New Approaches to Treatment of Hereditary Angioedema

Aleena Banerji, MD
Assistant Professor
Assistant Training Program Director
Division of Rheumatology Allergy & Clinical Immunology
Harvard Medical School
Massachusetts General Hospital
Boston, MA
Disclosures

- Shire: Advisory Board, Research
- CSL Behring: Advisory Board
- Dyax: Consulting
Objectives

- Discuss novel treatment options for hereditary angioedema
- Review consensus guidelines for the treatment of hereditary angioedema
- Compare long-term prophylaxis vs. on-demand treatment
- Discuss the benefits of self-administration for patients
Hereditary Angioedema Treatment Goals

- On-demand treatment of acute attacks
  - To abort an ongoing attack of angioedema
  - To prevent an angioedema attack from affecting quality of life

- Prophylactic treatment
  - Short-term prophylaxis to prevent an expected attack especially in the setting of exposure to known triggers
  - Long-term prophylaxis to minimize the frequency and severity of recurrent attacks
“Older” Options for Treatment of HAE

- Treatment of acute attacks
  - Supportive Care
  - FFP

- Long-term prophylaxis
  - Anabolic Androgens
  - Antifibrinolytics

- Short-term prophylaxis
  - FFP
  - Anabolic androgens
Side Effects of Antifibrinolytic Agents

- Most common side effects
  - Nausea, vomiting and diarrhea
  - Vertigo
  - Postural hypotension
  - Fatigue and myalgias

- Theoretical concerns
  - Risk of vascular thrombosis
  - Teratogenicity
Androgens

Danazol, Stanozolol, Oxandrolone, Methyltestosterone

Danazol: Freedom from HAE Attacks vs Placebo

- Placebo: >1%
- Danazol: 98%

Danazol: Cumulative Freedom from HAE Attacks at Varying Dosages

- 200 mg/d: 11%
- 300 mg/d: 56%
- 400 mg/d: 88%
- 600 mg/d: 95%

Frank M. Immunol Allergy Clin N Am 2006
Gelfand JA et al., N Engl J Med 1976
Androgens: Adverse Reactions & Side Effects

Virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, altered mood, altered libido

Széplaki et al. J Allergy Clin Immunol 2005
Bork K, Schneiders V. J Hepatol 2002
Treatment with Danazol

- Adverse effects increase with dosage and duration of therapy
- The lowest effective dose should be used for maintenance
- Can start with higher dose and taper every 2-4 weeks to achieve symptomatic control
  - Alternatively, start low dose and increase dose every 2-4 weeks to achieve symptom control
- Monitor liver function tests periodically
**FDA Approval of “Newer” Treatment Options**

- **Nanofiltered human plasma-derived C1INH (Cinryze):** routine prophylaxis in adolescents and adults
  - **March 2008**

- **Plasma kallikrein inhibitor (Ecallantide):** all types of attacks 16 yr old and above
  - **Aug 2011**

- **Pasteurized human plasma-derived C1INH (Berinert):** acute abdominal and facial attacks in adolescents and adults
  - **Oct 2009**

- **Bradykinin receptor antagonist (Icatibant):** self-administration for all types of attacks 18 yr old and above
  - **Dec 2009**
“Newer” Treatments for Hereditary Angioedema

- Trauma
- Prekallikrein
- Factor XIIa
- Plasmin
- C1 INH
- Kallikrein
- High Molecular Weight Kininogen
- Bradykinin
- Ecallantide
- Icatibant

Endothelial Cell

Vasodilation, Edema, Nonvascular Smooth Muscle Contraction
Plasma C1-INH Replacement Therapy

- Efficacy first demonstrated >25 years ago
- Response rate of virtually 100%
  - 629/630 attacks
  - 193/193 laryngeal attacks

Bork K, Barnstedt SE. Arch Intern Med 2001
Bork K, et al. Transfusion 2005
C1INH Concentrate

- Pasteurized C1INH Concentrate (Berinert)
- Nanofiltered C1INH Concentrate (Cinryze)
- Recombinant C1INH (Rhucin)
Pasteurized Plasma C1INH Concentrate (Berinert)

Phase III DBPC study: International Multicenter Prospective Angioedema C1INH Trial (IMPACT)

- Pasteurized product used for over 20 years in Europe with >300,000 acute attacks treated
- No drug-related safety issues

![Graph showing median time to onset of symptom relief with placebo and high plasma dose (hpd) C1INH 20 U/kg.](image)

*One-sided two-sample Wilcoxon test for comparison to placebo.

Note: Patient reported. Time to onset of symptom relief was set to 24 hours if a subject received rescue study medication.

Pasteurized Plasma C1INH Concentrate (Berinert)

![Bar chart showing median time to onset of symptom relief (min) for C1INH 20 U/kg (n=43) and Placebo (n=42) across severity levels.](image)

- C1INH 20 U/kg (n=43):
  - All: 30
  - Moderate: 47
  - Severe: 80

- Placebo (n=42):
  - All: 90
  - Moderate: 80
  - Severe: 30

P = 0.0025

*Significance testing was applied only for primary endpoints and not for subgroup analyses.

Craig TJ et al., JACI 2009;124:801-808.
Nanofiltered Plasma C1-INH Concentrate (Cinryze)

Acute Treatment

![Graph showing the effectiveness of C1 inhibitor and placebo over time.]

- C1 inhibitor (21 subjects reported relief)
- Placebo (14 subjects reported relief)

Time after First Dose (min)

Subjects (%)

Zuraw et al., NEJM 2010
Nanofiltered Plasma C1-INH Concentrate (Cinryze)

Prophylactic treatment: every 3-4 days

- 22 patients with at least 2 HAE attacks/month enrolled in a 24-week DBPC cross-over study
- Randomized to 12 weeks of C1INH or placebo, after 12 weeks patients switched treatment arms
- 52% reduction with C1INH therapy (p<0.0001), 66% reduction in days of swelling (p<0.0001)

Zuraw et al., NEJM 2010
Efficacy of Recombinant Human C1-INH (Rhucin)

Zuraw et al., JACI 2010
Recombinant C1INH (Rhucin): Time to beginning of relief and significant relief

Zuraw et al., JACI 2010
“Newer Treatments” for Hereditary Angioedema

- Trauma
- Prekallikrein
- Factor XIIa
- Plasmin

C1 INH

Kallikrein

High Molecular Weight Kininogen

Bradykinin

Ecallantide

Icatibant

Endothelial Cell

Vasodilation, Edema, Nonvascular Smooth Muscle Contraction
Ecallantide: Improvement of acute attack symptoms at 4 hours

*Mean Symptom Complex Severity (MSCS) score is a point-in-time measure of symptom severity. A decrease in MSCS score reflected an improvement in symptoms.*

Ecallantide: Improvement of acute attack symptoms at 4 hours

* Treatment Outcome Score (TOS) is a measure of symptom response to treatment. A TOS value >0 reflected an improvement in symptoms from baseline.

Primary Endpoint: Time to Onset of Symptom Relief

Median time (hours) to onset of symptom relief using VAS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST-1</td>
<td></td>
</tr>
<tr>
<td>Icatibant</td>
<td>2.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.6</td>
</tr>
<tr>
<td>P-value</td>
<td>0.142</td>
</tr>
<tr>
<td>FAST-2</td>
<td></td>
</tr>
<tr>
<td>Icatibant</td>
<td>2</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>12</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Consistent and clinically relevant results for Icatibant in both trials (Significant only for FAST-2).

FAST 3: December 2010

- Primary Endpoint: 50% reduction in the composite symptom score (p<0.001)
- No reports of anaphylaxis
<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Safety Concerns</th>
<th>Disadvantages</th>
<th>Advantages</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-derived C1-INH</td>
<td>• Infectious risk</td>
<td>• Needs IV access</td>
<td>• Extensive clinical experience</td>
<td>• Berinert: FDA approved acute treatment</td>
</tr>
<tr>
<td>(Berinert, Cinryze)</td>
<td>• Potential infusion</td>
<td>• Limited supply</td>
<td>• Corrects the fundamental defect</td>
<td>• Cinryze: FDA approved prophylaxis</td>
</tr>
<tr>
<td></td>
<td>reactions</td>
<td></td>
<td>• Relatively long half-life</td>
<td></td>
</tr>
<tr>
<td>Recombinant C1-INH (Rhucin)</td>
<td>• Potential allergic</td>
<td>• Needs IV access</td>
<td>• Corrects the fundamental defect</td>
<td>• Awaiting FDA review</td>
</tr>
<tr>
<td></td>
<td>reactions</td>
<td>• Short half-life</td>
<td>• No human virus risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Antibody formation to</td>
<td></td>
<td>• Scalable supply</td>
<td></td>
</tr>
<tr>
<td></td>
<td>protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecallantide</td>
<td>• Allergic reactions</td>
<td>• Short half-life</td>
<td>• No infectious risk</td>
<td>• FDA approved acute treatment</td>
</tr>
<tr>
<td></td>
<td>• Antibody formation to</td>
<td></td>
<td>• Subcutaneous administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Local injection reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icatibant</td>
<td>• Local injection</td>
<td>• Short half-life</td>
<td>• No infectious risk</td>
<td>• FDA approved, acute treatment, self administration</td>
</tr>
<tr>
<td></td>
<td>reactions</td>
<td></td>
<td>• Stable at room temperature</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Subcutaneous administration</td>
<td></td>
</tr>
</tbody>
</table>
New approaches to HAE Treatment

- Treatment should maximize patient health
  - Effective treatment readily available for attacks
  - Avoid significant side effects

- Treatment should be individualized
  - Based on attack frequency and severity

- Minimize disruption of normal life
  - Home therapy
  - Prophylactic therapy

Adapted from B Zuraw
Long Term Prophylaxis: Who?

- **British consensus document 2004:**
  - Joint decision between physician and patient
  - Recognition of the role of individualized therapy and burden on QOL

- **Gompels et al., 2005:**
  - >1 episode of severe abdominal pain or head/neck swelling
  - Frequent peripheral swelling
  - C1INH more than once a year

- **Canadian Hungarian consensus document 2007:**
  - >1 severe event per month
  - Disabled more than 5 days per month
  - History of airway compromise

Bowen Annals Allergy Asthma Immunol 2008
Agostoni, JACI 2004
Bowen et al., Allergy Asthma Clin Immunol 2010
Gompels et al., Clin Exp Immunol 2005
# Consideration Criteria for Prophylactic Therapy 2009

<table>
<thead>
<tr>
<th>Consideration Criteria</th>
<th>Episodic Therapy</th>
<th>Prophylactic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description of HAE Attacks</strong></td>
<td></td>
<td><strong>ANY ONE OF THESE</strong></td>
</tr>
<tr>
<td>Frequency of Attacks</td>
<td>&lt;1/Month</td>
<td>≥1/Month</td>
</tr>
<tr>
<td>Rapid progression of attacks</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Timely access to care</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nature of HAE Attacks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of laryngeal attacks</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Emergency visit to physician/hospital</td>
<td>&lt; 3/year</td>
<td>&gt; 3/year</td>
</tr>
<tr>
<td>Intubation due to HAE</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hospitalization due to HAE</td>
<td>&lt; 1/year</td>
<td>&gt; 1/year</td>
</tr>
<tr>
<td>ICU due to HAE</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Burden On Activities of Daily Living</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed days of school or work</td>
<td>≤10 days/year</td>
<td>&gt;10 days/year</td>
</tr>
<tr>
<td>Significant anxiety or compromise in quality of life</td>
<td>possible</td>
<td>consider</td>
</tr>
<tr>
<td>Impacts lifestyle (vacation, family, sports)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Analgesic dependency</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Craig T et al., Ann Allergy Asthma Immunol 2009
Is Prophylaxis Appropriate?

*Individualized Care*

- Goal of long-term prophylaxis is to decrease the frequency and severity of attacks.

- Evaluate nature and frequency of HAE attacks and associated disease burden of each patient.

- Consider access to emergency care, history of ED/physician visits, hospitalizations and intubations due to HAE attacks.

- Clinical course is unpredictable.
International HAE Conference Consensus
Gargnano, Italy

- All HAE patients should have on-demand treatment available
  - Patients should be trained in self-administration
  - Attacks at all locations are eligible for treatment
  - Attacks should be treated as soon as they are recognized
  - Hospitalize for progressing laryngeal involvement

- Long-term prophylaxis
  - Consider when optimized on-demand therapy fails
  - Androgens are contraindicated in patients who are:
    - $\leq 16$ years old
    - Pregnant/breastfeeding
    - Does not tolerate or accept androgens

Adapted from B Zuraw
Frequency of HAE Attacks Decreases Significantly After Initiation of Prophylaxis

- Attack frequency decreased from 4 attacks to 0.3 attacks per month

Levi et al., JACI 2006
Efficacy of Prophylactic Nanofiltered Plasma C1-INH Concentrate

Physician reporting of medications prescribed for prophylaxis in HAE

Riedl et al., Ann Allergy Asthma Immunol 2011
## Comparison of Prophylactic Therapies: Attenuated Androgens and C1INH

<table>
<thead>
<tr>
<th></th>
<th><strong>Anabolic Androgens</strong></th>
<th><strong>C1 INH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Low cost</td>
<td>Replaces abnormal protein</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Adverse effects</td>
<td>Intravenous access</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High cost</td>
</tr>
<tr>
<td><strong>Potential side effects</strong></td>
<td>Weight gain, Hepatitis, Hyperlipidemia, Hepatocellular carcinoma, Mood changes</td>
<td>Potential for blood-borne pathogens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Port thrombosis and infection</td>
</tr>
<tr>
<td><strong>Contraindicated populations</strong></td>
<td>Pregnant women, Children</td>
<td>Hypersensitivity to blood products</td>
</tr>
</tbody>
</table>
# On-Demand Therapy: Drug Comparisons

<table>
<thead>
<tr>
<th></th>
<th>pdC1-INH</th>
<th>rhC1-INH</th>
<th>Ecallantide</th>
<th>Icatibant</th>
<th>Androgen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute use efficacy</strong></td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>i.v.</td>
<td>i.v.</td>
<td>subQ</td>
<td>subQ</td>
<td>p.o.</td>
</tr>
<tr>
<td><strong>Approved in USA</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Primary safety issue</strong></td>
<td>infectious (?)</td>
<td>allergic (?)</td>
<td>allergic</td>
<td>? CV</td>
<td>multiple</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>i.v. stick; veins</td>
<td>i.v. stick; veins</td>
<td>multiple injections</td>
<td>local pain</td>
<td>fair to poor</td>
</tr>
<tr>
<td><strong>Home use</strong></td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>
Medical Costs of HAE

- **Mild** (n=121)
  - Average Annual Cost: US $14,379
  - 75% Emergency department and hospital visits for acute attacks
  - 11% Medications for both acute attacks and long-term disease management
  - 11% Clinical care including physician’s office visits and any procedures or tests; both short-term and long-term care are included
  - 4% Indirect costs, including travel, childcare, and missed work for acute attacks and reduced income and reduced productivity associated with chronic disease

- **Moderate** (n=212)
  - Average Annual Cost: US $26,914
  - 64% Emergency department and hospital visits for acute attacks
  - 19% Medications for both acute attacks and long-term disease management
  - 13% Clinical care including physician’s office visits and any procedures or tests; both short-term and long-term care are included
  - 5% Indirect costs, including travel, childcare, and missed work for acute attacks and reduced income and reduced productivity associated with chronic disease

- **Severe** (n=124)
  - Average Annual Cost: US $96,460
  - 21% Emergency department and hospital visits for acute attacks
  - 21% Medications for both acute attacks and long-term disease management
  - 6% Clinical care including physician’s office visits and any procedures or tests; both short-term and long-term care are included
  - 68% Indirect costs, including travel, childcare, and missed work for acute attacks and reduced income and reduced productivity associated with chronic disease

Wilson et al., Ann Allergy Asthma Immunol 2010
<table>
<thead>
<tr>
<th>Rx type</th>
<th>Agent name</th>
<th>Efficacy</th>
<th>Side effects</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Androgens</td>
<td>+++</td>
<td>+++</td>
<td>$736a</td>
</tr>
<tr>
<td></td>
<td>C1 inhibitor (nanofiltered)</td>
<td>+++</td>
<td>+++</td>
<td>$486,720b</td>
</tr>
<tr>
<td>Acute attacks</td>
<td>Cinryze</td>
<td>+++</td>
<td>+</td>
<td>$17,868c</td>
</tr>
<tr>
<td></td>
<td>Berlinert</td>
<td>++d</td>
<td>+</td>
<td>$47,700c</td>
</tr>
<tr>
<td></td>
<td>Plasma kallikrein inhibitor</td>
<td>+++</td>
<td>+++</td>
<td>Not FDA approved</td>
</tr>
</tbody>
</table>
Efficacy of Self-Administration of C1 INH

The time between the onset of a severe attack and self-administration of C1-inhibitor was $1.4 \pm 1.0\text{h}$ vs. $3.4 \pm 2.1\text{h}$ in historical controls before the start of the self-administration.

Levi et al., JACI 2006
Improved QOL with Self-Administration

- Similar improvement in SF-36 parameters
- Reduced use of emergency services (P<0.05)

Bygum et al., Eur J Dermatol 2009
Conclusions

- Novel therapies have been developed that are safe and effective

- Consensus guidelines about treatment strategies have emerged
  - All patients should have access to on-demand treatment with a well delineated treatment plan
  - Long-term prophylaxis is best reserved for patients in whom on-demand treatment is not sufficiently effective
  - Aim to minimize any side effects
  - Therapy needs to be individualized for each patient

- Self-administration can offer significant benefits