Nanofiltered C1 inhibitor Concentrate for Treatment of Hereditary Angioedema


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Background

**Hereditary Angioedema**

- Hereditary angioedema (HAE) is a rare genetic disorder previously called hereditary angioneurotic edema
- Characterized by recurrent acute attacks of angioedema, most frequently oropharyngeal and/or abdominal
- Total prevalence unknown – HAE association putting together a patient registry
- HAE type I (85%) – autosomal dominant inherited deficiency of C1 inhibitor (C1-INH)
- HAE type II (15%) – normal antigenic levels but low functional levels of C1-INH
- Recent reports have described HAE type III which is thought to be due to a mutation in Factor XII
Background

- Attacks are unpredictable – C4 and C1-INH levels do not predict attack frequency or severity
- Laryngeal attacks associated with a substantial risk of death
  - 30% of patients with airway attacks may die of asphyxiation
- Abdominal attacks can lead to unnecessary abdominal surgery
- Anabolic androgens and antifibrinolytic drugs have been used for prophylaxis but are associated with significant side effects and not useful for acute attacks
- Especially difficult for women to tolerate androgen therapy
Background

- C1-INH concentrate available for more than 30 yrs outside the US
- Use halted in 1980s due to HIV/AIDS, but subsequently restarted and used in other countries without viral transmission
- C1-INH concentrate has been shown to be effective to treat and prevent attacks
  - Partially purified C1-INH from pooled plasma infused into 8 patients with HAE during acute attacks, 5 patients had resolution of symptoms without any “untoward” effects (Gadek et al NEJM 1980)
  - Double-blind, placebo controlled study of vapor-heated C1-INH concentrate showed significant decrease in time to symptom improvement during an attack and significantly decreased number of attacks (Waytes et al NEJM 1996)
  - Randomized, double-blind, placebo controlled trial of C1-INH concentrate showed significant decrease in time to symptom resolution for acute attacks of HAE (Craig et al JACI 2009)
Background

- This study evaluates a nanofiltered C1 inhibitor concentrate (Cinryze®, ViroPharma) for treatment and prophylaxis of HAE attacks

- Nanofiltration is the new aspect of this drug (a similar C1-INH product made by Berinert is not nanofiltered but also used for treatment and prophylaxis)
Case

- 32 year old female presented with several months of lip and tongue angioedema
- Unresponsive to repeated courses of steroids, antihistamines, and injectable epinephrine
- During attacks she was unable to close her mouth or speak
- Never experienced airway compromise
- CBC, blood chemistries, C1-INH level and function, C3, C4, ANA, thyroid function and antibodies within normal limits
- Full hematologic evaluation negative for lymphoma or carcinoid tumor
- Prophylactic danazol and oral progesterone decreased but did not prevent repeated attacks
Methods – study oversight

- Two double-blind, placebo controlled trials
  - Acute attack treatment trial
  - Prophylactic trial
- Approved by appropriate institutional IRBs
- Sponsored by Lev pharmaceuticals
- Data analysis performed by investigators with consulting statisticians hired by Lev Pharma
Methods – study participants

- Participants 6 y/o or older
- Confirmed dx of HAE: low C4, normal C1q, low antigenic or functional C1-INH level or C1-INH gene mutation
- Excluded:
  - low C1q level
  - h/o B-cell cancer
  - presence of anti-C1-INH antibody
  - h/o allergic reaction to C1-INH or other blood/plasma product
  - pregnancy, narcotic addiction
- Included patients on androgen and antifibrinolytic therapy
Methods – C1-INH preparation

- C1-INH concentrate prepared by Sanquin in the Netherlands with plasma obtained in the US
- Purified by a combination of cryo-precipitation, ion-exchange chromatography, and polyethylene glycol precipitation
- Resulting C1-INH fraction was pasteurized, double nanofiltered, and lyophilized
Methods – Treatment of Acute Attacks

- Subjects with an acute attack were assessed to determine if the attack qualified for trial eligibility.
- Excluded if used narcotics within 7 days or increased use of androgens within 5 days.
- Attacks of laryngeal angioedema excluded (subjects treated with C1-INH concentrate).
- Subjects asked to rate their angioedema symptoms.
- Only those with moderate or severe attacks that involved the abdomen, face, or external genitalia were eligible for randomization.
Methods – Treatment of Acute Attacks

1A

Assessed for eligibility (n = 324)

Non eligible (n = 117)

Eligible for randomization (n = 207)

No randomized attack (n = 136)

Randomized attacks (n = 71)

Allocated to placebo (n = 35)

Did not meet criteria for attack (n = 2)

Allocated to C1 inhibitor (n = 36)

Did not meet criteria for attack (n = 1)

Analysed for primary endpoint (n = 33)

Analysed for primary endpoint (n = 35)
Methods – Treatment of Acute Attacks

- Subjects eligible for randomization receive C1-INH 1000U in 10mL sterile water or placebo (10mL saline), IV over 10 minutes.

- Asked to report severity of symptoms every 15 mins, if symptoms not absent or better at 60 mins a second injection of the same study drug was given:
  - Absent now and absent before
  - Absent now but present before
  - Present, symptoms new
  - Present, symptoms worse or the same
  - Present, symptoms better
Methods – Treatment Study

- Unequivocal relief defined as 3 consecutive reports of improvement at the defining site
- If 4 hrs elapsed without unequivocal relief rescue therapy with open-label C1-INH was offered
- Levels of C1-INH and C4 measured before infusion and 60 mins, 2 hrs, and 4 hrs after infusion
Methods – Treatment Study

- Primary endpoint – time from administration of the study drug to unequivocal relief at defining site

- Secondary endpoints –
  - percentage of subjects with unequivocal relief within 4 hr
  - time to complete resolution of attack
  - effects of treatment on C1-INH and C4 levels

- Blinded review of all screening and pretreatment C4 levels evaluated by independent expert to determine if true angioedema attacks
Methods – Prophylaxis Study

- C1-INH compared with placebo for preventing angioedema attacks
- Patients served as their own controls
- Eligible: subjects randomly assigned to study drug in acute-attack treatment arm with h/o at least 2 attacks per month
- Not allowed to change prophylactic androgen or antifibrinolytic meds during the prophylaxis trial
- Randomly assigned to receive C1-INH or placebo every 3-4 days x 12 weeks, during the second 12 weeks they received the other medication
- Acute attacks eligible for rescue treatment with open label C1-INH, prophylactic study drugs delayed 24 hrs after treatment for acute attack
Methods – Prophylaxis Study

- Primary endpoint: number of attacks of angioedema during treatment period

- Secondary endpoints –
  - average severity of attacks
  - number of open-label C1-INH injections
  - total number of days of swelling
  - changes in C1-INH level
Methods – Prophylaxis Study

1B

Subjects randomized in acute study (n = 71)

Eligible (n = 50)

Randomized (n = 26)

Dropped out prior to 1st randomized dose (n = 2)

Dropped out prior to 2nd period (n = 1)

Allocated to placebo 1st period (n = 12)

Allocated to C1 inhibitor 1st period (n = 12)

Dropped out prior to end of 2nd period (n = 1)

Completed 2nd period (n = 10)

Crossed over to placebo 2nd period (n = 11)

Crossed over to C1 inhibitor 2nd period (n = 11)

Completed 2nd period (n = 10)

Dropped out prior to end of 2nd period (n = 1)

Analyzed for primary endpoint (n = 11)

History of <2 attacks/month (n = 21)

Study limited to first 26 subjects who sign consent
Methods – Statistical Analysis

- Need for rescue medication (narcotics or open-label C1-INH) within 4 hrs of study drug injections was considered a treatment failure and competing event
- Rescue interventions precluded observation of the event of interest
- Data for subjects who did not have onset of unequivocal relief of symptoms by 4 hrs after treatment were censored at 4 hrs
Results: Baseline Characteristics of the Subjects in the Acute-Attack Treatment Trial and the Prophylaxis Trial

Table 1. Baseline Characteristics of the Subjects in the Acute-Attack Treatment Trial and the Prophylaxis Trial.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute-Attack Treatment Trial</th>
<th>Prophylaxis Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=33)</td>
<td>Placebo with Crossover to C1 Inhibitor (N=11)</td>
</tr>
<tr>
<td></td>
<td>C1 Inhibitor (N=35)</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>36.2±13.8</td>
<td>34.5±14.8</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>27 (81.8)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>77.4±22.6</td>
<td>76.3±25.7</td>
</tr>
<tr>
<td>Height — cm</td>
<td>167.8±10.4</td>
<td>163.2±8.8</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>20.5±18.8</td>
<td>16.8±7.9</td>
</tr>
<tr>
<td>Type II hereditary angioedema — no. (%)</td>
<td>6 (18.2)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>30 (90.9)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Site of defining attack — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>26 (78.8)</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>External genitalia</td>
<td>2 (6.1)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Face</td>
<td>5 (15.2)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Androgen therapy at baseline — no. (%)‡</td>
<td>11 (33.3)</td>
<td>16 (45.7)</td>
</tr>
</tbody>
</table>

* Plus—minus values are means ±SD. Differences between treatment groups were not significant.
† Race or ethnic group was self-reported.
‡ Androgen therapy in the prophylaxis trial consisted of oxandrolone in different doses.

*3 subjects judged by the independent, blinded expert to have had episodes that were not true attacks of angioedema so were excluded from the final analysis.
Results – Treatment Study

- Median time to onset of unequivocal relief was 2 hrs in the C1-INH group as compared to more that 4 hrs in the placebo group (estimated success ratio 2.41, 95% CI 1.17 to 4.95, p = 0.02)

- When the three subjects judged not to have true angioedema attacks were included in primary endpoint analysis the C1-INH group still have significant benefit (estimated success ratio 2.05, 95% CI 1.01 to 4.16, p = 0.048)

- No evidence of heterogeneity according to study site, BMI, sex, time from onset of attack to randomization, or defining attack site
Onset of unequivocal relief occurred within 4 hrs in 21/35 subjects in the C1-INH group and 14/33 in placebo group (p = 0.06)
Second dose of blinded study drug was administered to 23 subjects in the C1-INH group and 28 subjects in the placebo group.
Results – Treatment Study

- Median time to complete resolution of symptoms was 12.3 hrs in C1-INH group vs 25 hrs in the placebo group (p = 0.004)
- Both antigenic and functional levels of C1-INH increased in the C1-INH group but not the placebo group (p<0.001)
- C4 levels did not change significantly during the observation period
Results –Prophylactic Study

- 71 subjects randomized to the study group in the acute attack treatment trial, 24 were enrolled in the prophylaxis trial

- 12 randomized to each group: C1-INH every 3-4 days x 12 weeks then placebo every 3-4 days x 12 weeks or vice versa

- One subject in each group did not complete the prophylactic trial (included in the end point analysis)

- Average difference in attack rates between the C1-INH and placebo groups was 6.47 attacks (95% CI 4.21 to 8.73, p<0.001)

- No evidence of sequence effect (p = 0.54) or period effect (p = 0.42)
One subject did not respond well during treatment arm, under extreme stress at the time (stress can trigger attacks despite C1-INH treatment), currently doing well on active treatment.
Results – Prophylactic Study

- Severity of attacks were assessed on a 3-point scale (1 = mild, 2 = moderate, 3 = severe)
- C1-INH group had significantly lower severity scores than placebo group (1.3 vs. 1.9, p<0.001)
- Duration of attacks shorter in C1-INH group vs. placebo (2.1 vs. 3.4 days, p<0.002)
- 11 subjects in C1-INH group required open-label rescue vs 22 in the placebo group
- C1-INH prophylaxis associated with fewer open label injections (4.7 vs 15.4, p<0.001)
- C1-INH prophylaxis associated with fewer days of swelling (10.7 vs. 29.6, p<0.001)
Major Events during the Prophylaxis Trial
Results – Open Label Extension

- After completion of both trials, 88 subjects chose to enroll in open-label extension study for treatment of acute attacks
- C1-INH was given for 447 attacks (range 1-57 attacks, median 3)
- Median time to response was 30 minutes
- Proportion of attacks that responded to treatment within 4 hrs was 93% (Kaplan-Meier estimate)
Results – Adverse Events

- Acute attack trial
  - 6/36 subjects in C1-INH group had adverse events
  - 7/35 subjects in the placebo group had adverse events
  - 3 possibly related to the study drug – tetany, contact dermatitis, rash

- Prophylactic trial
  - 21/24 subjects had adverse events
  - 3 possibly related to study drug – pruritis/rash, lightheadedness, fever
## Adverse Events in the Acute-Attack Treatment Trial and the Prophylaxis Trial

<table>
<thead>
<tr>
<th>Placebo (N=35)</th>
<th>Acute-Attack Treatment Trial</th>
<th>C1 Inhibitor (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject No.</strong></td>
<td><strong>Adverse Event</strong></td>
<td><strong>Level of Severity</strong></td>
</tr>
<tr>
<td>1</td>
<td>Anorexia and fatigue</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Vertigo</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Decrease in blood pressure‡</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Nausea</td>
<td>Mild</td>
</tr>
<tr>
<td>5</td>
<td>Carpal pedal spasm</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>Chest pain¶</td>
<td>Severe</td>
</tr>
<tr>
<td>7</td>
<td>Contact dermatitis</td>
<td>Mild</td>
</tr>
<tr>
<td>8</td>
<td>Chest discomfort†</td>
<td>Severe</td>
</tr>
<tr>
<td>9</td>
<td>Chipped tooth</td>
<td>Mild</td>
</tr>
</tbody>
</table>

### Prophylaxis Trial

#### During Placebo Period (N=12)

<table>
<thead>
<tr>
<th><strong>Subject No.</strong></th>
<th><strong>Adverse Event</strong></th>
<th><strong>Level of Severity</strong></th>
<th><strong>Related to Study Drug†</strong></th>
<th><strong>Date of Adverse Event</strong></th>
<th><strong>Date of C1 inhibitor Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Chest discomfort†</td>
<td>Severe</td>
<td>Definitely</td>
<td>3/26/07</td>
<td>3/22/07</td>
</tr>
<tr>
<td>8</td>
<td>Cough</td>
<td>Moderate</td>
<td>Definitely</td>
<td>3/26/07</td>
<td>3/22/07</td>
</tr>
<tr>
<td>8</td>
<td>Erythema</td>
<td>Moderate</td>
<td>Possibly</td>
<td>3/9/07</td>
<td>3/9/07</td>
</tr>
</tbody>
</table>

#### During C1 inhibitor Period (N=12)

<table>
<thead>
<tr>
<th><strong>Subject No.</strong></th>
<th><strong>Adverse Event</strong></th>
<th><strong>Level of Severity</strong></th>
<th><strong>Related to Study Drug†</strong></th>
<th><strong>Date of Adverse Event</strong></th>
<th><strong>Date of C1 inhibitor Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Pruritus and rash</td>
<td>Mild</td>
<td>Definitely</td>
<td>11/7/05</td>
<td>11/4/05</td>
</tr>
<tr>
<td>8</td>
<td>Lightheadedness</td>
<td>Moderate</td>
<td>Possibly</td>
<td>12/26/06</td>
<td>12/26/06</td>
</tr>
<tr>
<td>16</td>
<td>Fever</td>
<td>Moderate</td>
<td>Possibly</td>
<td>3/27/06</td>
<td>3/27/06</td>
</tr>
</tbody>
</table>

* For the acute-attack treatment trial, all adverse events, irrespective of their relationship to the study drug, are listed. For the prophylaxis trial, only adverse events that were possibly or definitely related to the study drug are listed; adverse events not related to the study drug are listed in Table 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The date of the C1 inhibitor dose (month/day/year) is the date of the last dose received (closed-label or open-label) before the adverse event.

† This column reflects the judgment of the study site investigators, who were not aware of the treatment assignments.

‡ Blood pressure was 89/69 mm Hg before randomized C1 inhibitor treatment and fell to 86/64 mm Hg 30 minutes after therapy.

¶ Blood pressure was 160/100 mm Hg before randomized placebo treatment; 4 hours later, before open-label C1 inhibitor treatment, blood pressure was 112/90 mm Hg, and it fell to 108/80 mm Hg 30 minutes after open-label C1 inhibitor treatment.

†† Severe chest pain occurred 19 days after randomized placebo treatment plus open-label C1 inhibitor rescue therapy.

†‡ Severe chest discomfort after the placebo injection was relieved with intravenous fluids plus antacid treatment.
Discussion

- Several trials, some placebo controlled, have supported the use of C1-INH replacement therapy for acute attacks of HAE.

- In this acute attack trial, nanofiltered C1-INH significantly reduced the time to the onset of unequivocal relief of symptoms as compared with placebo.

- 40% of subjects in the C1-INH group still did not have unequivocal relief in 4 hrs, higher than other published studies.

- Craig et al found 15% failure rate with high dose C1-INH and 27% with low dose C1-INH at 4 hrs (Craig et al JACI 2009).

- In the open-label assessment 93% of subjects had improvement within 4 hrs, efficacy much higher in open label than placebo-controlled trials.
Discussion

- HAE patients often require prophylaxis before dental procedures etc, C1-INH has been shown to be effective for this short-term prophylaxis (DeSerres et al Transfus Apher Sci 2003, Prematta et al Ann All Asthma Immunol 2007)

- This prophylactic trial of C1-INH showed significant decreases in frequency of acute attacks compared with placebo during a 12 week period (with patients serving as their own controls)

- Results consistent with a prophylactic trial of vapor-heated C1-INH (Waytes et al NEJM 1996)
Discussion

- Optimal dosing for C1-INH as both treatment for acute attacks and for prophylaxis has yet to be determined.
- Most participants in the acute-attack treatment trial required a second dose of study drug.
- In the prophylaxis trial some patients still required rescue injections for attacks.
- This is the first preparation to combine nanofiltration with pasteurization to theoretically improve the safety profile of this pooled plasma product.
- Both Berinert and Lev Pharma products are now approved by the FDA – either can be used for prophylaxis or treatment.
- Ability to self-infuse C1-INH can give HAE patients increased security and independence.
Case - Resolution

- Pt saw Dr. Busse for consultation, during the visit had a severe attack of angioedema and received C1-INH with complete resolution of her symptoms

- The next night she was admitted to our ICU where on several occasions she responded to infusion of C1-INH with rapid and complete resolution of her symptoms

- Eventually started on C1-INH infusion at home with much improvement in symptoms

- Genetic analysis did not reveal a mutation in the Factor XII gene (T309R, nucleotide position 1032).
Presentation

5 minutes after C1-INH 1000U IV

Photo credit: Dr. Joon Park
Conclusions

- A recently developed preparation of C1 inhibitor concentrate was evaluated in patients with hereditary angioedema in two trials.
- In the acute-attack treatment trial, the time to relief of an acute attack of angioedema was significantly shorter with the C1 inhibitor than with placebo.
- In the prophylaxis trial, the attack rate over a 12-week period was significantly lower with the C1 inhibitor than with placebo.
Other New Drugs

Cicardi et al NEJM 2010

- Ecallantide – recombinant plasma kallikrein inhibitor
- Double-blind, placebo-controlled trial in patients with acute HAE attacks
- Patient-reported treatment outcome scores ($p = 0.004$) and mean symptom complex severity scores ($p = 0.01$) significantly better in the ecallantide group vs. placebo

Cicardi et al NEJM 2010

- Icatibant – selective bradykinin B2 receptor antagonist
- Double-blind, placebo-controlled and tranexamic acid arms, patients with acute HAE attacks
- Primary endpoint was time to clinically significant symptom relief: Icatibant found to be significantly better than tranexamic acid ($p<0.001$) but not placebo ($p = 0.14$)
Dysregulation of Complement, Coagulation, and Contact Cascades in Hereditary Angioedema.