Association of lumefantrine pharmacokinetics and resistance selection following artemether-lumefantrine treatment in children with and without HIV in Uganda

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Background

• Artemether-lumefantrine (AL) is the most widely used artemisinin-based combination therapy (ACT) in sub-Saharan Africa.
• It is essential to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ACTs in vulnerable populations at risk of suboptimal dosing.
• We developed a population PK/PD model using data from a previous study of AL in HIV-uninfected and HIV-infected children living in a high-transmission region of Uganda (Parikh et al, Clin Infect Dis, 2016).
• HIV-infected children were on either efavirenz (EFV), nevirapine (NVP), or lopinavir-ritonavir (LPV/r) based antiretroviral regimens, with daily trimethoprim-sulfamethoxazole (TS) prophylaxis.
• In this high transmission setting, reinfection was extremely common, and our wide range of lumefantrine exposure allowed us to more fully explore the relationship between recurrent parasitemia and drug exposure.
• We assessed selection for resistance in two key parasite transporters, pfcr1 and pfmdr1, over a 42-day follow-up to ascertain how drug exposure impacts resistance genotype and recurrence risk.

Methods

• For the population PK analysis, n=277 children with n=364 malaria episodes were included (Table 1).
• A population PK model for lumefantrine was developed using nonlinear mixed effects modeling with a qualified installation of NONMEM®. Population and individual model parameters were estimated using the stochastic approximation expectation maximization (SAEM) method followed by Monte Carlo importance sampling (IMP).
• Drug exposure response models were developed using time-to-event (TTE) analyses with new infections captured as independent events. The exposure metric was the concentration of lumefantrine at the time of event (microscopically-detectable recent parasitemia) or when censored at 42 days.
• The first TTE model included all patients with a malaria infection and compared hazards in children with and without HIV (n=274 children with n=355 malaria episodes).
• The second TTE model included only patients with microscopically-detectable recurrent infections (either recrudescence or new infection) within the 42-day follow-up period for which genotyping information was available (n=176).

Table 1: Patient characteristics for population PK cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV-uninfected children</th>
<th>EPV-based ART</th>
<th>LPV/r-based ART</th>
<th>NVP-based ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria episodes, no.</td>
<td>Overall</td>
<td>186</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>% Episodes in male children</td>
<td>53.2</td>
<td>33.3</td>
<td>35.3</td>
<td>53.2</td>
</tr>
<tr>
<td>Weight, kg, median (range)</td>
<td>14.1 (9.60 – 27.0)</td>
<td>18.0</td>
<td>15.4</td>
<td>16.0</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>3.58 (1.26 – 7.91)</td>
<td>6.00</td>
<td>4.50</td>
<td>4.50</td>
</tr>
<tr>
<td>Parasite density, geometric mean, parasites/μL (95% CI)</td>
<td>15 (256 / 3922)</td>
<td>11 (720 / 6523)</td>
<td>4 (86 / 37)</td>
<td></td>
</tr>
</tbody>
</table>

Results

Population PK of lumefantrine in the setting of antiretroviral therapy

A two-compartment population PK model with first-order absorption provided the best fit to the data and also estimated the effect of age on bioavailability and the effect of antiretroviral therapy on lumefantrine clearance.

Figure 1. Lumefantrine exposure by treatment arm. Lines represent the median predicted lumefantrine concentration. Lumefantrine is metabolized by cytochrome P450 (CYP) 3A4.

• Lopinavir/ritonavir is a potent CYP 3A4 inhibitor, which significantly increases lumefantrine exposure.
• Nevirapine and HIV-uninfected children have identical lumefantrine exposure.
• Efavirenz induces CYP 3A4, which dramatically decreases lumefantrine exposure.

Risk of recurrence by HIV-status

C50 is defined as the concentration of lumefantrine that reduced the risk of recurrence by half on a log-scale.

Figure 2. Cumulative probability of malaria over time in patients by HIV status. Median hazard and 95% CI.

HIV-infected children on daily TS were less likely to present with recurrent parasitemia compared to HIV-uninfected children.

Post-treatment period of chemoprophylaxis by treatment arm

Figure 3. Period of chemoprophylaxis (PoC) in patients by antiretroviral therapy. Reference subject was an HIV-uninfected patient with a median time to recurrence of 35 days following AL. HIV+ children on NVP had a PoC of 51 days. HIV+ children on LPV/r had a PoC of 58 days. Despite equivalent lumefantrine exposure (Fig 1), HIV-infected children on NVP plus daily TS had a PoC 16 days longer than HIV-uninfected children.

Figure 4. Cumulative probability of malaria over time in patients by pfcr1 K76T genotype. Median hazard and 95% CI.

K76 wild-type (less sensitive) parasites were more likely to cause recurrent infection.

Lumefantrine C50 by recurrent pfcr1 K76T genotype

Figure 5. Lumefantrine C50 in patients by recurrent K76T genotype. Reference subject had a K76 wild-type infection with a median lumefantrine C50 of 120 ng/mL. K76 wild-type (less sensitive) parasites were able to survive lumefantrine concentrations 3.5X higher than 76T mutant (more sensitive) parasites.

Conclusions

• TS prophylaxis provides significant protection against malaria in those with HIV; the independent effect of TS on post-treatment prophylaxis is evident through our assessments of lumefantrine PK over time.
• Significant selection was demonstrated for pfcr1 N86 and pfcr1 K76 wild-type parasites (less sensitive to lumefantrine).
• No evidence of selection was seen for pfmdr1 Y184F.

Acknowledgements

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