Eculizumab Dosing Strategies in Pediatric Patients with Stem Cell Transplant-Associated Thrombotic Microangiopathy (TA-TMA): PK/PD Model based assessment

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Poor survival of stem cell transplant-associated thrombotic microangiopathy (TA-TMA)

- A severe post-transplant complication with high-risk of death
- Multifactorial disease with a 20-30% incidence in stem cell recipients
- Low survival rates with conventional treatments such as plasma exchange, defibrotide, and/or rituximab
- **Key for survival** of high-risk TA-TMA is early intervention before severe multi-organ endothelial injury occurs.

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**Poor survival in patients with TA-TMA**

<table>
<thead>
<tr>
<th>Time from HSCT (month)</th>
<th>Probability of survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>20</td>
<td>0.8</td>
</tr>
<tr>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td>60</td>
<td>0.4</td>
</tr>
<tr>
<td>80</td>
<td>0.2</td>
</tr>
<tr>
<td>100</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Anti-C5 monoclonal antibody Eculizumab for TA-TMA

- **Mechanism of action:**
  A monoclonal antibody (mAb) targeting complement C5

- **Indications:**
  Paroxysmal Nocturnal Hemoglobinuria (PNH)
  Atypical Hemolytic Uremic Syndrome (aHUS)

- **Recommended dose**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Induction dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 40kg</td>
<td>900 mg weekly</td>
<td>1200 mg biweekly</td>
</tr>
<tr>
<td>30 - ≤ 40kg</td>
<td>600 mg weekly</td>
<td>900 mg biweekly</td>
</tr>
<tr>
<td>20 - ≤ 30kg</td>
<td>600 mg biweekly</td>
<td></td>
</tr>
<tr>
<td>10 - ≤ 20kg</td>
<td>300 mg weekly</td>
<td>600 mg biweekly</td>
</tr>
<tr>
<td>5 - ≤ 10kg</td>
<td>300 mg biweekly</td>
<td>300 mg biweekly</td>
</tr>
</tbody>
</table>

- **Cost:**
  $6,143 or more for 1 vial (300 mg)

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Big challenges with eculizumab dosing

- Large “between” and “within” patient variability in PK is observed!
- Current dosing strategies need to be optimized!

PK/PD guided-precision dosing promises to increase treatment success

Monitoring biomarkers for dose adjustment

<table>
<thead>
<tr>
<th>PK:</th>
<th>Eculizumab concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD:</td>
<td>sC5b-9 (soluble terminal complement complex): Indicator of disease severity</td>
</tr>
<tr>
<td></td>
<td>CH50 (total hemolytic complement activity): Indicator of the effectiveness of complement blockade by eculizumab</td>
</tr>
</tbody>
</table>

Purpose

• To characterize eculizumab PK and PD over the course of treatment

• To develop a population PK model as part of a precision dosing strategy considering target mediated disposition

• To develop an optimal dosing strategy using a model-based approach to achieve higher PK target attainment resulting in better outcomes
Methods

Sample collection
- Eculizumab serum concentrations: Once daily during induction therapy
- sC5b-9 monitoring: At least 3 times per week during therapy.

Population Pharmacokinetic Modeling
- NONMEM 7.2 with FOCE-I method
- Evaluated covariates: Body weight, sC5b-9 level, number of dosing cycles

Monte Carlo Simulations
Optimal dosing intervals to achieve high PK target attainment ($C_{\text{trough}}>100$ mg/mL) were explored based on the PK simulation using the developed model considering:
- Initial sC5b-9 burden (200-800 ng/mL)
- A cohort of representative patients (n=1,000; weight ranging from 3-80 kg)
Large eculizumab target mediated PK variability during treatment

Patient demographics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number</th>
<th>Parameters</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>Time course available (weeks)</td>
<td>2 (0-25)</td>
</tr>
<tr>
<td>Number of observations</td>
<td>384</td>
<td>Age (years)</td>
<td>4.8 (1.1-29.8)</td>
</tr>
<tr>
<td>Number of dose cycles</td>
<td>5 (2-23)</td>
<td>Body weight (kg)</td>
<td>15.0 (5.5-80)</td>
</tr>
<tr>
<td>Induction dose: 300 mg/600 mg/900 mg</td>
<td>4 / 10 / 7</td>
<td>Pre-treatment sC5b-9 level (ng/mL) (normal&lt;244 ng/mL)</td>
<td>337 (131-1700)</td>
</tr>
</tbody>
</table>
**Eculizumab PD marker changes in parallel with PK**

**Eculizumab Clearance (PK)**

**sC5b-9 Levels (PD)**

**Final Population PK Model**

\[
CL = CLNL(\text{nonlinear}) + CLL(\text{linear})
\]

- \[CLNL = CLNL_{pop} \times \left( \frac{\text{predose} \text{S5b9}}{337} \right) \times e^{-\theta_{\text{dose}} \times (N_{\text{dose}}-1)} \times \left( \frac{WT}{70} \right)^{0.75} \]
- \[CLL = CLL_{pop} \times \left( \frac{WT}{70} \right)^{0.75} \]

*PD marker change over the course of treatment*
Population PK modeling and model validation

Final model
- CL=CLL (linear) + CLNL (non-linear)
  \[ CL = C_{LL_{pop}} \cdot \left( \frac{WT}{70} \right)^{0.75} \]
  \[ CLNL = C_{NL_{pop}} \cdot \left( \frac{\text{predoseC5b9}}{3.37} \right) \cdot e^{-0.75(N_{dose} - 1)} \cdot \left( \frac{WT}{70} \right)^{0.75} \]
- \( V_d = V_{d_{pop}} \cdot \left( \frac{WT}{70} \right)^{1.0} \)

Parameter | Mean (%RSE)
--- | ---
**Fixed effects**
\( C_{LL_{pop}} \) (mL/h/70kg) | 22.8 (17%)
Exponent of allometry for CL | Fixed to 0.75
\( V_{d_{pop}} \) (L/70kg) | 8.15 (8%)
Exponent of allometry for Vd | Fixed to 1.0
\( C_{NL_{pop}} \) (mL/h/70kg) | 40.5 (17%)
\( q_{NDose} \) | 0.20 (29%)

**Inter-individual variability**
\( \omega_{CL} \) (%CV) | 43.5% (27%)
\( \omega_{Vd} \) (%CV) | 25.3% (33%)
\( \omega_{IOV} \) (%CV) | 30.7% (17%)

**Random residual variability**
\( \epsilon_{prop} \) | 0.104 (14%)

88% CL variability

Unexplained 43%
Body weight 35%
sC5b-9 decrease 12%

43% CL variability

Observed concentration (µg/mL)
Population predicted concentration (µg/mL)
Individual predicted concentration (µg/mL)

Time after dose (hours)
Intensifying dosing scenarios for higher target attainment

Population PK Simulation

Current weekly dose regimen

Simulation 1
Weight: 6 kg
Dose: 300mg

Simulation 2
Weight: 20 kg
Dose: 600mg

Simulation 3
Weight: 40 kg
Dose: 900mg

Probability of target attainment (C_{trough} > 100 \, \mu g/mL)

Interval 2 days 4 days 7 days (current regimen)

Eculizumab concentration (\mu g/mL)

Time after first dose (days)

Dose intervals (days)

Probability of target attainment (%)
Conclusion

Our PK/PD model-based optimal dosing strategy indicated that eculizumab precision dosing with consideration of body weight and sC5b-9 levels will increase the probability of PK target attainment resulting in better outcomes.
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Sonata Jodele, MD

Patients and Families
All medical staff for patient care