Introduction to Human Challenge Models (HCMs) for Respiratory Viruses and the Application of Quantitative Pharmacology to Enhance Drug Development

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22nd August 2016
Disclosures and Acknowledgements

The information is derived from publically available sources and key material for further reading is provided. Any representation/interpretation does not necessarily reflect perspectives of others.

Data presented represents the efforts of many colleagues, over many years across many organizations
- Roche / Genentech
- d3 Medicine LLC
- ICPD, University at Buffalo, Monash University
- Alios Biopharma, hVIVO, University of Tennessee
- 360 Biolabs

Primary investigators and clinical trials staff

Clinical trials participants
Related Work

• Publications


Related Work

- Abstracts


7. Patel K et al. Modelling the kinetics of human respiratory syncytial virus (RSV) and clinical disease symptoms. ACOP (2014).


Background

- Human challenge models (HCM) are employed as part of many development programs for ARI such as influenza, rhinovirus and respiratory syncytial virus (RSV)

- Infections are deliberately induced under carefully controlled and monitored conditions, involving virus inocula of known virulence and provenance

- Key variables, such as baseline infection load, timing of Rx, and immunological status can be tightly controlled to isolate drug effect

- PK, PD (Virologic, clinical, biomarker) and safety can be diligently evaluated

- Quantitative pharmacology can optimize HCM study design and analysis to enhance drug development for respiratory viruses.
HCMs as Applied to Respiratory Viruses

**Pro’s**
- Highly controlled nature of experimental pharmacology HCMs enables “rich and clean” interrogation of drug effect
- Intensive safety surveillance
- Specialist units creates opportunity for novel designs (eg. adaptive design to capture ER surface, expansive dose ranges, frequent invasive sampling) to mitigate expense and accelerate
- Not dependent on seasonal disease, means study durations can be short

**Con’s**
- Regulatory challenges in obtaining an acceptable inocula
- Ethical considerations (infecting volunteers, transmission risk)
- Transferability to the field is debated as important variability ignored including virus (strains, virulence, replication, IC50, tropism, baseline VL), time to Rx, host immune status etc), abrogated/different clinical course of disease
- Artefact of study including inoculation techniques, impost of frequent invasive sampling (dilution, loss of virus)
- Specialist clinical trial units, strain availability and need to pre-screen to obtain sero-negative subjects can create availability bottlenecks and high costs

**Rich data enables quantitative pharmacological approaches (MBM) to support development**
Considerations for Quantitative Pharmacology Application to HCM of Respiratory Viruses

- Case 1: HCM for Oseltamivir for influenza
- Case 2: HCM for ALS-008176 for RSV
CASE 1 - HCM FOR OSELTAMIVIR FOR INFLUENZA
Methods – Pooled Available Ph2 Studies

- Healthy volunteers in Studies PV15616 and NP15717 were experimentally infected with influenza (TCID50 of virus $10^6$) and treatment was initiated with oseltamivir or placebo after 24h.
- Symptoms (feeling feverish, headache, muscle ache, sore throat, cough, overall discomfort, nasal symptoms) individually ranked b.i.d. for symptom severity (0, 1, 2, or 3) for 9 days.
- Nasal lavage b.i.d. for viral culture Days 1–3 and o.d. on Days 4–8.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects (infected)</th>
<th>Virus</th>
<th>$IC_{50}$ (nM)</th>
<th>Dosing regimens</th>
<th>PK Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV15616</td>
<td>80 (69)</td>
<td>Influenza A/Texas</td>
<td>0.18</td>
<td>20, 100 or 200mg b.i.d. or 200mg q.d. or placebo for 5 days</td>
<td>Sparse PK samples pre-dose and on Days 3, 4 and 7</td>
</tr>
<tr>
<td>NP15717</td>
<td>60 (46)</td>
<td>Influenza B/Yamagata</td>
<td>16.76</td>
<td>75 or 150mg b.i.d. or placebo b.i.d. for 5 days</td>
<td>Intensive PK on Days 1 and 5</td>
</tr>
</tbody>
</table>
Methods - PK

- A robust population PK model based on nine clinical studies was developed to provide individual OC exposures

\[ \text{Central (OP)} \quad V_{\text{op}} \]

\[ \text{Peripheral (OP)} \quad V_{\text{p}} \]

\[ \text{CL}_{\text{op}}/V_{\text{op}} \]

\[ \text{CL}_{\text{oc}}/V_{\text{oc}} \]

\[ \text{Ka} \]

\[ (F) \]

\[ Q/V_{\text{op}} \]

\[ Q/V_{\text{p}} \]

\[ (\text{Fm}) \]

\[ \text{CL}_{\text{op}} = \text{clearance of OP} \]

\[ \text{CL}_{\text{op}} = \text{clearance of OP} \]

\[ F = \text{fractional bioavailability of OP} \]

\[ F_{\text{m}} = \text{fractional bioavailability of oseltamivir that is metabolised} \]

\[ \text{Ka} = \text{the first order rate of absorption} \]

\[ Q = \text{inter-compartmental clearance term} \]

\[ V_{\text{oc}} = \text{volume of OC} \]

\[ V_{\text{op}} = \text{central volume of OP} \]

\[ V_{\text{p}} = \text{peripheral volume of OP} \]

- Individual predicted steady-state exposures for OC were determined: AUC0–24h, Cmin, Cmax
Methods:

## Independent Variables

<table>
<thead>
<tr>
<th>Exposure, PK-PD or potency measure</th>
<th>Demographic / other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC$_{0–24h}$</strong></td>
<td>Age</td>
</tr>
<tr>
<td><strong>AUC$<em>{0–24h} \cdot IC</em>{50}$ ratio</strong></td>
<td>Race</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Sex</td>
</tr>
<tr>
<td>$C_{\text{max}} \cdot IC_{50}$ ratio</td>
<td>Height</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Weight</td>
</tr>
<tr>
<td>$C_{\text{min}} \cdot IC_{50}$ ratio</td>
<td>Body mass index</td>
</tr>
<tr>
<td>Total daily dose</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Antipyretic anilides</td>
</tr>
<tr>
<td>$IC_{50}$</td>
<td></td>
</tr>
</tbody>
</table>

Note: co-linearity reduced focus to AUC related metrics consistent with PKPD index from preclinical models
The viral titer area under the curve value was lower in the combined oseltamivir group (n=56) compared with placebo (n=13); P = .02.

"Typical" time-course of viral load (PV15616)

Detection of PK/PD effect influenced by VT time-course and form of dependent variable (eg. Peak VT<rate of decline< AUC<<( T_{SVR} = T_{shed} ))

- Inoculation
- Serial nasal washings
- Measurement
HCM viruses can provide biophase PK, VK, cytokines and symptoms to inform MBMs

The total symptom score area under the curve value was lower in the combined oseltamivir groups (n=56) compared with placebo (n=13); P=.05; Cytokine levels for days 1, 3, 5, and 9 were determined using commercially available enzyme-linked immunosorbent assay kits. Asterisk indicates P≤.01; dagger, P≤.001; and double dagger, P<.05.

Patel et al. ICAAC 2015

Patel et al. PAGANZ 2015
Understand the inputs!

12.2 Nasal Wash Procedure for Viral Culture

1. The volunteer should extend their neck approximately 30 degrees, from the horizontal, while in a sitting position.

2. Lubricate the collection swab with the provided lubricant.

3. Insert the swab into the nasal passage, rotate gently, and retrieve the swab.

4. Place the swab into the provided transport medium tube.

It is essential to have a detailed understanding of the sampling and measurement methodologies:

Sampling procedures
- Procedure (disruptive, dilutive)
- Replicate (same/different site)
- Pooled/Combined (wash + swab)
- Standardisation (within study, across studies)

VT / biomarker measurement
- Sampling error
- Method (culture/ PCR)
- Performance (BLQ)

CROs and PROs
- Validated instruments
- Relevance to HCM
  - Fever
  - Composite vs individual symptom scores
- Frequency / learning
Methods:
A diverse set of univariate and multivariable PK-PD analyses were performed against the following dependent variables:

<table>
<thead>
<tr>
<th>Time-to-event</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time to alleviation of composite symptom score</td>
<td>• Composite symptom score AUC</td>
</tr>
<tr>
<td>• Time at which any of the seven individual</td>
<td>– Symptom scores added together and AUC of composite score calculated</td>
</tr>
<tr>
<td>symptoms scores were &gt;1 to the time at</td>
<td>from the time at which any of the seven individual symptoms scores were</td>
</tr>
<tr>
<td>which all applicable individual symptom</td>
<td>&gt;1 to the time at which all applicable individual symptom scores were</td>
</tr>
<tr>
<td>scores were ≤1</td>
<td>≤1</td>
</tr>
<tr>
<td>• Time to cessation of viral shedding</td>
<td>• Viral titre AUC</td>
</tr>
<tr>
<td>• Time from the first positive viral culture to</td>
<td>– The AUC of the viral titre values spanning the time from the first</td>
</tr>
<tr>
<td>the time of the first negative viral culture</td>
<td>positive viral culture to the time of the first negative viral culture</td>
</tr>
<tr>
<td></td>
<td>• Peak viral titre</td>
</tr>
<tr>
<td></td>
<td>– The maximum viral titre value achieved for each subject during study</td>
</tr>
<tr>
<td></td>
<td>Days 1–9</td>
</tr>
</tbody>
</table>
Results

- Higher OC Exposures are Associated with a Faster Cessation of Viral Shedding - Peak VT and AUC - ND

- Higher OC Exposures are Associated with a Lower Severity of Illness

- A Faster Time to Alleviation of Composite Symptoms is Seen with Higher OC Exposures

Findings consistent with observations of exposure-response nested within Phase III trials\(^1,2\)

\(^1\)Evaluation of Pharmacokinetic-Pharmacodynamic (PK-PD) Relationships for Influenza Symptom and Quality of Life (QOL) Endpoints Among Oseltamivir- Treated Patients (ICAAC 2014); \(^2\)Pharmacokinetic-Pharmacodynamic (PK-PD) Evaluation of the Impact of Oseltamivir on Influenza Viral Endpoints (ICAAC 2014)
Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study

John P. DeVincenzo, M.D., Matthew W. McClure, M.D., Julian A. Symons, D.Phil., Hosnieh Fathi, M.D., Christopher Westland, B.A., Sushmita Chanda, Ph.D., Rob Lambkin-Williams, Ph.D., Patrick Smith, Pharm.D., Qingling Zhang, Ph.D., Leo Beigelman, Ph.D., Lawrence M. Blatt, Ph.D., and John Fry, B.S., R.G.N.
-008176 is an oral nucleoside prodrug converted intracellularly to its active triphosphate ALS-008112.

- **PCR guided Rx start**
- **Adaptive design (safety, PK, PD) to establish ER/DR**
Results
ALS-8176 Dose-Response in a Human RSV Challenge Model

Longer VT time-course than influenza HCM
ALS-8176 had significant improvements on VT AUC, Time to undetectable PCR, Peak VT and AUC symptom score
Rich PK/PD data provided in RSV HCM enables quantitative pharmacology approaches to address complex nucleoside pharmacology.
Considerations for Quantitative Pharmacology for Respiratory Virus HCMs

• Critical to understand sampling and assay methods as they can impact integrity of observations and assumptions.

• Consider the time-course of PD markers (e.g., VK) to guide the most appropriate form of a PD variable.

• Don’t forget about other endpoints, as HCM virus can cause symptoms.

• Consider potential for MBM to connect PK, VK, immune-system components, and symptoms to enable better extrapolation to clinic (especially for complex examples such as nucleoside analogues).

• Numerous opportunities to optimise HCMs through quantitative pharmacology methods (adaptive design, optimal design based on ER).