) analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. INTensive and sparse PK data totaling 1394 LPV concentrations from 338 subjects, aged 2 to 24 years old, were analyzed. For 3TC, ABO, and ZDV, a total of 927 patients with 3820 concentrations, 188 patients with 1232 concentrations, and 756 patients with 3131 concentrations were included.

Results: The simulations indicated that the WHO dosing recommendations resulted in more than 95% of subjects with Cmin > 1 mg/L. However, using the recommended drug ratios, the combination dosage for the 6-kg weight band (LPV/200 mg, 20 mg RTV, 15 mg 3TC and 30 mg ABC) resulted in high ZDV concentrations associated with high risk of neutropenia. This dosing reduction targeted LPV Cmin >1 mg/L, in more than 95% of subjects and did not adversely affect efficacy the NRTIs target level.

Conclusions: The proposed dosage fully corresponded to the WHO guidelines for all NRTIs. The pharmacokinetic (PK) analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. The patients characteristics are summarized below.

INTRODUCTION

The 2013 WHO Antiretroviral Guidelines recommend lopinavir/ritonavir (LPV/r) for all HIV-infected children under three years of age. Current LPV/r liquid formulations (short shelf-life, cold chain requirement, large storage volumes) and high birth to adolescence have poorly-tolerated taste, significant toxicity, severe logistical constraints of combinations is that the metabolic pathway and elimination routes of each component differ, and that the mechanisms involved in absorption, distribution, metabolism and excretion do not mature at the same rate from birth to adolescence.

METHODS

We executed a meta-analysis of the pediatric PK data available for LPV, ABC, ZDV, and 3TC to model the pharmacokinetics of each drug and performed simulations using the original FDA dosing recommendations, the 2010 WHO weight band dosing, and its subsequent modifications. We estimated the proportions of children above efficacy targets and the proportion of children at risk of toxicity for each of the weight bands.

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RESULTS

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Population pharmacokinetic models

Dosing simulations

PHARMACOKINETIC SIMULATION RESULTS

The optimal exposure targets were defined as follows:

- LPV: >95% subjects with Cmin>1 mg/L; >75% subjects with Cmin>3 mg/L (continuous curve) and WHO guidelines (discontinuous curve) without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined with a Markov Chain Monte Carlo procedure.

- ABC: >95% subjects with AUC0-24 > 8 mg.h/L
- ZDV: >75% of subjects with AUC0-24 > 19.2 mg.h/L (associated with neutropenia) and the dosing curve corresponds to the WHO guideline simulations. The horizontal lines represent the targets: > 95% and >75% of patients that reach >1 mg/L and >3 mg/L, respectively.

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A pediatric fixed-dose LPV/3TC/20D or ABC formulation can be developed to achieve targeted therapeutic levels for all ARV components with the following dosing through the full range of weight bands. Each unit would contain 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to the weight bands, i.e. 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic doses would be 2, 3, 4, 5, or 6 units of this formulation twice daily.

CONCLUSIONS

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