Population Pharmacokinetic-Pharmacodynamic-Viral Dynamics Modelling of Maraviroc Monotherapy Data Using MONOLIX

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INTRODUCTION

Maraviroc (MVC), a selective antagonist of the human chemokine CCR5 receptor, has been approved for use in treatment-experienced human immunodeficiency virus type-1 (HIV-1) infected subjects with exclusively CCR5-tropic virus.

A 4-differential equation viral dynamics (VD) model was used to describe the kinetics and interaction of target cells, actively infected cells, latently infected cells and viruses in HIV-1 infected asymptomatic patients.[1]

NONMEM has been previously used for fitting PKPD-VD model to the MVC monotherapy data.[2] Not only are computation times very long but there are often convergence problems resulting from numerical difficulties in optimizing the linearized likelihood. Moreover, only a few of the parameters can be estimated and it is not feasible to perform simultaneous PKPD-VD modelling.

MONOLIX implements a stochastic approximation of the standard expectation maximization (SAEM) algorithm for nonlinear mixed effects models without approximations. The SAEM algorithm replaces the usual estimation step of EM by a stochastic procedure which has been shown to be very efficient with improved convergence toward the maximum likelihood estimates.[3]

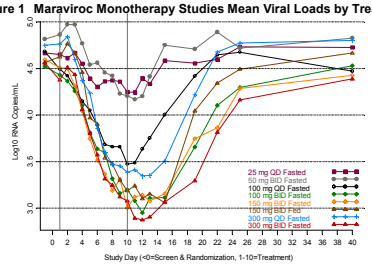
OBJECTIVES

- To compare population PKPD-VD modelling of monotherapy MVC data using MONOLIX with NONMEM
- To assess MONOLIX functionality for complex mechanistic models

DATA

- Plasma MVC concentrations (1250 samples) and viral loads (1169 observations) arising from 63 asymptomatic HIV-1 patients were available

Figure 1 Maraviroc Monotherapy Studies Mean Viral Loads by Treatment



METHODS

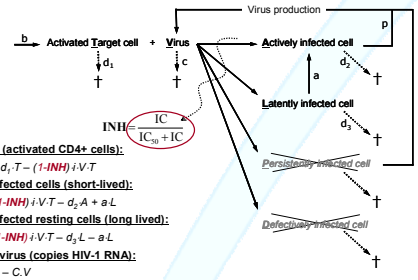
PKPD-VD Model

PK

- Two compartment disposition model, parameterized as clearances and volumes, with first-order absorption, food effects on KA and F1 (bioavailability) and an additive residual error model was fitted to log-transformed MVC concentrations

PD-VD

Figure 2 Viral Dynamics Model with Inhibitory Emax Model for Drug Effects



Target cell (activated CD4+ cells):

$dT/dt = b - d_1 \cdot T - (1\text{-}INH) \cdot i \cdot V \cdot T$

Actively infected cells (short-lived):

$dA/dt = f_1 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_2 \cdot A + a \cdot L$

Latently infected resting cells (long lived):

$dL/dt = f_2 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_3 \cdot L - a \cdot L$

Infectious virus (copies HIV-1 RNA):

$dV/dt = p \cdot A - C \cdot V$

$$RR0 = \frac{b}{d_1} \cdot i \cdot \frac{p}{c} \cdot \left(\frac{f_1}{d_2} + \frac{f_2 \cdot a}{d_2 \cdot (d_3 + a)} \right)$$

- Delay in onset and offset of viral response modelled with a lag time (LagE) and/or an effect compartment model (Ke0)
- An additive residual error model was used for the $\log_{10}$ transformed viral loads

Software

- NONMEM version VI level 1.2 with the NM-TRAN subroutines (TRANS4) version IV level 1.1, and PREDPP model library (ADVAN4) version V level 1.0 and GNU Fortran (GCC) 3.4.6 20060404 (Red Hat 3.4.6-8)
  - ➢ Estimation method: FOCE with INTERACTION
- MONOLIX version 2.4 (implemented in MATLAB R2007b)
  - ➢ Diagnostic package: conditional means and standard errors, log likelihood profile (LLP), visual predictive checks (VPC) and normalized prediction distribution errors (NPDE)

Analysis Plan

Part 1: Assessing Model Viability in NONMEM and MONOLIX with Simulated Data

- Simulate MVC concentrations and viral loads in NONMEM using a model determined from previous PKPD-VD analysis
- Fit the simulated MVC concentrations and viral loads separately in NONMEM and MONOLIX using a sequential PKPD approach
- Viral inhibition is driven by the predicted PK profile based on the Empirical Bayes Estimates (EBE) obtained from separate PK analysis

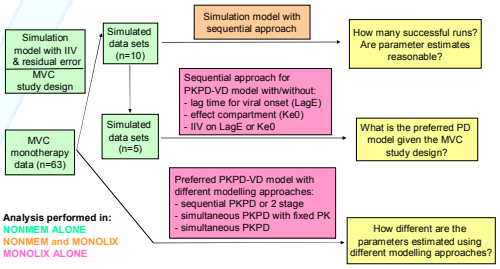
Part 2: Determination of Preferred Model in MONOLIX with Simulated Data (Given the MVC Monotherapy Study Design)

- Fit the simulated viral load data with different PD models
- Select the preferred model based on SE, correlation of estimates, AIC, BIC and log-likelihood (by Monte-Carlo Importance Sampling)

Part 3: Comparison of Parameter Estimates Obtained from Sequential and Simultaneous Modelling Approaches with Preferred Model in MONOLIX using the MVC Monotherapy Data

Figure 3 Schematic Analysis Plan

Simulation model = PKPD-VD with LagE and Ke0,
IIV on IC50 and VD parameters (RR0, b and d_2)



RESULTS

Part 1 Assessing Model Viability in NONMEM and MONOLIX with Simulated Data

Table 1 Summary of Termination Messages Based on 10 Simulated Data Sets

	Number of runs terminated with			Number of runs with unreasonable parameter estimates
	Numerical Difficulties	Rounding Errors	Minimization Successful	
NONMEM	5	3	2	1 out of 2 runs Ke0=378 [true=2.86] 1/d
MONOLIX	-	-	10	1 out of 10 runs IC50=418 [true=8.66] ng/mL RR0=38.4 [true=5.94]

- Computation time
  - ➢ NONMEM: 2.5 to 25 hours without diagnostics
  - ➢ MONOLIX: 4.5 to 5.5 hours including diagnostics using default settings (number of simulation samples: VPC=100, NPDE=500, LLP=10000)

Part 2 Determination of Preferred Model in MONOLIX with Simulated Data

Table 2 Selection of Preferred Model Given the Maraviroc Monotherapy StudyDesign

	PKPD-VD model with component of:		Model Assessment Criteria		
	Lag time for viral onset (LagE)	Effect compartment (Ke0)	-2 x log-likelihood	AIC	BIC
Simulation model	Yes	Yes	-		
Simulation Data Set 2	-	-	385	403	423
	Yes	-	253	273	294
	-	Yes	339	359	381
	Yes	Yes	255	277	301
Simulation Data Set 4	-	-	423	441	461
	Yes	-	287	307	328
	-	Yes	383	403	424
	Yes	Yes	296	318	341
Simulation Data Set 6	-	-	464	482	501
	Yes	-	351	371	392
	-	Yes	422	442	463
	Yes	Yes	349	371	394
Simulation Data Set 8	-	-	411	429	448
	Yes	-	286	306	327
	-	Yes	380	400	421
	Yes	Yes	289	311	335
Simulation Data Set 10	-	-	476	494	513
	Yes	-	336	356	377
	-	Yes	436	456	477
	Yes	Yes	338	360	384

- In general, it was difficult to determine both Ke0 and LagE
- Inclusion of IIV on LagE increased:
  - ➢ -2 x log-likelihood: 4 - 34 units
  - ➢ AIC: 6 - 36 units
  - ➢ BIC: 8 - 38 units
- Estimates of RR0 and IC_{50} varied from one model to another depending on the choice of PD model
- Preferred model (PKPD-VD with LagE) was taken forward for part 3 analysis

Part 3 Comparison of Parameter Estimates Obtained from Sequential and Simultaneous Modelling Approaches with Preferred Model in MONOLIX using the MVC Monotherapy Data

PK

- Food effects on Ka and F1 were modelled using a linear function with fasted status as the reference group

Table 3 Comparison of PK Parameter Estimates Obtained From Sequential and Simultaneous PKPD Modelling Approaches in MONOLIX

	Sequential PKPD		Simultaneous PKPD	
	Pop_Est	RSE (%)	Pop_Est	RSE (%)
CL (L/d)	5500	6	5180	6
V1 (L)	274	12	349	10
Q (L/d)	1140	8	1290	8
V2 (L)	1040	9	1130	9
Ka (1/d)	8.11	10	9.36	10
Food on Ka	-0.755[a]	36	-0.141[c]	222
F1	1 FIX	-	1 FIX	-
Food on F1	-0.244[b]	45	-0.476[d]	14
LagC (d)	0.0211	10	0.0178	13
ω[CL] (%)	46.6	9	46.9	9
ω[V1] (%)	60.6	16	55.5	15
ω[Q] (%)	35.1	20	47.2	15
ω[V2] (%)	40.0	22	51.4	15
ω[Ka] (%)	64.1	11	69.9	11
ω[LagC] (%)	39.0	26	60.2	20
Additive error (%)	45.4	2	44.6	2

[a] p value = 0.0049; [b] p value = 0.028; [c] p value = 0.65; [d] p value < 0.0001
Pop_Est = population parameter estimate; RSE = relative standard error

- PK parameter and IIV estimates were similar between sequential and simultaneous PKPD model approaches, with or without food effect on KA

PD and VD

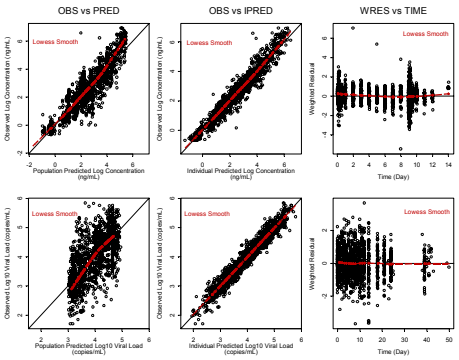
Table 4 Comparison of PD and VD Parameter Estimates Obtained From Sequential and Simultaneous PKPD Modelling Approaches in MONOLIX

	Sequential PKPD		Simultaneous PKPD with Fixed PK		Simultaneous PKPD	
	Pop_Est	RSE (%)	Pop_Est	RSE (%)	Pop_Est	RSE (%)
RR0	5.33	10	5.92	11	4.96	9
b	1.22	15	1.18	13	1.36	14
d_2	0.797	4	0.755	3	0.841	3
IC_{50} (ng/mL)	8.27	19	6.73	22	8.57	24
LagE (d)	1.52	1	1.35	3	1.43	6
ω[RR0] (%)	78.6	10	79.4	10	64	10
ω[b] (%)	114	9	103	9	110	9
ω[d_2] (%)	29.3	11	20.6	12	19.6	13
ω[IC_{50}] (%)	137	11	160	10	175	10
Additive Error (%)	47.9	2	48.1	2	47.9	2
RMIC (ng/mL)	35.8	-	33.1	-	33.9	-
-2 x log-likelihood	-		2367		2390	
AIC	-		2387		2440	
BIC	-		2409		2493	

RMIC = Reproduction Minimum Inhibitory Concentration; $(RR0 - 1) \cdot IC_{50}$
Pop_Est = population parameter estimate; RSE = relative standard error

- RMIC was the parameter of interest due to RR0 and IC_{50} being highly correlated
- RMIC and other VD parameter and IIV estimates were comparable across different modelling approaches for the given PD model
- For simultaneous PKPD-VD modelling approach, no computation time gained by fixing PK parameters (run time 13 to 15 hours)

Figure 4 Basic Goodness of Fit for the Final PKPD-VD Model Using a Simultaneous PKPD Modelling Approach. Top Panel for Maraviroc Concentration; Bottom Panel for Viral Load



CONCLUSIONS

- Disadvantages of NONMEM
  - ➢ Difficulties in performing PKPD-VD parameter estimations
  - ➢ Long computation time with no guarantee of successful minimization
- Advantages of MONOLIX
  - ➢ SAEM algorithm allows estimation of PKPD-VD parameters using either sequential or simultaneous modelling approach
  - ➢ Computation time was relatively short (including diagnostics for model assessment)
- Given the MVC study design:
  - ➢ It is difficult to separate PD lag due to drug effects from system delay
- Parameter estimates were similar with sequential and simultaneous PKPD approaches, with/without fixing PK parameters
- MONOLIX is a useful tool for complex mechanistic models

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