Dose Adjustments of Efavirenz Based on Therapeutic Drug Monitoring Maintains Virologic Suppression in HIV-Infected Children and Adolescents

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BACKGROUND
- Important efavirenz (EFV) pharmacokinetic interpatient and intrapatient variability exists, in particular in children and adolescents (Ref: Higgins NM et al. 8th INCPHT, 2008 # 8);
- Therapeutic drug monitoring (TDM) of EFV is done every 3 months in children and adolescents followed at the CHU Sainte-Justine (Montréal);
- EFV target concentrations are between 1 and 4 mg/L;
- In adults, EFV dose reductions in patients with high concentrations tends to decrease the risk of discontinuation due to toxicity (Ref: van Luin M et al. JAIDS; 2009; 52(2): 240-5).

STUDY OBJECTIVES
- Primary: Describe the pharmacokinetic, virologic, immunologic and clinical outcomes of EFV dose adjustments based on TDM in HIV – infected children and adolescents;
- Secondary: Describe the virologic outcomes and CNS adverse effects in patients with subtherapeutic and supratherapeutic EFV concentrations.

METHODS
- Retrospective study
- Inclusion criteria
  - HIV infected patients < 18 years of age
  - Followed at CHU Sainte-Justine
  - On an antiretroviral regimen containing EFV
  - EFV TDM done between June 2006 and December 2009
- Data collection
  - Database review of EFV concentrations, viral load and CD4+ results (done every 3 months at the same time)
  - Central nervous system adverse effects collected by retrospective review of clinic visit notes
  - Genotypes available in patients with virologic failure
- Pharmacokinetic sampling and analysis
  - TDM samples taken within the dosing interval, at random times
  - Validated LC/MS/MS assay used to quantify EFV concentrations (inter-assay CV 5.2%, limit of quantification 0.05 mg/L)
- Statistical analysis
  - Descriptive statistics using medians and interquartile ratios
  - Comparison of mean EFV concentrations in patients with or without virologic failure at 6 months using Mann-Whitney test

RESULTS

PATIENT DEMOGRAPHICS AT 1ST TDM (n=31)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (IQR) unless otherwise specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12 (10 - 14)</td>
</tr>
<tr>
<td>% Male</td>
<td>64.5 %</td>
</tr>
<tr>
<td>% Black</td>
<td>83.8 %</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>16.1 %</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>38.6 (32.9 - 49.1)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.28 (1.16 – 1.44)</td>
</tr>
<tr>
<td>EFV dose (mg)</td>
<td>600 (400 - 600)</td>
</tr>
<tr>
<td>EFV dose (mg/kg)</td>
<td>10.7 (9.6 - 12.4)</td>
</tr>
<tr>
<td>Time on EFV (years)</td>
<td>2.6 (0.2 – 4.3)</td>
</tr>
<tr>
<td>% viral load &lt; 50 copies/mL</td>
<td>84 %</td>
</tr>
<tr>
<td>CD4+ (cell/mm³)</td>
<td>630 (480 - 851)</td>
</tr>
<tr>
<td>Indication TDM</td>
<td></td>
</tr>
<tr>
<td>% Control / % Toxicity</td>
<td>89.4 / 1.4</td>
</tr>
</tbody>
</table>

PHARMACOKINETICS OF EFAVIRENZ

- EFV concentrations (n=31 patients, 283 samples):
  - median (IQR) 2.58 (1.69 – 4.08) mg/L
  - range 0.05 – 30.7 mg/L
  - median (range) time post-dose: 12.8 (1.25-24) hours

EFAVIRENZ DOSE ADJUSTMENTS

29 dose adjustments prescribed in 12 patients
- 92.3% due to supratherapeutic concentrations
- 15% of these subsequently gave therapeutic concentrations
- 3 patients needed multiple dose reductions

Dose increases (n=16, from 11 patients)
- 62.5 % dose despite therapeutic concentrations (likely related to increased body weight)
- 18.8% due to subtherapeutic concentrations
- 66% of these subsequently gave therapeutic concentrations
- Overall, only 9.7% of subtherapeutic concentrations were followed by a dose increase

SUPRATHERAPEUTIC EFAVIRENZ CONCENTRATIONS

- 4/31 patients had virologic failure
- All had subtherapeutic EFV concentrations and suspected non adherence
- 3 patients did not have dose increases and the one that did (↑ by 400 mg) had persistent virologic failure
- 3 patients developed reverse transcriptase mutations conferring EFV resistance

DISCUSSION / CONCLUSIONS

- Suboptimal EFV concentrations are frequent in children and adolescents;
- Dose reductions in patients with high EFV concentrations maintain virologic suppression and decrease CNS adverse effects;
- It may be warranted to be more aggressive with dose adjustments to prevent virologic failure and CNS adverse effects.

ACKNOWLEDGMENTS

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