21507924

462

Efavirenz Level in Hair Predicts Virologic Response Better Than Level in Blood

Laura Dickinson[1], Marco Siccardi[1], Kathryn Anastos[2], Mardge H. Cohen[3], Deborah Gustafson[4], Gerald B. Sharp[5], Stephen J. Gange[6], Seble Kassaye[7], Peter Bacchetti[8] and Ruth M. Greenblatt[8]

1 University of Liverpool, Liverpool, UK; 2 Montefiore Medical Center, Bronx, NY, USA; 3 Stroger Hospital of Cook County, Chicago, IL, USA; 4 SUNY Downstate Medical Center, Brooklyn, NY, USA; 5 NIAID, Bethesda, MD, USA; 6 Johns Hopkins University, Baltimore, MD, USA; 7 Georgetown University, Washington D.C., USA; 8 University of California, San Francisco, San Francisco, CA, USA.

Background

- We have previously shown that levels of several antiretroviral drugs measured in scalp hair are strong and independent predictors of response to potent antiretroviral therapies. (PMID: 26053176, 21507924, 29265084)
- Because drug concentration in hair reflects uptake over 6-8 weeks of time, we hypothesized that efavirenz (EFV) level in hair would be a better predictor of virologic response than drug measured in plasma (which reflects exposure to EFV over 12-72 hours).
- We now report a comparison between AUC (area under the curve of the plot of drug concentration and time) measured directly via level in hair, and AUC estimated from EFV measured in a single plasma sample using population PK methods.

Methods

- The Women's Interagency HIV Study (WIHS) has conducted pharmacological studies on antiretroviral treatments for over a decade, yielding an extensive data set that includes levels measured in proximal scalp hair samples, single plasma samples obtained at each semi-annual study visit and 12-24 hour intensive pharmacokinetic protocols (iPK) conducted in approximately 120 women per drug to generate multivariate models of AUC in women taking cART under real life conditions
- Drug levels (hair, plasma, intensive PK) were measured by the UCSF Drug Studies Unit, using liquid chromatography tandem mass spectroscopy as previously reported.
- Nonlinear mixed effects (NONMEM v.7.2) was applied to sparse and iPK EFV concentration-time data simultaneously.
- Potential relationships between covariates (such as weight, age, ethnicity) and EFV apparent oral clearance (CL/F) were assessed.
- EFV AUC over the dosing interval was determined using the final model (AUC=Dose/CL/F).
- The relationship of sparse AUC was compared with hair AUC directly via random effects multivariate logistic regression.

Results

1. For participants who provided both iPK and sparse data, AUC determined by iPK was typically about 50% greater than that estimated from sparse samples, though these values were correlated (median ratio of AUC by iPK to AUC by sparse= 1.47, correlation coefficient= 0.83, p<.0001, n=92.
2. In univariate analysis, the occurrence of virologic suppression or non-suppression (below or above level of detection for viral load) was predicted by self-reported adherence of 1-74%, and EFV level in hair.
3. When AUC estimated from levels in single plasma samples (sparse) were compared to levels measured in hair (models with 1071 observations made in 315 individuals), log EFV level in hair was a statistically significant predictor of virologic suppression, while AUC from sparse samples was not in analyses which were adjusted for self reported adherence (average over 6 months), decade of age, ethnicity and individual.

Predictors of virologic suppression; univariate and random effects logistic regression models

315 WIHS participants contributed 1071 hair and single blood level measures

Predictor		Univariate OR	Multivariate OR	95% CI	p-value
self-reported adherence/ 6 mos	95-99%	1.017	1.023	0.54-1.95	0.95
self-reported adherence/ 6 mos	75-94%	0.684	0.789	0.31-2.00	0.62
self-reported adherence/ 6 mos	1-74%	**0.136***	0.224	0.04-1.16	0.075
self-reported adherence/ 6 mos	0	0.042	0.131	<0.01-7.50	0.32
	Decade of age	1.529	1.460	0.90-2.40	0.13
self-reported Ethnicity	African American	0.250$^{\Delta}$	0.270	0.07-1.00	0.051
	Hispanic	0.753	0.744	0.17-3.20	0.69
	Other	2.515	2.623	0.14-50.00	0.52
	LOG2 EFV in hair	**1.452$^{\Omega}$**	**1.557**	**1.20-2.00**	**0.0010**
	LOG2AUC EFV in single plasma	1.008$^{\Sigma}$	**0.725**	**0.48-1.09**	**0.12**

univariate p-values of interest: *p=0.019; $^{\Delta}$p=0.051; $^{\Omega}$p=0.0017; $^{\Sigma}$p=0.33

Conclusions

- Study findings support our hypothesis that the measure which reflected longer-term exposure to EFV (level in hair) was a stronger predictor of treatment outcome than the measure which reflected a much shorter period of EFV exposure.
- These findings have several implications:
  - The first is that the traditional measurement used for therapeutic monitoring, a single level of treatment drug in blood, may not optimally predict long term outcome. For cART, which must be used for very long periods of time, if therapeutic monitoring is needed, methods that evaluate long term exposure are probably better.
  - Measurement of EFV in hair reflects average exposure over many weeks of time. Pattern of exposure is not ascertained.
  - We have found that ARV levels in hair are strong predictors of treatment outcome for NNRTIs, PIs, tenofovir and some integrase inhibitors, but use of these measures in routine clinical care should not occur until additional testing is done. In particular trials of the impact of therapeutic monitoring in using hair samples would be particularly useful.
- Our study adjusted for self reported adherence. It is possible that single plasma levels may aid in understanding treatment outcome when adherence is not reported accurately. Additionally, exposure may also be influenced by drug bioavailability and clearance factors, which include GI conditions, drug/drug interactions, body mass, hepatic and renal function, and host pharmacogenetics.
- There are other potential explanations of the failure of AUC estimated from single plasma EFV levels to predict virologic response:
  - the accuracy of estimates from sparse samples relies on accurate reporting of the dose time.
  - Hair testing is less susceptible to the "white coat effect" in which patients adhere to treatment more rigorously as medical care appointments approach than single blood measures.
- Appropriate selection of drug was not assessed in our study; selection of ARVs for which an individual's HIV is resistant to could also result in treatment failure, but it is unlikely that this factor was a major contributor to our findings.

Sponsored and supported by