Pharmacokinetic Evaluation of Liposomal Amikacin for Inhalation in Patients with Treatment-Refractory Nontuberculous Mycobacteria Lung Infection

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ABSTRACT

Background: Descriptive liposomal amikacin inhalation is in the lack of effective treatment options. NAAM is a novel antibiotic pharmacodynamic development for the treatment of NTM lung infection. Amikacin systemic exposure after LAI administration was characterized by a population pharmacokinetic model to describe pharmacokinetic disposition and safety.

Methods: Data from a subset of patients enrolled in a phase 2, randomized, double-blind study assessing LAI efficacy and safety with pretreatment NTM lung infections (TRD-012). The primary endpoint was the change from baseline on the full semi-quantitative scale for mycobacterial culture to 3 months.

Results: The population mean estimate for the apparent total serum clearance (CLt/F) was 34.2 L/h in the current study compared with values ranging from 58.8 L/h to 106.2 L/h in previously published studies. The systemic bioavailability of LAI is sufficiently low to result in minimal systemic exposure relative to the site of aerosolization and is potentially therapeutic for patients with NTM lung infection.

STUDY OBJECTIVES

The objectives were to characterize systemic exposure after LAI administration using a population pharmacokinetic (PK) model to elucidate therapeutic disposition in serum and sputum.

STUDY DESIGN

Data: 153 patients (96 male, 57 female). 64% of patients were randomized to the treatment group, and 36% to the placebo group. Patients received LAI 590 mg QD or placebo via nebulizer added to their ongoing stable multidrug regimen for 84 days followed by up to 84 days of open-label LAI 590 mg QD for treatment-refractory NTM lung infection with persistently positive mycobacterial cultures while on stable multidrug therapy.

Eligibility Criteria:
- Patients ≥18 years of age
- History of nontuberculous mycobacteria lung infection
- No history of treatment-refractory NTM lung infection
- No history of bronchiectasis

Endpoints:
- Serum concentrations of amikacin
- Sputum concentrations of amikacin

Study Assessments:
- Measurement of serum concentrations of amikacin and sputum for the concentration-time (C-T) curve at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours postdose

Population PK Analysis Methods:
- All data transformation was performed using a qualitative instruction of SAS Version 9.4 software (SAS Institute, Inc.)
- Steady-state serum concentration-time data were transformed using logarithmic transformation
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- Patient PK analysis was performed using the NONMEM computer program (version 7.5)
- The final model was selected based on the lowest objective function value and the lowest value of the scaled absolute residuals
- The systemic bioavailability of LAI is sufficiently low to result in minimal systemic exposure relative to the site of aerosolization and is potentially therapeutic for patients with NTM lung infection.

CONCLUSIONS

- Amikacin systemic exposure was well tolerated in patients with treatment-refractory NTM lung infection.

REFERENCES


ACKNOWLEDGMENTS

The authors acknowledge Connexion Healthcare (Newtown, PA) for providing editorial, layout, and design support for this manuscript. The authors confirm they had full access to all the data in the study and that the study sponsor had no role in the analysis or interpretation of data. The study was funded by a Co-operative Research and Development Agreement between Insmed Incorporated and NIAID/NIH.

DISCLOSURES

-Christopher M. Babuša is involved in clinical trials sponsored by and is a consultant for Insmed Incorporated.

Poster presented at the 2015 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 17-21, 2015, San Diego, California.