6 December 2012: 15:30-17:00 G.04 (HICC)  
The Hyderabad International Convention Centre (HICC) in Hyderabad, India

WISC 2012; WAO International Scientific Conference  
Postgraduate Course 22: URTICARIA & ANGIOEDEMA TRACK  
-Diagnosis and Treatment of Hereditary Angioedema (HAE)

**Acute and Prophylactic Management**

Since HAE is a disease due to C1-INH gene disorder, management of the symptoms, rather than cure-oriented treatment, is important in daily practice.

Chairpersons: Jonathan Bernstein (United States), Ramesh B Ramaiah (India)

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Department of Dermatology,  
Graduate School of Biomedical Sciences  
Hiroshima University
Principles for the management of HAE

- Avoid aggravating factors:
  Infection, psychological stress, fatigue, etc.

- Avoid and/or be prepared for triggering factors:
  Trauma, dental actions, surgical operation, etc.

- Medications:
  - Acute treatment for attacks: Acute on demand treatment
  - Short-term prophylaxis: For scheduled operation, special event, etc.
  - Long-term prophylaxis: For frequently occurring severe and unpredictable attacks
Action mechanism of C1-INH

Contact system

Coagulation system

Kinin system

Pre-kalikrein

HMW-Kininogen

Bradykinin

Kinin system

FXII

FXIIa

Negative surface exposed by trauma/unknown precipitants

C1-INH

Complement system

FXI

FXIa

Fibrin

FBD, D-dimer

Fibrinolysis

ACE inhibitor

Inactivated peptides

Kininase II (ACE)

Bradykinin receptor 2

Angioedema

Action point of C1-INH

Activation ➔ Inhibition
Action mechanism of C1-INH and treatments of HAE

Kinin system
- Pre-kalikrein
- Kaikrein
- HMW-Kininogen
- Bradykinin

Coagulation
- FXII
- FXIIa
- FXIa

Contact system
- C1
- C1qrs

Complement system
- Enhance C1-INH production (anabolic steroids)
- Replace external C1-INH (purified from plasma, recombinant, FFP)
- Anti-fibrinolysis (ε-aminocaproic acid, tranexamic acid)

ACE inhibitor
- Kininase II (ACE)

Inactivated peptides

Bradykinin receptor 2

Angioedema

Action point of C1-INH
Action mechanism of C1-INH
Drugs historically used for HAE

For long-term prophylaxis:

1. **Anabolic steroids (po)**
   - Danazol, stanozol, oxandrolone, methyltestosterone
   - Efficacy and side effects are dose-related
   - Recommended at the lowest dose that achieves control

2. **Anti-fibrinolytic agents (po)**
   - Epsilon aminocaproic acid, tranexamic acid
   - Less effective, but safer
   - (unusual side effect; enhanced thrombosis)

For acute action:

3. **C1-INH replacement (iv)**
   - Fresh frozen plasma (FPP)
   - Generally effective in treating acute attacks, but
   - Sometimes lacks efficacy, or can cause sudden worsening

Side effects:
- Weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile
- Nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes
- Risk of infection by unknown microorganisms, May worsen symptoms
Acute management of HAE attacks

Epinephrine, corticosteroids or antihistamines do not have a sufficient effect and not recommended.
<table>
<thead>
<tr>
<th></th>
<th>Berinert®</th>
<th>CINRYZE®</th>
<th>Ruconest®</th>
<th>Firazyr®</th>
<th>KAIBITOR®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
<td>Plasma-derived human C1-INH pasteurized, nanofiltered (20nm &amp;15nm) Berinert-unique formulation</td>
<td>Plasma-derived human C1-INH pasteurized, nanofiltered (15nm &amp;15nm) Cinryze-unique formulation</td>
<td>Recombinant human C1-INH</td>
<td>Bradykinin 2 receptor antagonist Peptide (MW 1,304)</td>
<td>Kallikrein inhibitor Small protein (MW 7,053)</td>
</tr>
<tr>
<td><strong>Human plasma</strong></td>
<td>Human plasma</td>
<td>Human plasma</td>
<td>Extracted from transgenic rabbit milk</td>
<td>Synthetic</td>
<td>Recombinant (in yeast <em>Pichia pastoris</em>)</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>22.4-36.1 hrs</td>
<td>56-62 hrs</td>
<td>2-3 hrs</td>
<td>1-2 hrs</td>
<td>2.0 hrs</td>
</tr>
<tr>
<td><strong>Formulation / Storage</strong></td>
<td>Lyophilized / 2-25°C</td>
<td>Lyophilized / 2-25°C</td>
<td>Lyophilized/ refrigerated (?)</td>
<td>Liquid, prefilled syringe/ 2-25°C</td>
<td>Liquid/ refrigerated (2-8°C)</td>
</tr>
<tr>
<td><strong>Shelf-life</strong></td>
<td>30 months</td>
<td>24-36 months</td>
<td>4 years</td>
<td>24 months</td>
<td>3 years (2-8°C)</td>
</tr>
<tr>
<td><strong>Pack size / Volume</strong></td>
<td>500 U in 10 ml</td>
<td>500 U in 5 ml</td>
<td>2100 U in 14 ml</td>
<td>3ml(30mg)</td>
<td>3 x 1 ml(10mg)</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Label for all acute attacks</td>
<td>Label for all acute attacks (EU, AU, CA, IL)</td>
<td>Label for all acute attacks, only if negative rabbit allergy (IgE)</td>
<td>Label for all acute attacks</td>
<td>Label for all acute attacks</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>Suitable (but off-label)</td>
<td>On Label: Long &amp; Short Term Prophylaxis (US, EU, AU, CA, IL)</td>
<td>not suitable</td>
<td>not suitable</td>
<td>not suitable</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v.</td>
<td>S.c.</td>
<td>S.c.</td>
</tr>
<tr>
<td><strong>Self-administration/Home therapy</strong></td>
<td>Approved in US, EU</td>
<td>Approved in US, EU, Australia, Canada &amp; Israel</td>
<td>Not approved</td>
<td>Approved for up to 3 injections in 24hrs</td>
<td>Not approved</td>
</tr>
</tbody>
</table>

Berinert and Cinryze are in the same class therapeutics, but have different pharmacological characteristics due to different excipients.
Per-patient analysis of efficacy pdC1-INH in I.M.P.A.C.T. (Berinert-P®)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>All attacks (n = 57)</th>
<th>Abdominal (n = 51)</th>
<th>Peripheral (n = 30)</th>
<th>Facial (n = 21)</th>
<th>Laryngeal (n = 16)</th>
<th>Placebo (n = 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset of symptom relief (h)</td>
<td>Median (range)</td>
<td>0.46 (0.17–497.0)†</td>
<td>0.39 (0.17–497.0)†</td>
<td>0.43 (0.17–27.16)</td>
<td>0.48 (0.10–5.61)</td>
<td>0.44 (0.20–1.25)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>0.39; 0.53</td>
<td>0.33; 0.48</td>
<td>0.29; 0.55</td>
<td>0.25; 0.79</td>
<td>0.31; 0.69</td>
</tr>
<tr>
<td>Number (%) of patients with individual average time to onset of symptom relief of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 h</td>
<td>51 (89.5)</td>
<td>49 (96.1)</td>
<td>27 (90.0)</td>
<td>18 (85.7)</td>
<td>14 (87.5)</td>
<td>n.a.</td>
</tr>
<tr>
<td>&lt;4 h</td>
<td>55 (96.5)</td>
<td>50 (98.0)</td>
<td>29 (96.7)</td>
<td>20 (95.2)</td>
<td>16 (100)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Time to complete resolution of HAE symptoms (h)</td>
<td>Median (range)</td>
<td>15.48 (0.64–497.0)†</td>
<td>12.75 (0.64–497.0)†</td>
<td>22.73 (5.07–497.0)†</td>
<td>26.63 (0.95–61.83)</td>
<td>5.79 (0.63–48.25)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>11.64; 21.59</td>
<td>8.19, 15.19</td>
<td>18.73, 27.16</td>
<td>7.38, 43.01</td>
<td>2.05, 25.90</td>
</tr>
</tbody>
</table>

bw, body weight; C1-INH, C1 esterase inhibitor; CI, confidence interval; HAE, Hereditary Angioedema; N, number of patients; n.a., not applicable.

*Of the total of 1085 attacks, the dose of C1-INH concentrate was 40–60 U/kg bw for 12 attacks (in six patients).
†The maximum time to complete resolution of 497 h occurred in a patient for whom retrospective genetic testing did not confirm the diagnosis of HAE; the patient was treated for one event. This value was also used for conservative imputations of some missing values.
‡Based on actual values recorded; see Craig et al. (9). No imputation was used for the time to onset of symptom relief. Missing values of time to complete resolution were imputed with the maximum value of 1486 h.
§Data for time to onset of symptom relief are missing for one patient.
Open Label Extension: Study 2006-1 Demographics

• Total of 113 subjects received CINRYZE
  – 101 subjects were treated for a total of 609 separate HAE attacks (GI: 353, Extremity: 86, Laryngeal: 84, Facial: 72, GU: 13, Unk: 1)
  – 12 subjects received CINRYZE only for pre-procedure prevention (1,000 unit/attack) n=101 subjects

<table>
<thead>
<tr>
<th>Number of attacks with unequivocal relief of the defining symptom, relative to the start of CINRYZE dosing</th>
<th>Within 1 h</th>
<th>Within 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>412/609</td>
<td>529/609</td>
</tr>
<tr>
<td></td>
<td>(68%)</td>
<td>(87%)</td>
</tr>
</tbody>
</table>

Unequivocal Relief = 3 consecutive assessments of improvement at 15 min intervals

• Median # attacks treated per subject = 3 (range 1-57)
• For subjects with >1 HAE attack, the efficacy of CINRYZE did not diminish with subsequent repeat administrations.


Provided by ViroPharma Inc.
<table>
<thead>
<tr>
<th>Agent (Brand)</th>
<th>Study designation/ reference</th>
<th>Time to improvement</th>
<th>Response at 4 h</th>
<th>Time to complete resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-INH, purified from sera (Berinert)</td>
<td>IMPACT1 (Craig et al, 2009)</td>
<td>0.5 h (20U/kg)</td>
<td>86 %</td>
<td>4.9 h (20 U/kg)</td>
</tr>
<tr>
<td>C1-INH, purified from sera (Cinryze)</td>
<td>CHANGE 1 (Zuraw et al, 2010)</td>
<td>2 h</td>
<td>60 %</td>
<td>12.3 h</td>
</tr>
<tr>
<td>C1-INH, recombinant (Rhucin)</td>
<td>(Zuraw et al, 2010)</td>
<td>66 min (median) (100 U/kg)</td>
<td>86.2 %</td>
<td>N/A</td>
</tr>
<tr>
<td>Ecallantide (Kalbitor)</td>
<td>EDEMA3 (Cicardi et al, 2010)</td>
<td>67 min</td>
<td>54.5 %</td>
<td>N/A</td>
</tr>
<tr>
<td>Ecallantide (Kalbitor)</td>
<td>EDEMA4 (Levy et al, 2010)</td>
<td>N/A</td>
<td>68.8 %</td>
<td>N/A</td>
</tr>
<tr>
<td>Icatibant (Firazyr)</td>
<td>FAST-1/FAST-2 (Cicardi et al, 2010)</td>
<td>2.5 h/2.0 h</td>
<td>66.7 %</td>
<td>8.5 h/10.0 h</td>
</tr>
<tr>
<td>Icatibant (Firazyr)</td>
<td>FAST-3 (Lumry et al, 2011)</td>
<td>1.5 h</td>
<td>80.6 %</td>
<td>8.0 h</td>
</tr>
</tbody>
</table>
Subgroup analyses. Times to onset of symptom free and complete resolution of HAE symptoms in I.M.P.A.C.T.2

Kinetics of C1-INH plasma activity after the infusion of Berinert-P

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (on demand; n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC* (for dose of 15 U/kg [(U × hr)/mL])</td>
<td>13.4</td>
<td>2.9-29.4</td>
</tr>
<tr>
<td>T$_{max}$† (hr)</td>
<td>0.6</td>
<td>0.1-2.0</td>
</tr>
<tr>
<td>t$_{1/2}$‡ (hr)</td>
<td>32.9</td>
<td>7.3-70.5</td>
</tr>
<tr>
<td>MRT§ (hr)</td>
<td>47.5</td>
<td>10.5-101.7</td>
</tr>
<tr>
<td>Cll (mL/[kg × hr])</td>
<td>1.1</td>
<td>0.5-5.2</td>
</tr>
<tr>
<td>Vss¶ (mL/kg)</td>
<td>50.0</td>
<td>41.6-62.3</td>
</tr>
<tr>
<td>Adults (IRD; n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (for dose of 15 U/kg [(U × hr)/mL])</td>
<td>15.7</td>
<td>6.3-86.1</td>
</tr>
<tr>
<td>T$_{max}$ (hr)</td>
<td>0.5</td>
<td>0.3-8.0</td>
</tr>
<tr>
<td>t$_{1/2}$ (hr)</td>
<td>30.9**</td>
<td>10.3-96.0</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>44.6**</td>
<td>14.9-138.5</td>
</tr>
<tr>
<td>Cl (mL/[kg × hr])</td>
<td>1.0</td>
<td>0.2-2.4</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>37.5††</td>
<td>24.1-66.4</td>
</tr>
<tr>
<td>Adults (on demand; n = 19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (for dose of 15 U/kg [(U × hr)/mL])</td>
<td>16.7</td>
<td>9.5-69.7</td>
</tr>
<tr>
<td>T$_{max}$ (hr)</td>
<td>1.0</td>
<td>0.3-32.0</td>
</tr>
<tr>
<td>t$_{1/2}$ (hr)</td>
<td>39.1</td>
<td>19.4-90.4</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>56.5</td>
<td>28.0-130.5</td>
</tr>
<tr>
<td>Cl (mL/[kg × hr])</td>
<td>0.9</td>
<td>0.2-1.6</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>56.7</td>
<td>23.3-69.2</td>
</tr>
</tbody>
</table>

* Area under the elimination curve.
† Median time to maximum functional pC1-INH level.
‡ Terminal elimination half-life.
§ Mean residence time.
¶ Total clearance.
‖ Volume of distribution at steady state.
** p = 0.052 versus adults on demand.
†† p = 0.004 versus adults on demand.

C1 INH Plasma Concentration after 1 and 2 Injections of 1000 IU CINRYZE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Dose</th>
<th>Double Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{baseline}}$ (U/ml)</td>
<td>$0.31 \pm 0.20$ ($n = 12$)</td>
<td>$0.33 \pm 0.20$ ($n = 12$)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (U/ml)</td>
<td>$0.68 \pm 0.08$ ($n = 12$)</td>
<td>$0.85 \pm 0.12$ ($n = 13$)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>$3.9 \pm 7.3$ ($n = 12$)</td>
<td>$2.7 \pm 1.9$ ($n = 13$)</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-t)}$ (U·h/ml)</td>
<td>$74.5 \pm 30.3$ ($n = 12$)</td>
<td>$95.9 \pm 19.6$ ($n = 13$)</td>
</tr>
<tr>
<td>Clearance (ml/min)</td>
<td>$0.85 \pm 1.07$ ($n = 7$)</td>
<td>$1.17 \pm 0.78$ ($n = 9$)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>$56 \pm 36$ ($n = 7$)</td>
<td>$62 \pm 38$ ($n = 9$)</td>
</tr>
</tbody>
</table>

Failure of treatment timing may be fatal

- Tranexamic acid 1g
- Methyl predonisolon 125mg

Bonzol® 100mg/day
Celcect® (antihistamine) 30mg/day

Dyspnea hoarseness

AM 10:00 Admission
14:00 tooth extraction
20:00 0:00 edema
Failure of treatment timing may be fatal

Bonzol® 100mg/day
Celcect® (antihistamine) 30mg/day

Dyspnea hoarseness
Severe laryngeal edema

Cannot be intubated, received tracheotomy

Tranexamic acid 1g
Methyl predonisolone 125mg
Self-administration / home therapy for HAE

Berinert®: iv
in US, EU

CINRYZE®: iv
in US, EU, Australia, Canada & Israel

Firazyr®: sc
US, Europe, Russia, Australia, South America

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Step 6: Infusion
As instructed by your healthcare provider:
- Insert the butterfly needle of the infusion set tubing into your vein (Figure 11).
- If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.
- To make sure that the needle is in a vein, gently pull back on the syringe plunger and check to see if blood is in the tubing (Figure 12). If there is blood present, then the needle is in a vein. If there is no blood present, remove the needle and repeat this step using a new needle, new administration tubing, and a different injection site.
- Remove the tourniquet.
- Inject the BERINERT solution slowly at a rate of approximately 4 ml per minute (Figure 13).

Figure 11

4. After infusing CINRYZE, remove the infusion set and discard. Cover infusion site with an adhesive bandage. The amount of drug product left in the infusion set will not affect your treatment. Dispose of all unused solution, the empty vials, and the used needles and syringe in an appropriate container used for throwing away waste that might hurt others if not handled properly.

Figure 12

It is a good idea to record the lot number from the CINRYZE vial label every time you use CINRYZE.

Figure 13

Figure L

Step 13. Push the plunger, at the top of the syringe, over at least 30 seconds until no FIRAZYR is in the syringe. See Figure M.

Figure M

Step 14. Release the skin fold and gently pull the needle out. See Figure N.

Figure N

Disposal of your used FIRAZYR prefilled syringe
Prophylactic management of HAE symptoms

- Short-term prophylaxis: For a scheduled operation, special events, etc.

- Long-term prophylaxis: For frequently occurring unpredictable and severe attacks

Patients not managed successfully with on demand therapy should be considered for long-term prophylaxis.

Very expensive; ca $3,000 / treatment
Phase 3 Study of HAE Prevention: Study 2005-1/B by C1-INH

Subject Event Chart

In conclusion, prophylactic regular administration of C1-inhibitor with Cinryze twice a week largely reduces attacks of HAE. However, it is also important to take a balance between the effect and cost.
Points should be considered for the decisions of pharmacological treatment of HAE

- Severity
- Location
- Access to acute care
- Other co-morbid conditions
- Individual circumstances
- Patient values and preferences, including cost

Clinical symptoms of HAE should be evaluated both in terms of severity of individual symptoms (attacks) and frequency (intervals).

- **Severity of individual symptoms**
  - Airway obstruction: suffocation, risk of death
  - Pain: intolerability
  - Function: ADL, eating, finger manipulation, etc.

- **Frequency of the symptoms**
  - How frequently they occur?
    - Every few days, weekly, monthly or a few times a year
The countries where the modern five medications for HAE is licensed (Berinert, Cinryze, Firazyr, Kalbitor, Ruconest)
Importance of

- **Education**: patients, physicians
- **Drug access**: physical, economical
- **Public support**: government, other organization
- **Individual management plan**: minimum and sufficient
Thank you for your attention