Lack of Placental Transfer of Certolizumab Pegol During Pregnancy: Results from CRIB, a Prospective, Postmarketing, Multicenter, Pharmacokinetic Study

Alexa B. Kimball1, Xavier Mariette2, Bincy Abraham3, Ann Flynn1, Frauke Förger4, Anna Molto5, René–Marc Fippo6, Astrid van Tubergen1, Laura Shaugnessy7, Jeff Simpson1, Marie Tei8, Eric Helmer9, Maggie Helmer10, Eliza Krakowc11

1Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA; 2Université Paris-Sud, Le Kremlin-Bicêtre, France; 3Houston Methodist Hospital, Houston, TX; 4University of Utah, Salt Lake City, UT; 5University of Bonn, Bonn, Germany; 6Center Hospitalier Régional Universitaires de Lille, Lille, France; 7Maastricht University Medical Center, Maastricht, Netherlands; 8UCB Pharma, Raleigh, USA; 9UCB Pharma, Slough, UK; 10UCB Pharma, Brussels, Belgium; 11Aston Medical Research Foundation, Oklahoma City, OK

OBJECTIVE
- To accurately measure the level of potential transfer of certolizumab pegol (CZP) from mother to infants using a highly sensitive CZP-specific assay.

BACKGROUND
- Women affected by chronic inflammatory diseases, such as psoriatic disease, need effective and safe treatments during pregnancy.1
- Adequate disease control is important to reduce the risk of adverse pregnancy outcomes.2
- Anti-TNF therapy is effective, but because most chronic diseases fall into this category, treatment is often stopped during pregnancy.3
- Certolizumab pegol (CZP), due to itsโฟr-free molecular structure, is not expected to undergo active placental transfer compared to other antibody-based anti-TNFs.4
- CRIB (NCT03046091) is the first prospective, industry-sponsored study designed to evaluate placental transfer of CZP from the mother to her infant.

METHODS

PATIENTS AND STUDY DESIGN
- CRIB was a pharmacokinetic (PK) study of pregnant women receiving commercial CZP for an approved indication.
- The primary endpoint was the concentration of CZP in the infants’ plasma at birth (Figure 2).
- Key exclusion criteria:
  - Patients had 32 weeks’ gestation with a singleton or twins at the time of informed consent.
  - Patients were being treated with CZP as per the locally approved label and pregnancy was not planned.
  - Patients started or decided to continue CZP treatment independently from and prior to participating in the study in accordance with the treating physician.
  - Infants received a CZP dose within 35 days prior to delivery.
- Key exclusion criteria:
  - Patients had any pregnancy-related, clinically significant anomaly noted on obstetric ultrasound or other imaging assessment; or had significant laboratory abnormalities during their pregnancy.
  - Patients were taking or had taken any medication with strong positive evidence of human fetal risk or teratogenicity during pregnancy.
  - Patients had received treatment with any biological therapeutic during their pregnancy.
- Detection of CZP and Anti-CZP Antibodies
  - CZP concentrations in blood were measured using a highly sensitive, CZP-specific enzyme-linked immunosorbent assay (ELISA) (Figure 2).
- Sensitivity: 100 times more sensitive than the previous used assay in other CZP PK studies (lowest detectable amount of LLOQ: 0.032 µg/mL).
- Specificity: Requires binding of CZP to TNF and detection with anti-CZP antibody.
- The presence of anti-CZP antibodies in blood was determined using a previously validated enzyme-linked immunosorbent assay (ELISA). Samples were defined as positive if anti-CZP antibody levels were ≥ 24 units/mL.

Stud Assessments
- Blood samples were collected from the mothers, umbilical cords, and infants at delivery; and from infants again at Weeks 4 and 8 post-delivery (Figure 3).
- Safety analyses included all mothers who received at least one dose of CZP and the infants of participating mothers. Adverse events (AEs) were coded according to the MedDRA v18.1.

Statistical Analyses
- No formal sample size calculations were performed, as no statistical hypotheses were tested. All P values were based on the observed values, no imputation for missing data was used.

RESULTS

Baseline Characteristics
- Baseline characteristics are presented in Table 1.
- Median (min, max), unless stated otherwise
- Mothers (n=16): Age years, median (18–40). Median gestational age at birth, weeks, 36 (30–40).
- Median (min, max), unless stated otherwise
- Infants (n=21): Birth weight, kg, 3.3 (2.2–4.8). Antenatal and neonatal APGAR scores, both 7–10.
- Two infants were included in the per protocol analysis set: 1 due to missing data at birth and 1 due to inadequate RA at birth (i.e., data not consistent with a predefined PK model, based on the expected range for healthy infants).

CZP Plasma Concentrations
- In all mothers enrolled (n=16), CZP plasma levels at delivery were within the expected therapeutic range (median [range] 244 [150–448] µg/mL).
- Two infants were excluded from the per protocol analysis set: 1 due to missing data at birth and 1 due to inadequate RA at birth (i.e., data not consistent with a predefined PK model, based on the expected range for healthy infants).

Safety Follow-up
- Four SAEs were reported in two infants; all were mild to moderate except the infection. All SAEs were resolved.
- No anti-CZP antibodies were detected in the mothers, umbilical cords, or infants at any time point during the study.
- All AEs experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children (Table 2).
- Two SAEs were reported in two infants, all were mild to moderate except the infection. All SAEs were resolved. The infection in one infant was treated with antibiotics.
- No anti-CZP antibodies were detected in the mothers, umbilical cords, or infants at any time point during the study.

CONCLUSIONS
- CZP-specific immunoassay
- Infants (n=14): LLOQ < 0.032 µg/mL.
- Safety follow-up
- Infants (n=14): LLOQ < 0.032 µg/mL.
- Secondary Endpoint:
- C-reactive protein (CRP) and acute phase reactants (APRs) were determined in all infants at delivery and in all infant blood samples at Weeks 4 and 8.

Figure 1. CRIB study design

Figure 2. CZP-specific immunoassay

Figure 3. CZP plasma concentrations in mothers and infants (n=14 mother-infant pairs)

Table 1. Baseline characteristics of mothers and infants

Table 2. Safety overview

<table>
<thead>
<tr>
<th>Event</th>
<th>Mothers (n=16)</th>
<th>Infants (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs</td>
<td>3 (19%)</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Discontinuation due to TEAEs</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Drug-related TEAEs</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Disclosures
- Acknowledgements

REFERENCES

References provided by the authors. To view all supporting information, please visit the Online Repository at https://journals.jacionline.org.

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