Disclosure of Conflicts of Interest

Marc Riedl, MD, MS

- **Research Support**: Biocryst, CSL Behring, Ionis, Pharm ing, Shire
- **Consultant**: Arrowhead, Biocryst, CSL Behring, Global Blood Therapeutics, Pharm ing, Salix, Shire
- **Speakers Bureau**: CSL Behring, Salix, Shire
Angioedema Attacks: An Old Problem

- Marcella Donati (1586)
  - *De medica historia mirabili.*
- Heinrich Irenaeus Quincke (1882)

**Osler: Hereditary Angio-Neurotic Edema**

Briefly summarized, the affection in the family which I have studied has the following characteristics:

1. The occurrence of local swellings in various parts of the body, face, hands, arms, legs, genitals, buttocks, and throat. In one instance, possibly in two, death resulted from a sudden edema glottidis.

2. Associated with the edema, there is almost invariably gastrointestinal disturbance: colic, nausea, vomiting, and sometimes diarrhea.

3. A strongly marked hereditary disposition, the disease having affected members of the family in five generations.
HAE: Deficiency of C1 Esterase Inhibition

A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C1-Esterase

Virginia H. Donaldson, M.D.† and Richard R. Evans, M.D.

HAE Caused by C1-INH Mutations

Function of C1-INH

Activation of Endothelial Cells by Bradykinin

NO=nitric oxide; PGE₂=prostaglandin E₂; TPA=tissue plasminogen activator.
Types of HAE

- 3 documented types of HAE

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of all HAE</td>
<td>~85%</td>
<td>~15%</td>
<td>Rare</td>
</tr>
<tr>
<td>C4 Level</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>C1-INH antigenic level</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>C1-INH antigenic function</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Anatomical Location of HAE Symptoms

- 221 HAE patients
- 5736 patient-years of observation
- 131,110 angioedema attacks

Hereditary Angioedema (HAE): Extremity Attacks

Abdominal Attacks

- Mild to severe pain
- Vomiting common; constipation/diarrhea may occur
- Fluid loss may lead to shock
- Abdominal distension, tenderness
- Symptoms mimic surgical emergencies, resulting in misdiagnosis and unnecessary surgery

HAE: Abdominal Attacks

Courtesy of Dr. Marco Cicardi, personal archive.

Facial Edema in HAE

Photo from Frank MM
Oropharyngeal and Laryngeal Attacks

• Require emergency visits or hospitalization
• May require intervention to prevent airway closure
• Life-threatening
• 50% of patients with HAE will suffer at least one laryngeal attack in their lifetime


Laryngeal Attacks
Hereditary Angioedema
Burden of Illness: Days Lost

Percentage of Patients Who Reported Missed Days Due to Most Recent HAE Attack

- Workers (N=308)
- Students (N=27)
- All Patients (N=457)

HAE patients miss work, school, and leisure days due to symptoms of their most recent attack.


Hereditary Angioedema
Burden of Illness: Education

Percentage of Patients Reporting HAE as Influencing Education and Work

- Career Advancement: 57.5% (n=263)
- Consideration of Certain Job Types: 69.1% (n=316)
- Educational Advancement: 100.0% (n=457)
- Educational Attainment: 48.4% (n=221)
- Educational Choices: 54.5% (n=249)

HAE: Burden of Illness

The impact of HAE on patients' work and activity functioning is comparable to impairment reported with severe asthma or Crohn's disease.

Psychological Impact of HAE

HAE Therapy: The Future is Now

Every Patient Needs an HAE Treatment Plan

Treatment of Hereditary Angioedema

• Conceptually divided into two approaches
  – Treatment of acute attacks
    • Terminate ongoing attack
    • Prevent disability and mortality
  – Prophylactic therapy
    • May be short-term or long-term
    • Minimize attack frequency and severity
    • Prevent hospitalizations and emergency room visits
Triggers of HAE Attacks

- Attacks often unpredictable; 40% of individuals with HAE can identify the cause of an episode
  - Physical trauma
  - Surgical/Medical procedures
  - Infection
  - Emotional stress
  - Some medications (ACE inhibitors, oral contraceptives)
- Hormonal influence
  - Estrogens increase attack severity/frequency

HAE Therapy Timeline

- Testosterones
- FFP
- EACA
- Danazol
- C1-INH Approved (Germany)
- C1-INH Pasteurized
- C1-INH (Cinryze*)
- C1-INH (Berinert®)
- Kalikrein Inhibitor (Kalbitor®)
- RhC1-INH (Rucore®)

FDA Approval Dates:
- 10/09
- 12/09
- 8/11
- 7/14
- 10/08

Ann Allergy Asthma Immunol 2008;100(Suppl2) S2-6 & S23-29; www.fda.gov
Modern Therapies for Hereditary Angioedema (HAE)

Comparison of Acute HAE Therapies

<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®: Approved in USA and many countries worldwide for HAE acute treatment¹</td>
</tr>
<tr>
<td></td>
<td>• Potential infusion reactions</td>
<td>• Dependent on plasma supply</td>
<td>• Relatively long half-life</td>
<td>• Cinryze®: Approved in USA for HAE long-term prophylactic therapy; in Europe for acute and prophylactic treatment²³</td>
</tr>
<tr>
<td>Recombinant C1-INH</td>
<td>• Potential hypersensitivity</td>
<td>• Needs IV access</td>
<td>• No human virus risk</td>
<td>• Rhucin®/Ruconest®: Approved in Europe and USA for HAE acute treatment</td>
</tr>
<tr>
<td>Ecallantide</td>
<td>• Allergic reactions</td>
<td>• Requires administration by a healthcare provider</td>
<td>• No infectious risk</td>
<td>• Kalbitor®: Approved in the USA for acute HAE therapy⁵; currently not approved in Europe</td>
</tr>
<tr>
<td>Icatibant</td>
<td>• Local injection reactions</td>
<td>• Requires administration by a healthcare provider</td>
<td>• Stable at room temperature</td>
<td>• Firazyr®: Approved in USA and numerous other countries for acute HAE therapy⁶</td>
</tr>
</tbody>
</table>

1. Berinert SPC; 2. CINRYZE USPI; 3. CINRYZE SPC; 4. Ruconest SPC; 5. Kalbitor SPC; 6. Firazyr SPC.

B2R=B₂-receptor; BK=bradykinin; EACA=epsilon-aminocaproic acid; HK=high-molecular-weight kininogen; PK=prekallikrein.

Long-Term Prophylactic Treatment for HAE

• Does the patient require long-term prophylaxis?
  – Not everyone with HAE
  – Need varies by individual
    • Frequency, severity, and type of attacks
    • Availability of care
    • Failure of on-demand therapy

• Modalities
  – Anabolic androgens (attenuated or impeded)
  – C1-INH replacement
  – Antifibrinolytics
  – Progestin

• **Acute treatment should be available for ALL patients on prophylaxis**

Efficacy of Androgens for Long-Term Prophylaxis in HAE

Contraindications to Androgens

• Pregnancy
• Lactating women
• Hepatic disease (viral hepatitis, etc.)
• Children
• CA (prostate / breast)
• Nephrotic syndrome

58 of 118 subjects discontinued androgens: 41 due to adverse effects, 7 due to inefficacy

Reported Androgen Side Effects in 118 Patients

- Virilization
- Weight gain
- Menstrual disorders/immenorrhea
- Psychological abnormalities
- Headache
- Myalgia
- Acne
- Increased sweating
- Bilirubinostasis
- Hepatocellular adenoma

Maurer et al. JDDG 2011; 9:99-107

Side Effects of Anabolic Androgens

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

Bork K, Schneiders V. J Hepatol. 2002;36:707-709
Monitoring with Androgen Therapy

- At treatment initiation and every 6 months:
  - Blood count
  - Liver enzyme values
  - Lipid profile
  - Urine status
  - Ultrasound of the liver for danazol dosages exceeding 200 mg daily and in prepubescent patients (once a year if ≤ 200 mg daily)


C1-IHN Prophylaxis Associated With Lower HAE Attack Rates

- 3 mo crossover comparing C1INH q 3-4 days vs placebo q 3-4 days
- Average normalized attack rate
  - 12.73 vs 6.26, placebo vs C1-INH
- Average difference in attack rates
  - 6.47 (P<0.001)

Efficacy of Prophylactic Plasma-derived C1-INH Concentrate

Attacks (primary)
Severity of attacks
C1-INH rescue treatments
Duration of attacks
Days of swelling

Favors Prophylaxis  Favors Placebo

C1-INH Prophylaxis – Side Effects


C1INH Prophylaxis – Side Effects

Table 3 Adverse Reactions in the Open-Label Follow-On Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number (%) of Subjects (N=146) with Adverse Reaction</th>
<th>Number (%) of Infusion Days (N=11,436) with Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>28 (19)</td>
<td>62 (0.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (10)</td>
<td>29 (0.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (10)</td>
<td>30 (0.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (10)</td>
<td>17 (0.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (2)</td>
<td>7 (0.1)</td>
</tr>
<tr>
<td>Infusion Site Pain</td>
<td>4 (2)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (2)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (2)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (2)</td>
<td>4 (0.1)</td>
</tr>
</tbody>
</table>

C1-INH and Thrombosis

- Physician Survey – Kalaria et al.
- 66 physicians
  - 856 HAE patients treated with C1INH
  - 5 patients with reported thromboembolic events (0.6%)
  - Of 17 patients with indwelling catheters, 3 with thromboembolic events (18%)

Kalaria S. Allergy Asthma Proc. 2013

### Comparison of Prophylactic Therapies: Attenuated Androgens and C1-INH

<table>
<thead>
<tr>
<th>Attenuated Androgens¹</th>
<th>C1-INH²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
</tr>
<tr>
<td>Low cost</td>
<td>Replaces missing (Type I HAE) or abnormally functioning (Type II HAE) C1-INH</td>
</tr>
<tr>
<td>Oral administration</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Intravenous access</td>
</tr>
<tr>
<td></td>
<td>High cost</td>
</tr>
<tr>
<td><strong>Potential side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>Potential for blood-borne pathogens</td>
</tr>
<tr>
<td>Liver damage</td>
<td>Port thrombosis and infection</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Mood changes</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindicated populations</strong></td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Hypersensitivity to blood products</td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
</tbody>
</table>

¹. Danzol SPC; ². CINRYZE SPC.
Guidance on Treatments for HAE

• Consensus Statements/ Working Groups
  – Hereditary Angioedema International Working Group (HAWK): Evidence-based treatment consensus publication; Cicardi et al.
  – WAO Guideline for the Management of Hereditary Angioedema; Craig et al.
  – International Consensus on Hereditary and Acquired Angioedema; Lang et al.
  – US Hereditary Angioedema Association Medical Advisory Board Consensus Document; Zuraw et al.
  – Canadian Hereditary Angioedema Guideline; Betschel et al.


HAE Guidelines: Areas of Agreement

• On-demand treatment necessary for every HAE patient
  – Must be reliably and efficiently accessible
  – Includes patients receiving long-term prophylaxis
• All or nearly all attacks eligible for treatment
• Laryngeal attacks uniquely life-threatening and require special attention
• Early treatment of attacks beneficial in reducing morbidity and complications
• Prophylactic therapy indicated for patients in whom on-demand treatment alone is unsatisfactory
HAE Guidelines: Areas of Agreement

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HAE Guidelines: Areas Lacking Clarity

• Specific indications for prophylaxis
• “Preferred” agents for prophylactic or acute HAE treatment
  – Exception is special populations: pediatrics, pregnancy

Acute Treatment Plan

- Essential for every person/family with HAE
- Tailored to individual circumstances
- Rapidly and efficiently accessible
- Choices
  - Medication
  - Administration location(s)
  - Self-administration
- Develop a “back-up” plan
- Be equipped to navigate the health care system

Acute Treatment Plan Logistics

- Reliable, accessible and efficient
- Self-administration
  - Intravenous infusions
  - Subcutaneous injections
  - Personal comfort level
  - Education/technical instruction
  - Family or friend assistance
  - Medication labeling
- Home health nursing “on call”
- Hospital-based acute care
  - “Brown-bagging” medication

- What works best for the patient?
- Is the plan reliable?
Hereditary Angioedema Action Plan

To Whom It May Concern:

Ms./Mr. ________ has been diagnosed with Hereditary Angioedema (HAE) and is under my care to treat her/his condition. This genetic condition results in periodic episodes of cutaneous, intestinal, and/or laryngeal angioedema that may be severely disabling and life-threatening.

Effective treatment of HAE attacks requires one of the following medications be administered as quickly as possible to abort swelling episodes:

- C1INH (Berinert) 1000-2000 units intravenously
- Ecallantide (Kalbitor) 30 mg subcutaneously
- Incatibant (Firazyr) 30 mg subcutaneously

A second dose of these medications may be necessary in the event of a partial response or recurring angioedema symptoms.

In addition to this medication, management of acute attacks may include supportive care with airway monitoring, analgesic and antiemetic medication, and intravenous fluids as appropriate. Antihistamines and corticosteroids are not effective in treating this bradykinin-mediated form of angioedema.

Epinephrine may be useful as a temporizing measure for significant laryngeal edema, however airway compromise requires immediate dosing of the effective medications listed above and careful monitoring.

It is medically necessary that the patient carry the listed HAE medications and related treatment supplies while traveling. I may be reached with any questions regarding this condition at XXX-XXX-XXXX.

Sincerely,

• Letters
• Medical ID bracelets
• USB drives
• Flagging the electronic medical record

Home Administration of HAE Therapy

- Demonstrated benefits with proper implementation:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity / duration of attacks

- Considerations:
  - Individual patient
  - Route of administration
  - Training programs
  - Counseling / consent


Routine Prophylaxis vs. Acute Treatment Alone

• Consider:
  – Nature of HAE symptoms
    • Frequency
    • Severity
    • Rapidity of onset and progression
    • Anatomical location
    • Level of functional impairment
    • Degree of psychological impact
  – Availability of a rapid, efficient acute treatment plan
  – Impact of HAE on work or school
  – Restoring ‘normalcy’ to daily life


The Science and the Art of Medicine

[Diagram showing a pie chart with sections labeled “Resembles pacman” and “Does not resemble pacman”]

Individualization of HAE Therapy

- Patient factors
  - Attack frequency
  - Rapidity of progression
  - Laryngeal attacks
  - Access to medical care
  - History of frequent hospitalization
  - Treatment complications

- Medication factors
  - Efficacy
  - Safety
  - Administration route
  - Patient preference/tolerability
  - Administration location
  - Source
  - Cost

The Comprehensive Treatment Plan: Essentials of Modern HAE Therapy

- Components of the Medical Management Plan
  - Acute Treatment Plan for Every Person with HAE
  - Routine Prophylaxis for Some
  - Logistics of Treatment Plan
  - Monitoring for Efficacy and Side Effects
Monitoring for Efficacy and Side Effects

• Known and unknown risks of medications
  – Androgens
  – Plasma products
  – Local and systemic treatment reactions
  – IV access issues

• Individual patient variability in response to therapies

• HAE is a complex, highly-variable, chronic condition
  – benefits of periodic monitoring
Incorporating New Treatments for HAE

• Treatment in the U.S. circa 2010
  – 74% of treated HAE attacks seen in ED/hospital

According to MDs:
22% of patients dissatisfied with treatment
65% of patients somewhat satisfied with treatment
13% of patients very satisfied with treatment

20-30% MDs not familiar with C1INH products
40-50% MDs not familiar with ecalfantide or icatibant

Percentage of MDs using specific therapy to treat HAE attacks (N=172)

Prescribed Long-Term Prophylactic Therapies in U.S. 2010 vs. 2013

Prescribed Acute HAE Therapies in U.S. 2010 vs. 2013

Location of C1INH Administration in U.S. 2013

Location of HAE Attack Treatment in U.S. 2010 vs 2013


Current state of hereditary angioedema management: A patient survey

Aleena Banerji, M.D. 1 Paula Busse, M.D. 2 Sandra C. Christiansen, M.D. 3,4 Henry Li, M.D. 5 William Lumry, M.D. 6 Mark Davis-Lorton, M.D. 7 Jonathan A. Bernstein, M.D. 8 Michael Frank, M.D. 9 Anthony Castaldo 10 Janet F. Long 10 Bruce L. Zuraw, M.D. 3,11 and Marc Riedl, M.D., MS 5,11


Before and after, the impact of available on-demand treatment for HAE

Authors: Christiansen, Sandra C.; Bygum, Anette; Banerji, Aleena; Busse, Paula; Li, Henry; Lumry, William; Davis-Lorton, Mark; Bernstein, Jonathan A.; Frank, Michael M.; Castaldo, Anthony; Long, Janet F.; Riedl, Marc; Zuraw, Bruce L.

Source: Allergy and Asthma Proceedings, Volume 36, Number 2. March/April 2015, pp. 145-150(6)
Improvements in Quality of Life with C1INH IRT


C1INH Therapy: Patient Self-Administration

On demand treatment and home therapy of hereditary angioedema in Germany - the Frankfurt experience

HAE international home therapy consensus document
Challenges in Practice with the Treatment of Acute Attacks of HAE

- Not understanding risks associated with acute attacks (in particular laryngeal attacks)
- Not having treatment for an acute attack available
  - Hospital
  - At home
- Not knowing when to treat
- Lacking training on self-administration
- Costs of medication/administration
  - Local reimbursement policies


“Uh-oh, your coverage doesn’t seem to include illness.”
“The only thing constant is change”

- Heraclitus of Ephesus
  (500 BC)

Addressing Education and Knowledge Gaps for Rare Conditions

- HAE: Estimated prevalence of 1:50,000
- Increasing Awareness in the Medical Community
  - Physician/HCP education programs
  - Specialists, generalists, hospitals/clinics
  - Medical School/ Residency training programs
  - Medical publications
- Patient/Family education programs
  - Awareness of symptoms, complications
  - Importance of Family testing
  - Knowledge of treatment options
- HAEI and HAEA Efforts
- Industry Efforts
- Data collection on knowledge and clinical care in health care systems globally
**Unknowns in HAE Pathophysiology**

- What specifically...
  - Starts
  - Propagates
  - Ends
  ...episodes of hereditary angioedema

- Factors causing variability in clinical symptoms/course
  - Mediator-receptor variations
  - Kinin degradation variability
  - Genetic polymorphisms
  - Epigenetics

- Can we develop tests with prognostic value in HAE?
  - Diagnostic value in other forms of angioedema

**HAE Patient Registry and Biorepository**

---

**HAE Modifier Genes**


**Results:** Instead of a single, common disease-associated expression pattern, we found different transcriptome signatures in two of the families studied. In one of them (referred to as DR family), symptoms correlate with the upregulation of 35 genes associated to the biological response to viral infections (including RSADs, OAS, MX and IFG pathway members) and immune response. In another pedigree (Q family), disease manifestation is linked to the upregulation of 43 genes with diverse functions, including transcription and protein folding. Moreover, symptoms-free members of the Q pedigree display relatively higher expression of 394 genes with a wide diversity of functions.
Looking Ahead: Prophylactic HAE Therapy

• PHASE 3
  – Subcutaneous C1-INH Concentrate
  – Monoclonal Antibody against kallikrein

• Earlier Phase Development
  – Oral Kallikrein Inhibitors
  – Monoclonal Antibody against Factor XII
  – RNAi-based treatment
    • Prekallikrein
    • Factor XII
  – Gene Therapy
HAE in the Future

- Rapid treatment for every patient early in attack
- Convenient medication dosing
- Optimized and improved prophylaxis
- Understanding of disease variability (genetics, mediators, triggers): Scientific registries
- Studies to demonstrate to optimal treatment strategies for improved clinical outcomes and cost-effectiveness
- Centers to offer comprehensive education, evaluation, development of management plans, and support programs
Thank You