

Population Pharmacokinetic-Pharmacogenetic study of Efavirenz in combination with anti-TB treatment in HIV-Infected Cambodian Patients

Julie Bertrand*(1), Monidarin Chou (2), Laurence Borand (3), Céline Verstyuyt (4), Xavier Blanc (4), France Mentré (1), Anne-Marie Taburet (4) and ANRS 1295-CIPRA KH001 study group

(1) INSERM, University Paris Diderot, Paris, France ; (2) University of Health Sciences, Phnom Penh, Cambodia; (3) Institut Pasteur du Cambodge, Phnom Penh, Cambodia; (4) Bicêtre University hospital, Kremlin Bicêtre, France

Context

- In resource-limited countries, tuberculosis (TB) remains an important cause of death among patients infected with HIV
- HIV recommended treatment when combined to a rifampin (RMP)/isoniazide (INH) based TB treatment
 - efavirenz (EFV) with 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
- EFV pharmacokinetics (PK)
 - mainly metabolized through CYP2B6, yet also CYP3A4/5 and CYP2A6
 - auto-induction
 - 3 months of dosing in order to attain 95% of steady state¹
- Interaction between EFV and anti-TB treatments
 - RMP inducer of CYP via PXR
 - RMP induction to its maximum after the first 8 weeks of use³
 - INH inhibitor of CYP2A6⁴

Methods

Study

- ANRS 1295-CIPRA KH001 study⁵
 - Early (E) versus late (L) onset of antiretroviral after TB
 - HIV-TB co-infected patients in Cambodia
 - naïve of antiretroviral (ARV)
 - ARV treatment
 - efavirenz 600 mg QD (evening intake)
 - stavudine (30 mg)
 - lamivudine (150 mg) } combination BID
 - anti-TB treatment
 - 8 weeks: RMP / INH / pyrazinamide(PZA) / ethambutol (EMB)
 - up to week 26: RMP / INH
- ANRS 12154 – PECAN study
 - mid-dose interval sampling (14h) on 4 occasions
 - extensive PK profiles in 10 patients,
 - before and 1, 2, 4, 12, 18 hours following intake

	Weeks/Visit							Pk		
	0	2	4	8	10	14	22	26	50	N=10
anti-TB										
ARV E				X	X	X	X	X	X	X
ARV L				X	X	X	X	X	X	X

x : blood sampling

Pharmacokinetics

- Structural model
 - Built on the 10 extensive PK
 - one compartment model
 - 0-order delayed absorption, T_{k_0} (=1.5h) and T_{lag} (=0.8h)
 - volume of distribution, V (L)
 - linear elimination, CL (L/h)
 - scale parameter F with average value fixed to 1
- Between-subjects (BSV) and -occasions (BOV) variability
 - exponential model
 - on CL and F
- Proportional residual error model
- Estimation method
 - SAEM in NONMEM version 7.1.2, ADVAN1
- Covariate model
 - weight forced on CL (allometric function) and on V
 - non-genetic covariates explored
 - gender, ASAT, ALAT
 - anti-TB treatment
 - continuous covariate centred and imputed to the median when missing
 - step 1:** bivariate linear mixed effect regression on logCL and logF
 - step 2:** forward model inclusion based on LRT of parameter-covariate relationship with $p < 0.1$ in step1

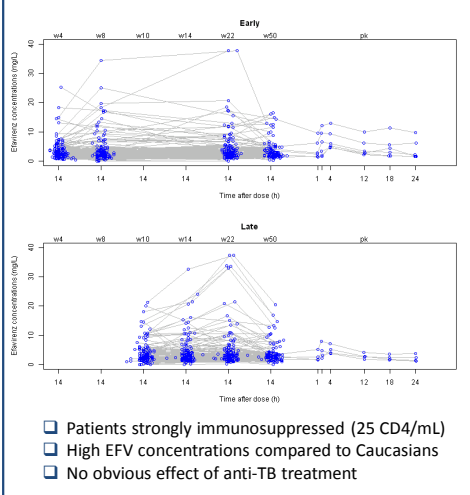
Pharmacogenetics

Polymorphism	Non-functional allele	Process
PXR A7635G	G	CYP and ABCB1 expression inducer
CYP3A4	A	EFV metabolism into 8-OH-EFV
CYP3A5 A6986G	G	EFV metabolism into 8-OH-EFV
CYP2B6 G516T	T	EFV metabolism into 8-OH-EFV auto-induction
CYP2B6 C1459T	T	EFV metabolism into 8-OH-EFV auto-induction
CYP2A6 CA	A	EFV metabolism into 7-OH-EFV
ABCB1 C3435T	T	RMP/EFV efflux
OATP1B1 T521C	C	RMP entrance in cells

- Genotypic model
 - $\theta_{PV} = \theta_{TV}(1 + \theta_{HET} + \theta_{HOMR})$
 - θ_{PV} : parameter individual value
 - θ_{TV} : parameter population value
 - θ_{HET} : coefficient associated to heterozygotes
 - θ_{HOMR} : coefficient associated to rare homozygotes
- Regroupment: allelic variant ABCB1 3435 T carrier
- Interaction analyses
 - anti-TB treatment
 - CYP2B6/2A6, OATP1B1/CYP2B6, OATP1B1/PXR, ABCB1/CYP2B6, ABCB1/CYP3A5, PXR/ABCB1, PXR/CYP3A5

Results

EFV concentrations



Model

- PK model parameters (relative standard error)

V (L)	CL (L/h)	BSV _F (% CV)	BSV _{CL} (% CV)	BOV _F (% CV)	BOV _{CL} (% CV)
196.4 (3)	9 (2)	28 (29)	34 (40)	16 (26)	9 (25)

- residual proportional error: 30 % (4)
- BSV shrinkage using variance estimates
 - F: 33% and CL: 37%
- CYP2B6 G516T effect on CL ($p < 10^{-6}$)
- CYP2B6 G516T/RMP interaction on CL ($p < 10^{-3}$)
- ASAT effect on F (0.2% per 1 U/l, $p < 10^{-4}$)
- Model evaluation through 90% prediction interval VPCs

2B6/anti-TB interaction

- CL estimates in the 3 CYP2B6 G516T genotypes

	GG	GT	TT
EFV alone	9.00 L/h	7.11 L/h	2.25 L/h
EFV + anti-TB drugs	10.35 L/h	5.85 L/h	0.90 L/h

- Hypothesis: inhibition effect of INH on CYP2A6 in carriers of CYP2B6 516T allele

- one patient carrier of genotypes CYP2B6 516TT and CYP2A6 AA with high concentration under anti-TB
 - hints to other pathways
 - heterozygote or missing genotype for the other polymorphisms under study

Discussion

- ANRS 1295-CIPRA KH001 study concluded in a benefit of starting ARV treatment early
- Important BSV and low BOV of EFV
 - interest of therapeutic drug monitoring with regards to EFV hepatic toxicity
 - CYP2B6 polymorphism explains 53% of CL/F BSV
 - ASAT effect is non specific and could be related to drugs toxicity or to HCV/HBV status, not informed in this study
- Complex PK interaction between EFV and anti-TB treatment
 - modest RMP induction on EFV CL in patients carrying CYP2B6 516 GG leading to a functional enzyme
 - in patients carrying CYP2B6 516 GT or TT (leading to low or inactive enzyme) INH inhibition of CYP2A6 explains higher EFV concentrations under anti-TB treatment
- No straightforward dosing recommendation for EFV under anti-TB treatment

References

- Zhu et al. Antimicrobial Agents and Chemotherapy, vol. 53 (6). 2009
- Lopez-Cortes et al. Journal of Antimicrobial Chemotherapy, vol. 58 (5). 2006
- Ngaimisi et al. Clinical Pharmacology & Therapeutics, vol. 90 (3). 2011
- Mc Illeron et al. 13th Int. Workshop on Clin. Pharmacology of HIV, Barcelona, Spain. 2012
- Blanc et al. New England Journal of Medicine, vol. 365 (16). 2011

Acknowledgments

All the patients who participated to this study, all health care providers in 4 clinical settings in Cambodia, all ANRS 1295-CIPRA KH001-Camelia investigators who supported this ANRS 12154 PK study and Fondation Mérieux, Institut Pasteur du Cambodge and ANRS for their support. Julie Bertrand was funded by ANRS at the time of the analysis.