Supporting a Pediatric Investigational Plan in liver transplantation – An example using a pharmacostatistical approach

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Summary

- The Paediatric Investigational Plan for everolimus included an extrapolation analysis to obtain a rational interpretation of limited paediatric data in the context of existing adult data.

- The assessment of similar efficacy between paediatric and adult populations was an important step in this interpretation.

- Given design differences between adult and paediatric studies, this assessment could not be obtained via a simple comparison of the study results.

- A pharmacostatistical approach was applied to account for the differences and obtain a valid assessment which supported similar efficacy between the two populations.
Indication: Prevention of acute rejections after solid organ transplantation (Tx)

Endpoint: Treated Biopsy Proven Acute Rejection (tBPAR)

Standard of care: Multitherapy including Calcineurin inhibitors (CNI), e.g., Tacrolimus (TAC)

Medical need at reducing CNIs (nephrotoxicity)

Everolimus (EVR)

- Mammalian target of rapamycin (mToR) inhibitor
- Approved in adults in Tx in combination with CNI at reduced exposure
Background

*Paediatric Investigational Plan (PIP) for Everolimus*

- **2009:** Determination of the PIP: *Liver* and Kidney* Tx
- **2010:** Design of the paediatric liver Tx (PIP) study:
  - Single-arm, with 75 patients under EVR + rTAC
- **2013-2014:** Request for modification of the PIP
  - Recruitment difficulties
  - Agreement that a Type-II variation can be submitted based on interim analysis data with (in Liver) reduced sample size of at least 20 patients
  - Inclusion of an extrapolation analysis as an additional measure

* Not covered here
TAC = Tacrolimus; EVR = Everolimus
rTAC = TAC at reduced exposure
Background

* General considerations about extrapolation*

- **Extrapolation concept:** Use a model to predict “target data”
  - Target: Paediatric data, e.g. drug concentration or efficacy
  - Model quantified from systematic synthesis of all relevant data (‘source’) + assumptions
    - include (but is not restricted to) adult data

- **Extrapolation plan:**
  - if necessary to **decrease uncertainty** associated with prediction (precision and model assumption)
  - Design **studies** in the target population, and plan analyses

- **Validation / confirmation:**
  - by comparing observed vs predicted paediatric data

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* EMA’s draft “Reflection paper on extrapolation of efficacy and safety in paediatric medicine development” (2016)
Everolimus PIP

Similar concentration-response: key assumption in extrapolation concept

- Assumption: Population similarity in concentration-response relationship
  
  *Same EVR concentration in adults and children leads to same efficacy*

- Assumption supported by semi-quantitative evidence
  - Target
  - Disease progression
  - Clinical evidence

- Under this assumption and given that concentration can be controlled in children by means of therapeutic drug monitoring (**TDM**), the model allows to determine a dosing regimen which delivers adequate efficacy in children
Everolimus PIP

**Validation of the concept cannot be done by simple comparison of adults and paediatric data**

- **Uncertainty** about extrapolation concept
  → Extrapolation plan: Use of paediatric data (PIP IA) study to validate the concept

- In general, the paediatric trial is designed such that validation can be done by a simple comparison of efficacy results vs adult data

- In our EVR case,
  - Major **design differences** between adult and paediatric studies prevented the simple comparison to be relevant
  - We have used **pharmacometric approaches** tailored to the design differences to obtain a valid assessment of the concept
Extrapolation analysis plan

Major design differences between adult and paediatric studies prevented the simple comparison to be relevant
Extrapolation analysis plan

*Relevant adult efficacy obtained via model-based assessment*

- Fair comparison of adults and children with same EVR concentration only possible if no confounders (immunological risk and possibly TAC)

- Adjusting for those confounders would allow to predict the counterfactual efficacy for adults with same EVR concentration as children of the paediatric study

- Requires to distinguish the ‘causal’ relative contributions of those confounders

- This was done using a time-to-event (hazard) model:

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TTE = Time to event model.
```
Extrapolation analysis plan

*Use time since transplantation as surrogate for immunological risk*

TTE = Time to event model.

- **EVR conc**
- **TAC conc**
- **Time since Tx**
- **tBPAR**

TTE = Time to event model.
Extrapolation analysis plan

Sparseness of PK samples and frequent dose changes require modeling the concentration time-course

Example of TAC dose and concentration for one study subject:

\[
\begin{array}{c|c|c}
\text{Day since rando} & \text{TAC conc. [ng/mL]} & \text{TAC dose [mg]} \\
0 & 0 & 0 \\
30 & 6 & 4 \\
60 & 2 & 2 \\
150 & 1 & 1 \\
240 & 0 & 0 \\
330 & 0 & 0 \\
\end{array}
\]
Extrapolation analysis plan

3 analysis steps

- **Step 1**: Estimate the time-to-event model on **adults only**

- **Step 2**: Predict efficacy for adults similarly treated* as children of the paediatric study (**predictive distribution**)
  - Same tacrolimus and everolimus concentrations at the same time

- **Step 3**: **Validation**: Compare this predictive distribution to the observed paediatric efficacy

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**Observed**

<table>
<thead>
<tr>
<th>PAEDIATRIC</th>
<th>ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBPAR</td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td></td>
</tr>
<tr>
<td>PREDICTED</td>
<td></td>
</tr>
<tr>
<td>ADULT</td>
<td>similarly treated</td>
</tr>
</tbody>
</table>

**Predicted**

<table>
<thead>
<tr>
<th>PAEDIATRIC</th>
<th>ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVR conc</td>
<td></td>
</tr>
<tr>
<td>TAC conc</td>
<td></td>
</tr>
<tr>
<td>tBPAR</td>
<td></td>
</tr>
</tbody>
</table>

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*Similar treatment conditions as the paediatric study.
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies TAC, but no EVR, conc. effect and confirmed the expected higher early immunological risk

N pats (EVR + rTAC): 237  N (%) tBPAR: 15 (6%)
Step 1: Estimate concentration-tBPAR model in adults

Model prediction consistent with proportion of tBPAR events

Final adult model (EVR + rTAC): \[ h_i(t) = \hat{h}_0(t)e^{\hat{\alpha}*\max(TAC_i(t),\hat{\gamma})} \]
Step 2 - Prediction from adult model

Better survival for hypothetical adults with same exposure as children at the same time, given the delayed start of paediatric analysis period.

Predicted concentration

Predicted survival (under adult model)

Predictive distribution
Step 3: Validation and interpretation

*From comparison of the predictive distribution to the observed paediatric efficacy*

- No event observed in 22 patients of the paediatric study
- This observed efficacy is at the mode of the predictive distribution
- This support **validation** of the extrapolation concept
The PIP for everolimus included an extrapolation analysis to obtain a rational interpretation of limited paediatric data in the context of existing adult data

- The assessment of similar efficacy was an important step in this interpretation

Given design differences btw adult and paediatric studies, pharmacostatistical methods, combining dose and concentration and handling time-varying covariates, had to be used to obtain a valid assessment

The analyses showed a paediatric rejection similar to this predicted from the adult patient similarly exposed at the same time

- This supported validation of the extrapolation concept

The interim analysis data and the extrapolation analysis results were submitted, and paediatric information was included in the label
Thank you
BACK-UP
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies a TAC conc. effect and confirmed the expected higher early immunological risk

N pats = 461
N (%) tBPAR = 21 (4.5%)

239
25 (10.5%)
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies a TAC conc. effect and confirmed the expected higher early immunological risk
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies a TAC conc. effect and confirmed the expected higher early immunological risk.
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies a TAC conc. effect and confirmed the expected higher early immunological risk
Investigation of adult model

Final adult model (EVR + rTAC)

\[ h_i(t) = \hat{h}_0(t)e^{\alpha \ast \max(TAC_i(t), \hat{\gamma})} \]

*Grambsch (2005)* Diagnostic plots to reveal functional form for covariates in multiplicative intensity models
Final Adult model

Final adult model: \( h_i(t) = h_0(t)e^{\hat{\alpha}\max(TAC_i(t),7.1) + \hat{\beta}\cdot 1_{EVR_i}} \)

Probability being tBPAR–free (between Days 30 and 750) given constant TAC concentration

Baseline hazard \( \hat{h}_0(t) \)
(immunological risk)
Final adult model

\[ h_i(t) = h_0(t)e^{\alpha \max(TAC_i(t), 7.1) + \beta 1_{EVR_i}} \]
Validation of final adult model

Figure 5-20  Visual Predictive Check for Model MLp3, by treatment group

Probability of being event free (Survival)

Time (days since transplantation)