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

Nancy L. Sheehan[1,2,3], Valérie Lamarre[4,5], Hugo Soudeyns[5,6], Niamh M. Higgins[1,2], Normand Lapointe[4,5]

[1]Immunodeficiency Service, Montréal Chest Institute; [2]Québec Antiretroviral Therapeutic Drug Monitoring Program; [3]Faculté de pharmacie, Université de Montréal; [4]Centre Maternel et Infantile sur le SIDA, CHU Sainte-Justine; [5]Faculté de médecine, Université de Montréal; [6]Unité d'immunopathologie virale, Centre de recherche du CHU Sainte-Justine, Montréal, Canada

Poster 13

11th International Workshop on Clinical Pharmacology of HIV Therapy

Sorrento, Italy

April 7-9, 2010

CONTACT INFORMATION

Nancy Sheehan, Quebec Antiretroviral Therapeutic Drug Monitoring Program

Montreal Chest Institute, 3650 St-Urbain, D2.01, Montréal, Québec, H2X 2P4, Canada

@: nancy.sheehan@umontreal.ca

BACKGROUND

- Important efavirenz (EFV) pharmacokinetic interpatient and intrapatient variability exists, in particular in children and adolescents (Ref: Higgins NM et al, 9th 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

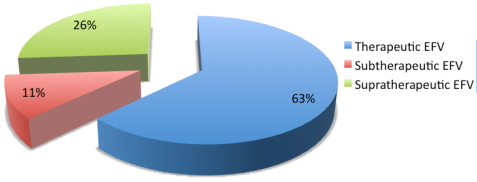
RESULTS

PATIENT DEMOGRAPHICS AT 1ST TDM (n=31)

Characteristics	Median (IQR) unless otherwise specified
Age (years)	12 (10 - 14)
% Male	64.5 %
% Black % Caucasian	83.8 % 16.1 %
Weight (kg)	38.6 (32.9 - 49.1)
Body surface area (m^2)	1.28 (1.16 – 1.44)
EFV dose (mg)	600 (400 - 600)
EFV dose (mg/kg)	10.7 (9.5 - 12.4)
Time on EFV (years)	2.6 (0.2 – 4.3)
% viral load < 50 copies/mL	84 %
$CD4^+$ (cell/mm^3)	630 (480 - 851)
Indication TDM % Control / % Toxicity	 89.4 / 1.4

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

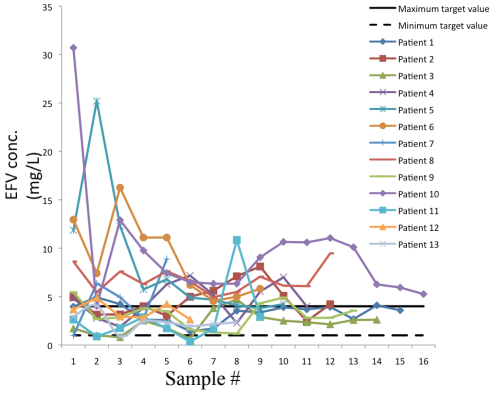
Dose reductions (n=13 from 4 patients)

- 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 % done 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

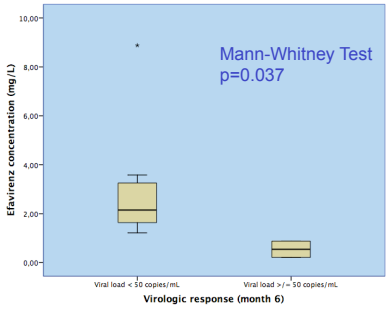


PATIENTS WITH SUPRATHERAPEUTIC EFAVIRENZ CONCENTRATIONS

PATIENT #	% EFV DOSE CHANGE FROM 1ST TDM	CNS EFFECTS	CNS EFFECTS AFTER DOSE CHANGE
1	⦸	⦸	n/a
2*	↓ 33 %	Insomnia	⦸
3	⦸	⦸	n/a
4	⦸	⦸	n/a
5*	↓ 50 %	↓ memory	⦸
6*	↓ 38 %	Prior severe HIV encephalo-pathy	Prior severe HIV encephalo-pathy
7	⦸	⦸	n/a
8	⦸	⦸	n/a
9	⦸	⦸	n/a
10*	↓ 58 %	Depression? (with severe weight loss)	⦸ (weight gain)
11	⦸	⦸	n/a
12	⦸	⦸	n/a
13	⦸	⦸	n/a

* After dose reductions, all patients maintained an undetectable viral load and were stable immunologically.

VIROLOGIC RESPONSE AT 6 MONTHS VS EFAVIRENZ CONCENTRATIONS (N=10)



- 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

We sincerely thank the patients and their parents. We are grateful to Silvie Valois and François Maurice for assistance with data collection, and the Ministère de la santé et des services sociaux du Québec for funding of the TDM program.