Ein rekombinanter humaner C1-inhibitor: Klinischer Überblick

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Deutschen Gesellschaft für Angioödeme e.V.
Univ. – Hautklinik Mainz
Pharming
Transgenic Technology Platform

Select protein
Generate genetic constructs
Develop founder/mini-herd
Purify protein from milk
Formulate protein therapeutic
Ruconest® is highly purified

Non-reduced SDS-PAGE analysis of rhC1INH and native C1INH

Ruconest < 0.002% non-product related impurities

In lane 1: Ruconest
In lane 2: pdC1INH

Proteins, 100 ng/lane, were visualized by silver-staining. The migration of the standard protein markers is indicated on the left ($10^{-3} \times M_r$).
rhC1INH activity similar to pdC1INH
Similar affinity towards target proteins

<table>
<thead>
<tr>
<th></th>
<th>k_{on} (M^{-1}.s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1s</td>
</tr>
<tr>
<td>rhC1INHa</td>
<td>6.1± 0.3 x 10^4</td>
</tr>
<tr>
<td>h-C1INHa</td>
<td>5.1± 0.3 x 10^4</td>
</tr>
</tbody>
</table>

Data generated at Pharming Technologies B.V. The data are mean ± SD of three experiments. The values for k_{off} were virtually zero. 
k_{on}: second-order rate constant of inhibition
rhC1INH 50 U/kg
PK parameters

Mean pharmacokinetic parameters following administration of rhC1INH 50 U/kg to asymptomatic HAE patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value ± SD (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (U/mL)</td>
<td>1.36 ± 0.306</td>
</tr>
<tr>
<td>C_{max} above baseline (U/mL)</td>
<td>1.18 ± 0.234</td>
</tr>
<tr>
<td>T_{max} (min)</td>
<td>18.3 ± 5.72</td>
</tr>
<tr>
<td>AUC above baseline (U.min/mL)</td>
<td>218 ± 55.6</td>
</tr>
<tr>
<td>CL (mL/min)</td>
<td>22.8 ± 7.34</td>
</tr>
<tr>
<td>Half life (min)</td>
<td>93.7 ± 8.45</td>
</tr>
<tr>
<td>Volume (L)</td>
<td>3.03 ± 0.794</td>
</tr>
<tr>
<td>C_{baseline} (U/mL)</td>
<td>0.201 ± 0.108</td>
</tr>
</tbody>
</table>
rhC1INH PK profile in asymptomatic HAE patients

Modified graph from M van Doorn et al., J Allergy Clin Immunol 2005;116:876-83
Functional C1INH target levels
No C4 cleavage at normal C1INH levels
rhC1INH
Mechanism of Action in HAE

• Insufficient (functional) C1inh results in oedema

• Treatment requires sufficient amounts of C1Inh activity
  – 1 Unit = quantity in 1ml of normal plasma
  – 2100U > normal quantity in 2l of plasma = 4 vials of Cinryze / Berinert

• C1inh binds to target proteases as a suicide inhibitor

• Once the cascade is switched off, the edema is absorbed passively

• Dose is more important than half life
Simulated \( C_{\text{max}} \) by weight for approved dosing regimen

\[\text{Weight (kg)} \quad \text{Maximum Functional C1INH (U/mL)}\]

C.Farrell et al, BJCP 2011 in Press
Ruconest® Controlled Trials
Overall VAS Scores over time at the most severe location

B. Zuraw, M. Cicardi et al., J Allergy Clin Immunol 2010;126:821-7
Ruconest® Controlled Trials

Time to onset of relief

B. Zuraw, M. Cicardi et al., J Allergy Clin Immunol 2010;126:821-7
All C1INH controlled trials
Placebo corrected dose response at 4 hours

Optimal efficacy achieved at 50 U/kg
No further improvement with 100 U/kg
Dose is more important than half-life

C. E. Hack et al., Allergy 2011
## Integrated safety findings

### Exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Subjects (n)</th>
<th>Administrations (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 1202/03</td>
<td>Symptomatic patients</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>C1 1205 RCT</td>
<td>Symptomatic patients</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>C1 1205 OLE</td>
<td>Symptomatic patients</td>
<td>62</td>
<td>168</td>
</tr>
<tr>
<td>C1 1304 RCT</td>
<td>Symptomatic patients</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>C1 1304 OLE</td>
<td>Symptomatic patients</td>
<td>57</td>
<td>194</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>Symptomatic patients</td>
<td><strong>155</strong></td>
<td><strong>424</strong></td>
</tr>
<tr>
<td>C1 1101</td>
<td>Asymptomatic patients</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>C1 1106</td>
<td>Healthy Volunteers</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>C1 1207</td>
<td>Asymptomatic patients</td>
<td>25</td>
<td>207</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>All population</td>
<td><strong>190</strong></td>
<td><strong>714</strong></td>
</tr>
</tbody>
</table>
Integrated clinical safety findings

Summary

• rhC1INH up to 100 U/kg was generally well tolerated, the AE profile being similar to that of placebo

• No severe TEAEs were considered to be probable or definitely related to rhC1INH administration

• No increase in the frequency of TEAEs upon repeated rhC1INH administration
Integrated immunosafety
Antibodies to C1INH

No induction of anti-C1INH antibodies
No neutralizing antibodies
Integrated immunosafety
Antibodies to HRIs

Occasional and transient antibodies to HRIs
None associated with clinical events
Integrated immunosafety
IgE antibodies

- Ruconest is contraindicated in patients with known or suspected rabbit allergy.

- In Europe Ruconest is only administered to patients who tested negative for rabbit epithelium (dander) antibodies, and re-testing is indicated once yearly or every 10 treatments.

- Subjects exposed to rhC1inh were tested for the presence of pre-existing IgE antibodies against rabbit epithelium.
  - No differences in pre- and post exposure blood samples.
  - No induction observed of IgE antibodies.

C. E. Hack et al, Poster IgE; EAACI 2010 London, Allergy 2010 Jun; 65 Suppl 92: 1-756
Recombinant C1INH
Safety conclusions

• 714 Ruconest® exposures in 190 subjects

• No increase in adverse events with repeated exposures

• No evidence for neutralizing antibodies to endogenous C1INH

• Confirmed anti-HRI antibodies are sporadic and transient, not associated with clinical events

• No induction observed of IgE antibody

Ruconest® has an unremarkable safety profile.
Conclusions

• Ruconest is a novel biotech alternative to plasma derived C1inh for the treatment of HAE attacks
  – Identical amino acid sequence
  – Differences in glycosylation profile
  – Highly purified

• Approved at a higher dose (50U/kg) achieving optimal efficacy
  – Similar affinity to target proteases
  – Functional units are directly comparable (1 vial of Ruconest > 4 vials of plasma product)
  – Dose is more important driver of efficacy than half-life
  – No relapse

• Reassuring safety profile
  – No pharmacological AEs
  – No induction of allergies observed
  – No induction of neutralizing antibodies
  – Contraindicated in pts with rabbit allergy