Dose-Timing Information Improves the Clinical Explanatory Power of Data on Patient Adherence to Antiretroviral Drug Regimens

B. Vrijens\(^{(1-2)}\), S.L. Mayer\(^{(1)}\), R. Rode\(^{(3)}\), R. Bertz\(^{(3)}\), J. Urquhart\(^{(1)}\)

(1) AARDEX Ltd., Zug, Switzerland
(2) Dept. of Biostatistics, University of Liège, Belgium
(3) Abbott Laboratories, Chicago, United States
Motivation

• Plasma viral load is the strongest predictor of the risk of progression to AIDS and death [Mellors et al. 1996, Hughes et al. 1997, Marchner et al. 1998, Delta Coordinating Committee 1999]

• New treatments (PI’s) are very effective in suppressing the virus but are not a cure for HIV disease

• Many patients receive clinical benefit from treatment; however, others do NOT or only temporarily receive clinical benefit

• Poor patient adherence to therapy is one of the most cited reasons for treatment failure [Montaner et al. 1998, Paterson et al. 2000]
PK sampling design

Lopinavir/ritonavir (QD: 800/200 mg or BID: 400/100 mg), stavudine, and lamivudine.

© AARDEX Ltd., 2003
Modeling PI concentrations

Differential equations leading to

\[ C_i(t) = C_{a_i}(t_d) \frac{(k_{a_i})}{(k_{a_i} - k_{e_i})} \left\{ e^{-(k_{e_i})t} - e^{-(k_{a_i})t} \right\} \]

\[ + C_i(t_d) e^{-(k_{e_i})t} \]

\[ C_{a_i}(t_d) = C_{a_i}(t_{d-1}) e^{-(k_{a_i})t_d} + \frac{\text{Dose}}{V_i} \]

Individual PK parameters to be estimated
First step

Estimation of the individual PK parameters: \( k_{a_i}, k_{e_i}, V_i \)

**NONMEM®**

Estimation based on a population approach

First Order Conditional Estimates (FOCE)

The model did not converge when using the last reported dose and the assumption of steady state!

More complex model with additional compartments

Same model introducing dosing history

Convergence

Individual expected values of the parameters:

\( \hat{k}_{a_i}, \hat{k}_{e_i}, \hat{V}_i \) (expected a posteriori values)

© AARDEX Ltd., 2003
Steady-State assumption vs Electronically Monitored dosing histories

© AARDEX Ltd., 2003
Internal exposure

\[
C_i(t) = Ca_i(t_d) \frac{(ka_i)}{(ka_i - ke_i)} \left\{ e^{-(ke_i)(t-t_d)} - e^{-(ka_i)(t-t_d)} \right\} \\
+ C_i(t_d) e^{-(ke_i)(t-t_d)} \\
Ca_i(t_d) = Ca_i(t_{d-1}) e^{-(ka_i)(t_d-t_{d-1})} + \frac{Dose}{(V)_i}
\]

© AARDEX Ltd., 2003
Examples (QD vs BID)

Patient number = 604

Patient number = 615

© AARDEX Ltd., 2003
Viral load observation

ID = 604
Dosing Date

Internal exposure

© AARDEX Ltd., 2003
Model for repeated ordered ordinal variables

Probability of

Deterioration

[0 - 50[

[50 - 400[

[400 - 2000[

[2000 - ∞[

Improvement

© AARDEX Ltd., 2003
Internal exposure summary between visits

- Mean concentration
- Median concentration
- Percent of time IE < EC50
- Actual time IE < EC50

Note: IE = Internal Exposure
EC50 = 70 ng/ml
## Model comparison

### Deviance table

<table>
<thead>
<tr>
<th>Model deviance</th>
<th>Deterioration</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null model</td>
<td>418.1</td>
<td>404.5</td>
</tr>
<tr>
<td>Mean</td>
<td>405.5 *</td>
<td>397.5 *</td>
</tr>
<tr>
<td>Median</td>
<td>402.0 *</td>
<td>395.7 *</td>
</tr>
<tr>
<td>% time(IE&lt;EC50)</td>
<td>392.9 *</td>
<td>392.1 *</td>
</tr>
<tr>
<td>time(IE&lt;EC50)</td>
<td>390.6 *</td>
<td>389.2 *</td>
</tr>
</tbody>
</table>

*comparisons against the null model
p-values < 0.05

© AARDEX Ltd., 2003
## Parameter estimation

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Std</th>
<th>t</th>
<th></th>
<th>Value</th>
<th>Std</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deterioration</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Improvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-2.32</td>
<td>0.28</td>
<td>-8.3</td>
<td>6.74</td>
<td>0.55</td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>[0-50[</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>-2.18</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>[50-400]</td>
<td>2.20</td>
<td>0.35</td>
<td>6.3</td>
<td>-4.21</td>
<td>0.36</td>
<td></td>
<td>-6.0</td>
</tr>
<tr>
<td>[400-2000]</td>
<td>4.06</td>
<td>0.48</td>
<td>8.4</td>
<td>-4.87</td>
<td>0.50</td>
<td></td>
<td>-8.4</td>
</tr>
<tr>
<td>[2000-∞]</td>
<td>4.81</td>
<td>0.48</td>
<td>10.1</td>
<td>-4.87</td>
<td>0.49</td>
<td></td>
<td>-9.9</td>
</tr>
<tr>
<td>Sub table 1</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Sub table 2</td>
<td>-2.21</td>
<td>0.37</td>
<td>-6.0</td>
<td>-1.53</td>
<td>0.43</td>
<td></td>
<td>-3.6</td>
</tr>
<tr>
<td>Sub table 3</td>
<td>-3.35</td>
<td>0.53</td>
<td>-6.3</td>
<td>-4.26</td>
<td>0.49</td>
<td></td>
<td>-8.7</td>
</tr>
<tr>
<td>time(IE&lt;EC50)</td>
<td>0.009</td>
<td>0.003</td>
<td>3.5</td>
<td></td>
<td>-0.009</td>
<td>0.002</td>
<td>-3.7</td>
</tr>
</tbody>
</table>

© AARDEX Ltd., 2003
Results

![Graph showing probability over time for various exposure levels: 0 - 50, 50 - 400, 400 - 2000, 2000 - 6000. The graph plots time (internal exposure < EC50) in hours on the x-axis and probability on the y-axis. The graph shows trends for both deterioration and improvement.](image-url)
Direct relationship?

Dosing histories

Viral load

© AARDEX Ltd., 2003
Timing Error (TE)

- $\delta_{ik} = \text{the } k^{th} \text{ dosing interval for the } i^{th} \text{ patient}$
- $\delta_0 = \text{prescribed dosing interval (12 h or 24 h)}$
- $\delta^*_{ik} = \left(\delta_{ik} - \delta_0\right) / \delta_0 : \text{standardized dosing interval}$

$$TE_i = 3 \sqrt{n_i \sum_k \left(\delta^*_{ik}\right)^3}$$

© AARDEX Ltd., 2003
## Adherence variables

<table>
<thead>
<tr>
<th></th>
<th>Deterioration</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null model</td>
<td>418.1</td>
<td>404.5</td>
</tr>
<tr>
<td>Timing compliance</td>
<td>414.9</td>
<td>403.8</td>
</tr>
<tr>
<td>Correct dosing</td>
<td>411.4 *</td>
<td>402.8</td>
</tr>
<tr>
<td>Taking compliance</td>
<td>401.5 *</td>
<td>396.6 *</td>
</tr>
<tr>
<td>Timing error</td>
<td>389.1 *</td>
<td>388.9 *</td>
</tr>
<tr>
<td>Time(IE&lt;EC50)</td>
<td>390.6 *</td>
<td>389.2 *</td>
</tr>
</tbody>
</table>

* comparisons against the null model
p-values < 0.05

© AARDEX Ltd., 2003
Results

Cubic distance

Probability

0.0 0.2 0.4 0.6 0.8 1.0

[0 - 50]
[50 - 400]
[400 - 2000]
[2000 - ]

Timing error

Deterioration

Improvement

Perfect dose timing

© AARDEX Ltd., 2003
Comparison between PIs

Improvement probabilities

Data from a cross-study comparison

© AARDEX Ltd., 2003
Comparison between PIs

Deterioration probabilities

Perfect dose timing

Timing error

Data from a cross-study comparison

© AARDEX Ltd., 2003
Conclusions

• PK estimates can be improved by using electronically monitored dosing histories obtained prior to blood sampling as model input.

• Dose timing information increases the explanatory power of patient adherence data and its association with antiretroviral treatment outcomes.

• The proposed methodology allows separate study of the “on” and “off” processes (improvement vs deterioration)

• After initial viral suppression, an antiretroviral regimen containing lopinavir/ritonavir was not highly dependent on timing errors.
Making it simple for the patient

Patient adherence → Model → Viral Load → Patient care

Timing error

Probability of Deterioration

- [0 - 50]
- [50 - 400]
- [400 - 2000]
- [2000 - ∞]

Probability to improve

Probability to déteriorate

Probability to stay

© AARDEX Ltd., 2003