Pharmacokinetic Profile of Liposomal Amikacin for Inhalation in Patients With Cystic Fibrosis and Chronic Pseudomonas aeruginosa Infection

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BACKGROUND
- Liposomal amikacin for inhalation (LAI) is a novel amikacin formulation in development for the treatment of serious pulmonary infections such as chronic Pseudomonas aeruginosa and nontuberculous mycobacterial lung infections in patients with cystic fibrosis (CF) [1].
- Amikacin is currently approved for intravenous (IV) and intramuscular use but is associated with a high rate of systemic side effects [2].
- The unique LAI formulation encapsulates amikacin in charge-neutral highly biocompatible liposomes (~0.3 μm) able to penetrate deeply into airway secretions and within P. aeruginosa biofilms, delivering the antibiotic where it is most needed, while possessing a longer lung half-life compared with nonliposomal antibiotics that may allow for once-daily dosing [3,4].
- Previous pharmacokinetic (PK) studies of LAI observed high amikacin-sputum levels simultaneously with low systemic amikacin levels, consistent with: a) prolonged exposure to amikacin in the lungs, and b) increased systemic clearance as amikacin exposure increases [5].
- LAI has demonstrated potent P. aeruginosa killing, while virulence factors secreted by LAI appear to trigger additional amikacin release.
- A phase 3 trial, Clinical Evaluation of ARIKAYCE™ (CLEAR)-108 study, compared the efficacy, safety, and tolerability of LAI vs tobramycin inhalation solution (TIS), USP, over 3 treatment cycles for the management of P. aeruginosa infection in patients with CF. LAI administered once daily was found to be comparable to TIS in cycles 1, 2, and 3: 7.66 (4.12) mg•h/L, 7.81 (4.34) mg•h/L, and 8.17 (4.08) mg•h/L, respectively (Figure 3). Amikacin exposure to amikacin as measured by mean serum AUC_{0-24} ranged from 7.66 (4.12 mg•h/L) to 1.15 (0.746) mg/L, an increase of 30%–70% compared with those treated with TIS.
- The majority of adverse events (AEs) associated with LAI were respiratory in nature and decreased from treatment cycle 1 to treatment Cycle 3, suggesting decreasing frequency of treatment-associated AEs with continued use of LAI.

STUDY OBJECTIVE
- This study evaluated the PK of LAI in the serum, urine, and sputum of patients with CF and chronic P. aeruginosa lung infection who participated in the CLEAR-108 study to determine the systemic exposure of patients to amikacin.

METHODS
- Data for PK analysis were taken from patients participating in the CLEAR-108 clinical trial.
- CLEAR-108 was a phase 3 international study involving 302 patients with CF randomized 1:1 to 3 cycles (28 days of treatment followed by 28 days off treatment) of once-daily LAI 590 mg delivered via a customized investigational nebulizer (PARI Pharma GmbH) or twice-daily TIS 300 mg delivered via a PARI LC Plus nebulizer.
- Key eligibility criteria for CLEAR-108 included: a confirmed diagnosis of CF, forced expiratory volume in 1 second (FEV1) ≥25% predicted, age ≥6 years, chronic P. aeruginosa infection, no history of use of inhaled antibiotics for 28 days prior to screening, and tolerance to TIS.
- The PK analysis population was defined as patients who received ≥3 dose of LAI and had ≥3 serum PK assessment (n = 29). The PK of LAI in serum, 24-hour urine, and sputum was assessed.

RESULTS
- The PK analysis included 29 patients from CLEAR-108, with a median age (range) of 13 (6-36) years and median body mass index (range) of 17.5 (11.8-23.1) kg/m² (Table 1).

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Mean ± SD</th>
<th>Median (range)</th>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (51.7)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>14.1 (6.12)</td>
<td>13 (6-36)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>42.0 (14.6)</td>
<td>39.9 (12-74.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>152 (96.0)</td>
<td>156 (101-180)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>17.4 (2.9)</td>
<td>17.5 (18.2-21.5)</td>
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<tr>
<td>Ideal body weight, kg</td>
<td>47.6 (18.6)</td>
<td>53.3 (34.6-75)</td>
</tr>
<tr>
<td>CrCl, ml/min/1.73 m²</td>
<td>136 (35.6)</td>
<td>134 (46.5-96)</td>
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- A total of 184 sputum, 29 urine, and 167 sputum samples were available for analysis.
- C_{max} (mean (standard deviation)) C_{max} of amikacin at Days 1, 57, and 113 was 1.15 (0.746) mg/L, 1.08 (0.72) mg/L, and 1.09 (0.741) mg/L, respectively (Figure 1). Serum amikacin concentrations vs. time since last dose are shown in Figure 2.

- Sputum concentrations: median concentrations of amikacin in sputum collected 0 to 1 hour postdose on Day 1 of Cycles 1, 2, and 3 are shown in Figure 4.
  - All median concentrations were ~300 to 500 times higher than the maximum observed serum concentration of 3.0 mg/L. Substantial variability was observed in the sputum data.
  - Biological availability: mean bioavailability for Cycles 2 and 3, relative to Day 1 of Cycle 1, was estimated to be 60.8% and 72.1%, respectively.

REFERENCES

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CONCLUSIONS
- In this study, LAI PK data were best described by a 3-compartment model (i.e., lungs, serum, and urine), with first-order absorption from lungs and a linear elimination process.
- The low systemic bioavailability of amikacin after LAI administration results in minimal systemic exposure compared with published data from other studies on parenteral administration of amikacin, which has been associated with nephrotoxicity and ototoxicity.
- These results are consistent with previous LAI PK data [1,2].
- Compared with previous PK data from patients with CF receiving IV amikacin 30 mg/kg daily, PK results from this study show that LAI treatment is associated with:
  - C_{max} levels >100-fold lower than those seen with IV amikacin
  - AUC_{0-24} levels 29-fold lower than those seen with IV amikacin
- Overall, substantial variability was seen in the sputum PK data.

DISCLOSURES
John Paul Clancy, MD, has served on the Arikayce Clinical Program Steering Committee.
Michael Konstan, MD, has served on the Arikayce Clinical Program Steering Committee and has served on the Advisory Committees for Genentech, Gilead, Novartis, Savara, and Vertex.
Isabelle Faja, MD, PhD, has received research contract support from Insmed Incorporated, has received a research grant from Actelion and has served on advisory boards for Gilead and Vertex.
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