Population analysis of plasma and intracellular pharmacokinetics of indinavir in HIV-1 infected patients with a stable antiretroviral therapy

Dubois A(1), Duval X(1,2), Peytavin G(2), Taburet AM(3), Goujard C(3), Mentré F(1,2) and the Cophar1-ANRS 102 Trial Group

(1) INSERM, U738, Paris, France; University Denis Diderot, Paris, France.
(2) AP-HP, Bichat University Hospital, Paris, France.
(3) AP-HP, Bicêtre University Hospital, Paris, France.

Context

- HIV protease inhibitor
  - Oligopeptides
  - Prevent viral replication by inhibiting the activity of HIV-1 protease
    - No viral protein cleaving → Production of non infectious virons
    - Intracellular activity
- Few studies on intracellular indinavir concentrations
  - In vitro studies on cellular accumulation [1, 2]
  - Studies on patients
    - Correlation with MDR-1 gene expression and low dose of ritonavir [3]
    - Intracellular pharmacokinetics compare to plasma pharmacokinetics [4]
      - computation of AUC and $t_{1/2}$
  - No conjoint analysis of plasma and intracellular concentrations

Objective

To characterize the intracellular pharmacokinetics (PK) of indinavir in connection with its plasma PK in HIV infected patients with a stable antiretroviral therapy

Data

- COPHAR1-ANRS 102 (feb. 2001- oct. 2002) [4]
  - Patients with
    - A stable antiretroviral treatment for 6 months
    - HIV RNA level < 200 copies/mL for at least 4 months
- Plasma concentrations
  - 42 patients
    - With different dosages of indinavir
      - 400mg to 1200mg twice or three times daily
    - 13 patients with a booster dose of ritonavir
      - 400mg to 800 mg twice daily
  - 5 sampling times
    - Before and at 0.5h, 1h, 3h, 6h after drug administration
- Intracellular concentrations
  - 8 patients among the 42 patients
  - 4 sampling times
    - Before and at 1h, 3h, 6h after drug administration
    - Cell preparation needing cautious handling
    - Cell freezing at -80°C until analysis
    - Complex method of measurement

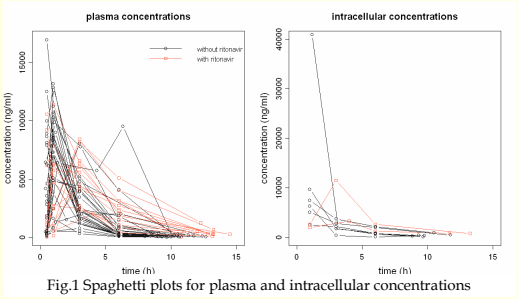

Fig.1 Spaghetti plots for plasma and intracellular concentrations

Methods

- Development of PK model for describing plasma and intracellular concentrations
- Nonlinear mixed effects model (NLMEM)

$$Y_{ij}^{(r)} = f(t_{ij}^{(r)}, \theta_i) + (a^{(r)} + b^{(r)} f(t_{ij}^{(r)}, \theta_i)) \times \varepsilon_{ij}^{(r)} \qquad \varepsilon_{ij}^{(r)} \sim N(0,1)$$

$$\theta_i = \mu \times exp(\beta) \times exp(\eta_i) \qquad \eta_i \sim N(0, \Omega)$$

$r=1, 2$ responses, $i=1,\ldots,N^{(r)}$ patients and $j=1,\ldots,n_i^{(r)}$ samples

- Parameter estimation: exact algorithm
  - SAEM algorithm (Stochastic Approximation Expectation Maximisation) [5]
    - Implementation in MONOLIX (version 2.1) [6]
- Model building
  - Model selection: Bayesian Information Criteria (BIC)
- Choice of pharmacokinetics model
  - Plasma concentrations described by a one or two-compartment model with first order absorption and first order elimination
    - Evaluation of lag time for absorption
  - Intracellular concentrations proportional to plasma concentrations or described by an additionnal compartment with transfert rate constants between plasma and intracellular compartment
- Evaluation of
  - Covariate model: effect of ritonavir
  - Random effects model
    - Variance
    - Correlation between random effects

Results

- Joint model
  - Plasma concentrations described with a two-compartment model
  - Intracellular concentrations proportional to plasma concentrations
    - $Y_{ij}^{(cell)} = \delta \times Y_{ij}^{(plasm)}$
  - Lag time for absorption (LRT: $p<10^{-16}$)
  - Effect of ritonavir on clearance (LRT: $p=2.7\ 10^{-5}$)

Parameter	Fixed effect (*rse %*)	Variation coefficient (*rse %*)
Tlag (h)	0.358 (19.4)	75.9% (19.9)
k_a (h^{-1})	1.86 (28.4)	79.4% (20.8)
V_p/F (L)	55.0 (13.7)	/
Cl/F (L/h)	44.1 (8.4)	40.9% (10.9)
k_{12} (h^{-1})	0.0842 (41.2)	/
k_{21} (h^{-1})	0.221 (37.7)	/
δ (-)	1.84 (19.3)	38.7% (50.9)
β(rito, Cl) (-)	-0.715 (20.1)	/

Parameter	estimates (*rse %*)
$a^{(plasm)}$	6.78 (96.0)
$b^{(plasm)}$	39.5% (8.2)
$a^{(cell)}$	254 (0.1)
$b^{(cell)}$	48.1% (24.9)

Tab.1 Population parameters estimates for joint pharmacokinetic model

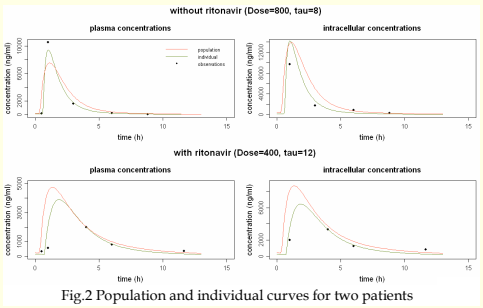

Fig.2 Population and individual curves for two patients

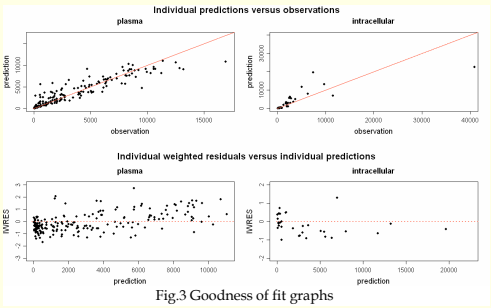

Fig.3 Goodness of fit graphs

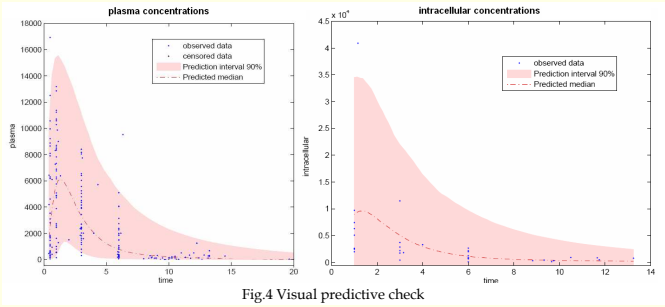

Fig.4 Visual predictive check

Discussion

- Intracellular concentrations at steady state proportional to plasma concentrations
  - Consistant with no cellular accumulation of indinavir [1, 2, 3]
- COPHAR1 – ANRS 102
  - Concentration measurement during a second visit
    - Estimation of within-subject variability
- COPHAR2 – ANRS 111
  - Intracellular and plasma concentrations of indinavir
    - Validation of developped model

[1] Nascimbeni, Lamotte, Peytavin et al. *Antimicrob Agents Chemother*. 2000
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[4] Hennessy, Clarke, Spiers et al. *Antivir Ther*. 2003
[5] Goujard, Legrand, Panhard et al. *Clin Pharmacokinet*. 2005
[6] Delyon, Lavielle, Moulines. *Ann Stat*. 1999
[7] http://www.monolix.org