Exposure - Response

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ANTIMICROBIAL EFFICACY
(Microbiological Cure)

CLINICAL EFFICACY
(Clinical Cure)

Other factors

DOSING regimen

CONCENTRATIONS
in vivo (PK)

ACTIVITY
in vitro (MIC)

Mouton et al., Drug Resistance Updates 2011
• The challenge is to power the CER study in such a way that the a meaningful answer is derived

• Until recently, individual factors that determined CER were not described adequately

• Wrong conclusions were therefore drawn: pk/pd does not matter (!)
Unravelling the relationship between dose and response

- Measures of exposure
  - Susceptibility, culture, pcr
  - PK in individual patients

- Measures of response
  - Microbiological
  - Clinical

- Covariates
Clinical phase 3 study

PK-data

PK population model

Individual PK parameters

Culture-results with MIC-values

MIC-values per individual

Individual exposure to CAZ

%\textit{fT}>MIC

Microbiological outcome

Clinical outcome
Ceftazidime in patients with nosocomial pneumonia

- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime

N=390 patients included

N=170 with MIC

N=154 with MIC and PK-estimates

220 without Gram negatives in cultures

16 without PK estimates

Muller et al, JAC 2013 68:900-906
Exposure-response Emax model
microbiological eradication

- Individual exposures to CAZ
- Categorised (% $fT>MIC$ per 10%)
- Eradication rate per group
- 154 patients
Exposure-response Emax model
microbiological eradication

- Individual exposures to CAZ
- Categorised (%\textit{fT} > MIC per 10%)
- Eradication rate per group
- 154 patients

\[ \text{%fT} > \text{MIC breakpoint} = 44.9 \% \]

\textbf{CART}

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
%fT>MIC & Success & Failure \\
\hline
\textgreater{}44.9 & 83 (90.2\%) & 9 (9.8\%) \\
\textless{}44.9 & 31 (50\%) & 31 (50\%) \\
\hline
\end{tabular}
\end{center}

Muller et al, JAC 2013 68:900-906
Exposure-response Emax model
microbiological eradication

• Baseline: 50%
• Max response: 99.7%
• Attributed cure: 50%
• Probability of cure further increases above the %fT>MIC breakpoint

%fT>MIC breakpoint = 44.9%
P < 0.0001

<table>
<thead>
<tr>
<th>%fT&gt;MIC</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;44.9</td>
<td>83 (90.2%)</td>
<td>9 (9.8%)</td>
</tr>
<tr>
<td>&lt;44.9</td>
<td>31 (50%)</td>
<td>31 (50%)</td>
</tr>
</tbody>
</table>

Muller et al, JAC 2013 68:900-906
When to measure microbiological eradication?

**NOT** at TOC – often three/four weeks after stopping therapy!!

EOT?
Probability plot of the logistic regression analysis for ceftazidime showing the relationship between \(tif > \text{MIC}\) (Gram-negatives at baseline/EOT) and probability of cure at TOC

Muller et al, JAC 2013 68:900-906
Probability plot of the logistic regression analysis for ceftazidime showing the relationship between \%fT>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC

- *Probability of cure further increases above the \%fT>MIC breakpoint*

**CART**

<table>
<thead>
<tr>
<th>%fT&gt;MIC</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥37.4</td>
<td>56 (78.9%)</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>&lt;37.4</td>
<td>15 (44.1%)</td>
<td>19 (55.9%)</td>
</tr>
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</table>

\%fT>MIC breakpoint = 37.4 %

P = 0.0007

Muller et al, JAC 2013 68:900-906
Probability plot of the logistic regression analysis for ceftobiprole showing the relationship between $\%{t>T\text{MIC}}$ (Gram-negatives at baseline/EOT) and probability of cure at TOC (nosocomial pneumonia [excluding VAP] PK/PD CE subjects with positive cultures, n=82)

Predicted probabilities for clinical cure at TOC - ceftobiprole

With 95% Confidence Limits

P=0.033
How can the power of a study be improved further?

- Quantify outcome parameters instead of dichotomous outcomes

- Microbiology
  - Quantify cfu (we do it in animal studies…….)
  - Time to negative

- Clinical
  - Quantitative parameter
  - Time to response
# Bactericidal and Sterilizing Activities of Antituberculosis Drugs during the First 14 Days

Amina Jindani, Caroline J. Doré, and Denis A. Mitchison

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>n</th>
<th>EBA0–2 Mean</th>
<th>SD</th>
<th>b2–14 Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>3 (all with RMP)</td>
<td>RMP20</td>
<td>8</td>
<td>0.383</td>
<td>0.326</td>
<td>0.154</td>
<td>0.086</td>
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<tr>
<td></td>
<td>RMP10</td>
<td>8</td>
<td>0.174</td>
<td>0.228</td>
<td>0.096</td>
<td>0.051</td>
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<tr>
<td></td>
<td>RMP5</td>
<td>3</td>
<td>0.062</td>
<td>0.175</td>
<td>0.072</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td>RM</td>
<td>4</td>
<td>0.564</td>
<td>0.176</td>
<td>0.125</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>SR</td>
<td>4</td>
<td>0.332</td>
<td>0.156</td>
<td>0.211</td>
<td>0.138</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27</td>
<td>0.305</td>
<td>0.275</td>
<td>0.132</td>
<td>0.084</td>
</tr>
</tbody>
</table>

\[ p = 0.0039^* \]

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### Early Bactericidal Activity of High-Dose Rifampin in Patients with Pulmonary Tuberculosis Evidenced by Positive Sputum Smears

A. H. Diacon, R. F. Patientia, A. Venter, P. D. van Helden, P. J. Smith, H. McIlneron, J. S. Maritz, and P. R. Donald
FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).
Relationship between AUC/MIC and Effect in CF patients

Tobramycin

- Individual exposures to tob
- Cohort, 13 patients
- MIC tob before
- FEV1 before and after

R square = 0.6451

AUC/MIC breakpoint = 35.8

P = 0.0003

<table>
<thead>
<tr>
<th>AUC/MIC</th>
<th>RI FEV1</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35.8</td>
<td>0.292</td>
<td>0.047</td>
</tr>
<tr>
<td>&lt;35.8</td>
<td>0.111</td>
<td>0.072</td>
</tr>
</tbody>
</table>
Conclusions

• In DD, CER **should** be part of the development plan

• Even **without** differences with the comparator, it will show its merit (or not…).

• (semi) Quantitative parameters used preferably and more precise measurements – (we could show efficacy in 13 patients!)

• Estimate the number of patients in each arm based on prior information on variability and predicted responses. A power analysis should be performed
Probability of cure after treatment with fluconazol
Oropharyngeal Candidiasis  n=132

Treatment with fluconazol
Doses 50 – 800 mg

Individual Dose

Culture-results with MIC-values

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)
Clinical outcome
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis  n=132

• Prob cure correlates with Dose/MIC
• POSITIVE correlation with dose
• INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez- Tudela et al, AAC 2007
Relationship between fAUC/MIC and Effect
121 patients with S. pneumoniae respiratory infection

- Relationship between fAUC:MIC ratio & microbiological response from a total 121 patients with respiratory tract infection involving S. pneumoniae.
- fAUC:MIC > 34 had 92.6% response rate.
- fAUC:MIC < 34 had 66.7% response rate.