Introduction

Simplification of antiretroviral therapy by reducing dosing frequency can enhance compliance to medication in both HIV-1 infected adults and children. Very little is known on once daily (q24h) use of nucleoside analogues in HIV-infected children.

Objectives

1. To compare the plasma pharmacokinetics (PK) of lamivudine (3TC) 8 mg/kg q24h with 4 mg/kg q12h and abacavir (ABC) 16 mg/kg q12h with 8 mg/kg q24h.

2. To evaluate age-related differences in the PK of these agents.

Methods

Study design

- Open label, single sequence, two-period cross-over study
- Children were enrolled 1 to 4 age strata of 2-6 years old and 6-13 years old
- Intensive plasma sampling was performed at steady state during use of 3TC q12h and ABC q12h and 4 weeks after switch to q24h.

Pharmacokinetic parameters of 3TC and ABC were determined by a validated method of HPLC.

Non-compartmental PK was applied. Geometric mean ratio (GMR) with 90% confidence intervals (CI) of PK parameters were calculated to compare q24h and q12h regimens.

Intra-BLA measures were performed at baseline and routinely during the follow-up.

Results

Baseline

- 24 HIV-1 infected children using antiretroviral combination therapy were enrolled.
- Median age (range): 5.5 (1.1-12.8) years; median body weight (range): 22.5 (12.8-35.9) kg

- 20/24 children (10 girls/10 boys) had complete PK data of 3TC (N=19) and/or ABC (N=14).

Inclusion criteria

- Children aged 2-13 years and confirmed HIV-1 infection
- Aged <13 years old willing to switch 3TC and/or ABC to q24h use
- Clinically stable
- HIV-1 RNA load suppressed, or non-suppressed but relatively low (400-20,000 copies/mL)
- CD4 - cell count stable or declining on study entry
- Children and/or parents able to give informed consent

Inclusion criteria

- Age 2-13 years and confirmed HIV-1 infection
- Using combination treatment consisting 3TC 4 mg/kg q12h and/or ABC 8 mg/kg q12h, willing to switch 3TC and/or ABC to q24h use
- Clinically stable
- HIV-1 RNA load suppressed, or non-suppressed but relatively low (≤20,000 copies/mL)
- CD4 - cell count stable or declining on study entry
- Children and/or parents able to give informed consent

PK of 3TC (Tables 1 and 2)

- The GMR of AUC0-24 q24h vs. q12h significantly exceeded 1.0, suggesting non-inferiority in terms of PK of the q24h regimen vs. q12h regimen.
- For Cmax, q24h vs. q12h, GMR approximates 2, suggesting linear pharmacokinetics of 3TC.

PK of ABC (Tables 1 and 2)

- AUC0-24 of ABC q12h vs. q24h significantly exceeded 1.0, suggesting non-inferiority in terms of PK of the q24h regimen vs. q12h regimen.
- For Cmax of q24h vs. q12h regimen, GMR exceeded 2, possibly reflecting more than dose-proportional pharmacokinetics of ABC.

These PK data, in addition to good 12-week efficacy, and safety suggest feasibility of q24h use of 3TC and ABC in HIV-1 infected children ≥2-<13 years old with suppressed viral load.

Therapeutic equivalence of q24h regimens of 3TC and ABC should be further evaluated in a comparative clinical trial.

Conclusions

- This PK data, in addition to good 13-week efficacy, and safety suggest feasibility of q24h use of 3TC and ABC in HIV-1 infected children ≥2-<13 years old with suppressed viral load.
- Therapeutic equivalence of q24h regimens of 3TC and ABC should be further evaluated in a comparative clinical trial.
- The tendency for lower plasma levels of 3TC in younger children poses the question, if higher doses of 3TC should be applied in younger children.

Data on intracellular PK may contribute to the evaluation of the clinical relevance of this finding.