Objectives

Pooled data from existing studies were used to describe the drug-drug interaction between rifabutin (RBN) and HIV-protease inhibitors (PI) to optimize doses in patients with HIV-associated tuberculosis (TB), with concurrently administered PIs.

Methods

13 published studies were pooled, and a population analysis approach was used to develop a pharmacokinetic model for RBN and its main active metabolite 25-O-desacetyl rifabutin (des-RBN) in NONMEM v 7.3

Drug-drug interaction with PIs in healthy volunteers and HIV/TB patients were explored

Covariates were tested collectively using a linearized stepwise covariate model (lin-SCM) building method in PsN

Final estimated model parameters were used to calculate the expected average steady-state concentrations (Cmax_ss) for RBN and steady state peak concentration (Cmax_p) for RBN and des-RBN in Berkeley Madonna software

Identify targets with an Cmax_p<0.18 g/L, which were associated with acquired rifamycin resistance and dose-related toxicity, respectively⁴, ⁵, ⁶

Results and Discussion

Data from 251 subjects:
- mean age, 36.4 years
- 138 male [75%]
- 163 HIV-infected [65%]
- 144 HIV-infected patients who had TB [57.3%]
- totaling 7749 pharmacokinetic observations

PIs included were RTV, SQVR, DRVIR, IND, LPVIR, NEF, AMPTR

Rifabutin doses ranged from 150 mg OD to 600 mg every 3 days

The final model is presented in Figure I and II

Key parameters of RBN affected by PI interaction were:
- CL/F reduced by 76% to 100%,
- Q/F reduced by 47%,
- V2/F increased by 606%,
- CL/F reduced by 76% to 100%,
- CLm/F was reduced by 35% to 76%,
- Cle/F increased by 224%
- V/F reduced by 47%

Key parameters of des-RBN affected by PI interaction were:
- CLm/F was reduced by 35% to 76%,
- V/F reduced by 67% to 240%

These changes resulted in overall increased exposure to RBN in TB/HIV patients with PIs by 210% and by 280% with ritonavir-boosted PIs.

Conclusions

150 mg once daily of RBN together with nonboosted or ritonavir-boosted PIs, provides similar or higher exposure to 300 mg once daily of RBN alone (Table I)

A combined Cmax_p<1 g/L would be uncommon in the average TB/HIV patients, unless dosage was 300 mg once daily with ritonavir-boosted PI (Table II)

300 mg every three days of RBN with ritonavir-boosted PI achieves an equivalent Cmax_p, but intermittent doses of RBN are not supported by current guidelines

References