High risk of neutropenia in HIV-infected children following treatment with artesunate-amodiaquine for uncomplicated malaria in Uganda

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Abstract

Background: Artemisinin-based combination therapies are rapidly being adopted for the treatment of malaria in Africa, but there are limited data on safety and efficacy among HIV-infected populations.

Methods: We compared malaria treatment outcomes between cohorts of HIV-infected and HIV-uninfected children in Uganda followed for 29 and 18 months, respectively. Malaria was treated with artesunate plus amodiaquine and outcomes assessed using standardized guidelines. HIV-infected children received trimethoprim-sulfamethoxazole prophylaxis and an antiretroviral therapy according to current guidelines.

Results: Thirty-five malaria episodes in 26 HIV-infected participants and 278 malaria episodes among 134 HIV-uninfected children were treated with AS/AQ. All HIV-infected children were treated with AS/AQ over the same time. There was a trend towards lower risk of recurrent malaria among those receiving AS/AQ compared to those not treated with AS/AQ (45% vs. 6%, respectively, p = 0.041). All neutropenia episodes in HIV-uninfected children were mild to moderate severity while 10% of neutropenia episodes in the HIV-infected cohort were severe or life-threatening (<750/mm3). Among HIV-infected children, the risk of neutropenia was significantly higher in those receiving antiretroviral therapy (73% vs. 26%, p = 0.008). We compared the risk of severe clinical events in HIV-infected children during the period of neutropenia to HIV-infected controls not treated with AS/AQ over the same time. There was a trend towards a higher risk of any significant clinical event in subjects treated with AS/AQ compared to those treated with AS/AQ (37% vs. 13%, p = 0.16).

Conclusions: Amodiaquine plus artesunate was highly efficacious for malaria treatment in HIV-infected children, but associated with a high risk of neutropenia, especially in the setting of concurrent antiretroviral therapy. Findings highlight an urgent need for evaluation of alternative antimalarial therapies in HIV-infected individuals.

Study design

• Prospective study comparing efficacy and safety of AS/AQ for the treatment of uncomplicated malaria in 2 cohorts of Mulago Hospital, Kampala, Uganda

• 601 healthy children 1–10 yrs randomly recruited from the community in Nov 04–Apr 05

• 300 HIV-infected children aged 1–10 yrs enrolled from a designated HIV clinic in Kampala, Uganda

Follow-up

• Standardized evaluation for clinical malaria

• Blood smear for patients with fever (subjective or T >=38°C) in previous 24 hrs

• Malaria: fever + malaria parasites

Follow-up (cont’d)

• Association between HIV and neutropenia 14 days following treatment with AS/AQ

Results

Baseline characteristics

<table>
<thead>
<tr>
<th>Trait</th>
<th>HIV-infected cohort (n=35)</th>
<th>HIV-uninfected cohort (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs</td>
<td>3.5 ± 2.6 yrs</td>
<td>3.6 ± 1.8 yrs</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>21/35 (60%)</td>
<td>202/258 (78%)</td>
</tr>
</tbody>
</table>
| Clinical consequences on neutropenia

• Neutropenia in HIV was likely due to:

– Increased risk of clinical events

– Nested case-control study comparing ART-naive children with neutropenia and HIV-uninfected children

– Relative risks of recurrent malaria, CD4-related events, and CD4-related events in the HIV-infected children

Response to AS/AQ therapy

<table>
<thead>
<tr>
<th>Trait</th>
<th>HIV-infected cohort (n=35)</th>
<th>HIV-uninfected cohort (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia of mild severity</td>
<td>14/35 (40%)</td>
<td>15/253 (6%)</td>
</tr>
<tr>
<td>Neutropenia of moderate severity</td>
<td>7/35 (20%)</td>
<td>10/253 (4%)</td>
</tr>
<tr>
<td>Neutropenia of severe severity</td>
<td>2/35 (6%)</td>
<td>9/253 (7%)</td>
</tr>
</tbody>
</table>

• Alternative antimalarial therapies should be identified for HIV children if these findings are confirmed.

• Clinical consequences on neutropenia

– Nested case-control study comparing clinical events in HIV-infected children treated with AS/AQ with neutropenia at age, CD4-related neutropenia

– Risk of pneumonia in those with neutropenia (43% vs. 19%, p=0.008)

Summary

• AS/AQ efficacious for treatment of malaria in HIV-infected and uninfected children

• Trend towards lower risk of recurrent malaria due to re-infection among HIV-infected children

• AS/AQ should be avoided in HIV-infected children

• Increased risk of clinical events

• Neutropenia in HIV was likely due to:

– Clinical consequences on neutropenia

– Increased risk of clinical events

– Association between HIV and neutropenia

– Relative risks of recurrent malaria, CD4-related events, and CD4-related events in the HIV-infected children

– Alternative antimalarial therapies should be identified for HIV children if these findings are confirmed.