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# Advances in Hereditary Angioedema: The Prevention of Angioedema Attacks With Subcutaneous C1-Inhibitor Replacement Therapy

William Lumry, MD ● Teri Templeton, LVN ● Laurel Omert, MD ● Donald Levy, MD

## ABSTRACT

Hereditary angioedema (HAE) is a debilitating condition caused by a functional C1-inhibitor (C1-INH) deficiency and characterized clinically by episodes of subcutaneous or submucosal swelling. C1-INH replacement is highly effective for preventing HAE attacks and can improve health-related quality of life. Once available only for intravenous use, C1-INH is now available as a subcutaneous formulation for self-administration, shown to provide sustained plasma levels of C1-INH and reducing the monthly median HAE attack rate by 95% versus placebo in the phase 3 COMPACT study. Subcutaneously administered C1-INH satisfies multiple unmet needs in the management of patients with HAE.

**Key words:** angioedema, C1-INH(SC), C1-inhibitor, HAE, HAEGARDA, hereditary angioedema, prophylaxis, subcutaneous

**Author Affiliations:** *AARA Research Center, Dallas, Texas (Dr Lumry); US HAEA Angioedema Center at University of California San Diego, San Diego, California (Ms Templeton); CSL Behring, King of Prussia, Pennsylvania (Dr Omert); University of California Irvine School of Medicine, Orange, California (Dr Levy).*

**William Lumry, MD,** is in private practice in Dallas, Texas, treating adults and children with allergic diseases and asthma. He actively participates in clinical research projects involving new treatments for asthma, allergic and immune deficiency diseases, and hereditary angioedema in his role as medical director of AARA Research Center. He is also clinical professor of internal medicine at the University of Texas Southwestern Medical School in Dallas and teaches at Parkland Memorial Hospital in Dallas. Dr Lumry is president of the Texas Allergy, Asthma and Immunology Society and a fellow of the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the American College of Physicians. He is also a member of the US Hereditary Angioedema Association Medical Advisory Board on the panels responsible for the Hereditary Angioedema International Working Group, International Consensus, and World Allergy Organization hereditary angioedema consensus documents. **Teri Templeton, LVN,** was the nurse navigator and senior nurse supervisor of the US HAEA Angioedema Center at University of California San Diego, where she also served as the lead nurse on all clinical and translational research. As a public speaker and nurse educator, and through service on advisory boards, she worked to reduce the time to diagnosis and bring awareness to health care professionals on the signs and symptoms of hereditary angioedema. **Laurel Omert, MD,** is currently chief medical officer at Hemanext in Lexington, Massachusetts, and a staff surgeon and intensivist at Albert Einstein Medical Center in Philadelphia. She served as medical director at CSL Behring for specialty products that included C1-INH(SC) and C1-INH(IV) during the development of this manuscript. **Donald Levy, MD,** is a professor of medicine at University of California Irvine School of Medicine in Orange, California. He is very active in teaching students, residents, and fellows. He has a special interest in hereditary angioedema and conducts research in this field.

Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency (C1-INH-HAE) is a rare genetic, autosomal dominant disease with an estimated prevalence of 1.1 to 1.6 per 100 000 people.[1] Patients with C1-INH-HAE experience angioedema attacks due to a lack of regulation of the contact system, resulting in the overproduction of bradykinin. C1-INH, a serine protease inhibitor, is an important regulator of the bradykinin generation pathway. In patients with C1-INH-HAE, coding mutations in the *SERPING1* gene result in either a quantitative deficiency of normal C1-INH protein (C1-INH-HAE type 1) or normal levels of dysfunctional C1-INH protein (qualitative deficiency; C1-INH-HAE type 2).[2,3] In both types, the deficit in C1-INH functionality results in overproduction of bradykinin, the primary mediator of swelling in HAE attacks. In addition to regulatory roles in the coagulation, fibrinolysis, and complement cascades, the C1-INH protein regulates 4 different steps in the bradykinin generation pathway. These include suppressing factor XII autoactivation, downregulating the conversion of prekallikrein to kallikrein, limiting the cleavage of bradykinin from high-molecular-weight kininogen, and inhibiting the kallikrein/factor XII feedback loop (Figure 1). Therapeutic replacement of C1-INH protein via intravenous (IV) or subcutaneous (SC) administration can restore these normal physiologic functions, allowing for effective treatment and prevention of HAE attacks; this principle is similar to replacing missing insulin in patients with type 1 diabetes.

Another type of HAE with similar symptomatology but normal C1-INH levels and function was identified as recently as 2000[4] and has been termed *HAE with normal C1-INH* (previously termed *HAE type 3*). Three separate genetic mutations have been identified in such patients, including genes that code for factor XII,[5] plasminogen,[6] and angiopoietin,[7] the consequences being increased factor XII activation or other mechanisms that increase bradykinin formation via the contact system pathway or other yet unidentified mediators of swelling.[8] Ongoing research will likely identify more genetic mutations causing HAE with normal C1-INH.

HAE has debilitating and potentially life-threatening clinical consequences. Patients with C1-INH-HAE suffer from unpredictable, recurring attacks of SC or submucosal swelling (angioedema) without hives. Attacks can last for up to 5 days and typically affect the skin of the extremities, trunk and face, the upper airway (potentially causing asphyxiation), the genitals, and the abdominal viscera (causing pain mimicking bowel obstruction). Swelling attacks often occur without an apparent triggering factor but can be triggered by factors such as psychological stress, local trauma (eg, dental or medical procedures), infection, and certain medications, including estrogens and angiotensin-converting enzyme inhibitors.

The symptoms and signs of C1-INH-HAE often go undiagnosed and mismanaged for many years before an accurate diagnosis and initiation of appropriate treatment.[9–11] Given



1. Suppresses autoactivation of factor XII
2. Down-regulates conversion of prekallikrein to kallikrein
3. Limits cleaving of bradykinin from kininogen
4. Inhibits the kallikrein/factor XII feedback loop
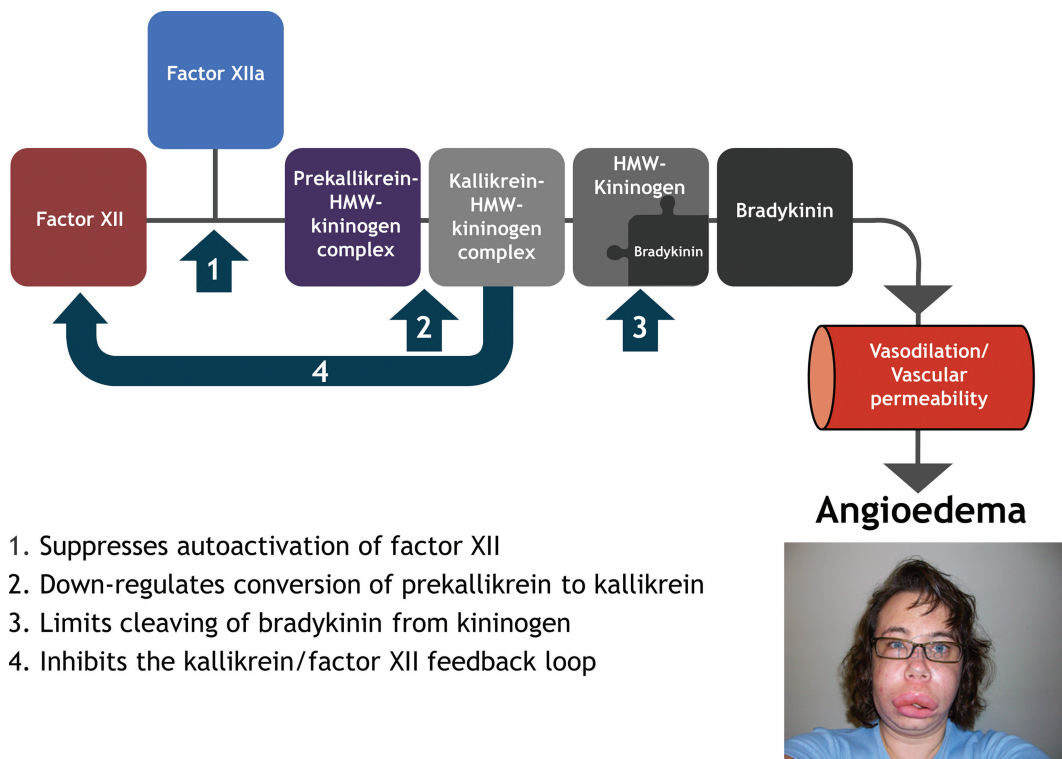
**Figure 1** Four primary sites of C1-INH physiologic regulatory activity within the contact system cascade. Deficiency of normal C1-INH activity in patients with C1-INH-HAE allows for excess bradykinin production leading to increased vascular permeability and angioedema. Image used with permission from the US Hereditary Angioedema Association. *Abbreviations: C1-INH, C1 esterase inhibitor; HWM, high molecular weight; Factor XIIa, activated factor XII.*

the rarity of HAE and its unfamiliarity to clinicians, the swelling attacks are often wrongly attributed to more common diagnoses, such as allergic (histamine-mediated) angioedema, appendicitis, and other gastrointestinal disorders[12] with potentially serious consequences. Delays in diagnosis have been reported to average well in excess of 10 years after onset of symptoms.[12,13] Historically, one third of patients with abdominal HAE attacks have undergone unnecessary abdominal surgery before being correctly diagnosed with HAE because of attacks misinterpreted as an acute surgical abdomen.[14]

The pain, discomfort, and disfigurement of HAE attacks are often disabling with negative effects on patients' health-related quality of life (HRQoL). Many patients with HAE are affected by anxiety and depression and report work or school absences and reduced productivity due to the unpredictability and severity of the angioedema attacks.[11,15–21] Study findings based on the European Quality of Life-5 Dimensions Questionnaire (EQ-5D) reveal that HAE attacks have a marked impact on perceived health status. As shown in Figure 2,[16,20,22–28] EQ-5D scores reflecting HRQoL during an HAE attack, as reported in a study conducted in Denmark, Germany, and Sweden, ranged from 0.08 during a severely painful attack to 0.61 during an attack with mild pain (1 = full health). Even between HAE attacks, the mean EQ-5D scores reflected impairment (0.72). In a separate study from Sweden, the mean EQ-5D "today" score was 0.83 as compared with 0.51 during an attack. These reported "between-attack" scores are very similar to, and in some cases worse than, those of patients living with other chronic diseases, such as asthma, migraine, epilepsy, multiple sclerosis, and hemophilia (Figure 2). Improving HRQoL has become an increasingly important goal of HAE management.

## DIFFERENTIAL DIAGNOSIS OF ANGIOEDEMA

The blood vessel leakage that results in angioedema can be mediated by bradykinin as in C1-INH-HAE or by histamine release. These 2 broad categories of angioedema (bradykinin-mediated and histamine-mediated) differ not only in their underlying pathophysiology but also in clinical manifestations and treatment requirements (Table 1).

Histamine- and bradykinin-mediated angioedema share a few similarities, but there are a number of differences that can be helpful in differentiating between the 2 (Figure 3). Histamine-mediated angioedema typically presents with swelling, hives, and itching and responds to treatment with epinephrine, antihistamines, and corticosteroids. Bradykinin-mediated angioedema is not associated with urticaria (hives), is not pruritic, and does not respond to epinephrine, antihistamines, or corticosteroids. Both types can cause oral and laryngeal swelling, as well as extremity (peripheral) and facial swelling and abdominal pain, although the latter is more common in bradykinin-mediated attacks. Bradykinin-mediated angioedema should be suspected any time angioedema presents without urticaria and is unresponsive to standard treatments for allergic/histamine-mediated angioedema. Other factors that should raise suspicion of HAE include a family history of angioedema, onset of attacks during childhood or adolescence, and repeated episodes of abdominal pain. Erythema marginatum is a nonpruritic skin rash often seen as a prodrome to an HAE attack and can be mistaken for urticaria, interfering with correct diagnosis.[37]

Blood levels of complement C4, C1-INH, and C1-INH function are used to diagnose C1-INH-HAE (Table 1).
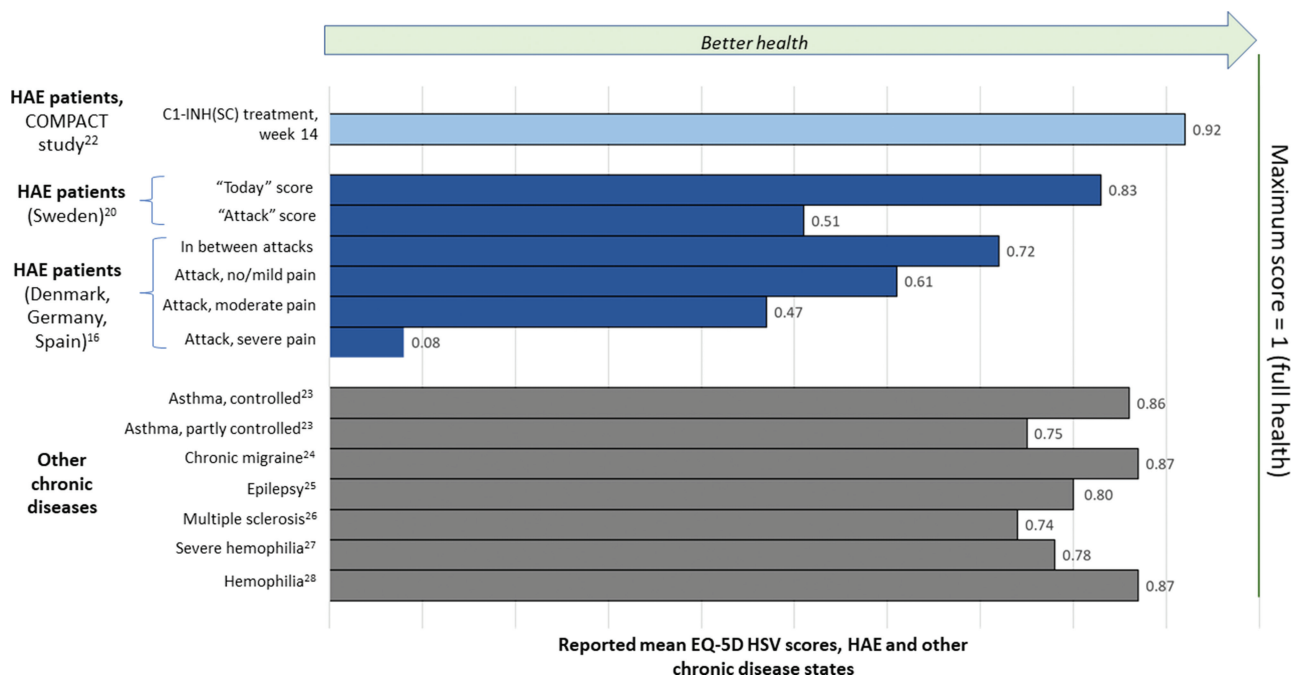


**Figure 2** Reported mean EQ-5D scores for study populations with HAE and other chronic diseases. *Abbreviations: C1-INH, C1 esterase inhibitor; EQ-5D, European Quality of Life-5 Dimensions Questionnaire; HAE, hereditary angioedema; HSV, Health State Value; SC, subcutaneous.*

## Clinical Features, Differential Laboratory Findings, and Acute Drug Treatment for Different Types of Angioedema Disorders[a]

| Angioedema Type | Description | Laboratory Findings | | | Drug Treatment for Attacks |
|---|---|---|---|---|---|
| | | C4 | C1-INH Level | C1-INH Function | |
| **Bradykinin-mediated** | | | | | |
| C1-INH-HAE type 1 (85% of HAE cases) | Onset <20 years; angioedema affects the face, oropharynx (including tongue, palate, and uvula), legs, arms, buttocks, and genitalia. Due to mutation(s) in the *SERPING1* gene on chromosome 11, which codes for C1-INH resulting in lower than normal levels of functional C1-INH; autosomal dominant disease with 75% having a family history and 25% being de novo mutations. | Low | Low | Low | C1-INH(IV) (human/plasma-derived or recombinant), plasma kallikrein inhibitor (ecallantide), or bradykinin-receptor inhibitor (icatibant). Corticosteroids, antihistamines, and epinephrine are ineffective. |
| C1-INH-HAE type 2[b] (15% of HAE cases) | Onset <20 years; angioedema affects the face, oropharynx (including tongue, palate, and uvula), legs, arms, buttocks, and genitalia. Due to a missense mutation interfering with the ability of mutant C1-INH to inhibit target proteases. | Low | Normal or high | Low | Same as for HAE type 1. |
| HAE with normal C1-INH | Less common; known mutations include genes coding for factor XII, angiopoietin-1, and plasminogen. In most cases, responsible genetic mutation not clear. | Normal | Normal | Normal | Various. |
| Acquired Angioedema | Less common; onset >40 years. Underlying MGUS, B-cell clonal disorders/paraproteinemia, lymphoreticular neoplasia, or autoimmune disorders (eg, systemic lupus). Can be a primary autoantibody as well. Symptoms same as HAE. | Low | Low | Low | Antifibrinolytic drugs, anabolic steroids, C1-INH(IV), bradykinin-receptor inhibitor. |
| ACEI-induced | Symptoms usually localized to face or upper aerodigestive tract. Characterized by erythema (without itching). More prevalent among black patients. | Normal | Normal | Normal | Possibly icatibant, although studies are conflicting. |
| **Histamine-mediated** | | | | | |
| Allergic/histamine mediated angioedema | Can occur at any age but usually younger patients; any gender; associated with urticaria; may progress to anaphylaxis; onset minutes to hours after contacting potential allergen. | Normal | Normal | Normal | Corticosteroids, antihistamines, epinephrine, omalizumab. |
| **Bradykinin- or histamine-mediated** | | | | | |
| Idiopathic angioedema | Diagnosis after exclusion of above diagnoses; both histaminergic and nonhistaminergic varieties have been described; absence of allergy, HAE, or medications. | Normal | Normal | Normal | Corticosteroids, antihistamines, omalizumab may be effective. C1-INH(IV) or bradykinin-receptor inhibitor have been used anecdotally. |

[a]Information in table sourced from references.[29-36]
[b]Formerly designated as "HAE type 3."
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; C1-INH, C1-inhibitor; C1-INH-HAE, hereditary angioedema due to C1-inhibitor deficiency; FFP, fresh frozen plasma; HAE, hereditary angioedema; MGUS, monoclonal gammopathy of uncertain significance.

In C1-INH-HAE type 1 (and acquired C1-INH deficiency angioedema), C1-INH protein, C1-INH function, and C4 levels are all low; in C1-INH-HAE type 2, C1-INH function and C4 is low, whereas C1-INH protein level is normal or high (Table 1). In all other types of angioedema, these 3 tests are normal.
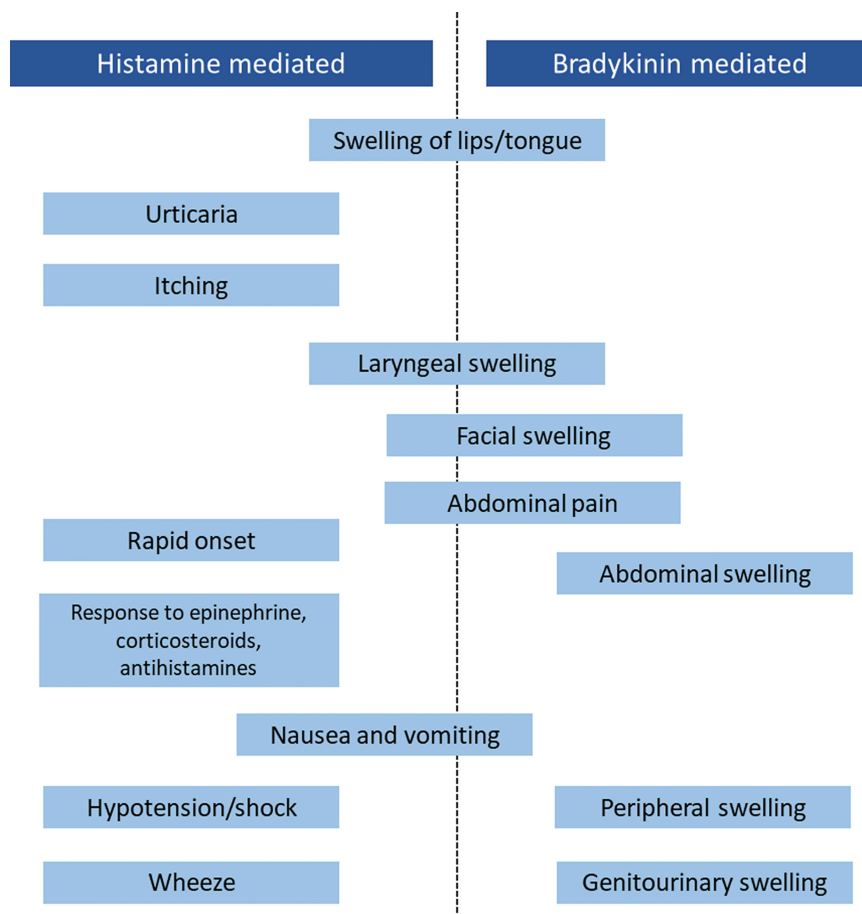
## MANAGEMENT OF HEREDITARY ANGIOEDEMA

Management of HAE should include treatment of swelling attacks when they occur and prevention of attacks in those

| Histamine mediated | Bradykinin mediated |
|---|---|

Swelling of lips/tongue

Urticaria

Itching

Laryngeal swelling

Facial swelling

Abdominal pain

Rapid onset

Abdominal swelling

Response to epinephrine, corticosteroids, antihistamines

Nausea and vomiting

Hypotension/shock

Peripheral swelling

Wheeze

Genitourinary swelling

**Figure 3** Clinical differentiation between histamine-versus bradykinin-mediated angioedema. Data from Bernstein et al.[31] This figure is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

who have a significant burden of disease associated with their HAE. All patients diagnosed with HAE should have access to at least 2 doses of a treatment to stop the progression of an attack. Preferably this on-demand treatment can be self-administered or given by a caregiver. Patients suffering from laryngeal attacks, particularly debilitating attacks, or attacks that do not respond sufficiently to initial on-demand treatment should seek treatment at a clinic or emergency department for additional assessment and treatment. Routine treatment to prevent angioedema attacks (long-term or routine prophylaxis) should be considered for patients who are more severely affected by their HAE, taking into account factors such as attack type, frequency, and severity; access to medical care; overall burden of disease; and patient preference. The World Allergy Organization/European Academy of Allergy and Clinical Immunology HAE guideline, updated in 2017 and published in 2018, recommends that HAE patients be evaluated at every visit for long-term prophylaxis.[30]

There are currently 4 US Food and Drug Administration (FDA)–approved medications for on-demand treatment including IV human plasma-derived C1-INH (C1-INH[IV]; Berinert/CSL Behring; Marburg, Germany); IV recombinant C1-INH (Ruconest; Pharming Healthcare; Leiden, The Netherlands); a plasma kallikrein inhibitor, SC ecallantide (Kalbitor; Shire/Dyax Corp, Burlington, MA); and a bradykinin B-2 receptor antagonist, SC icatibant (Firazyr; Shire, Lexington, MA). Plasma-derived C1-INH(IV), recombinant C1-INH(IV), and icatibant can each be self-administered after appropriate training. Ecallantide has a risk of anaphylaxis and must be administered by a health care professional with appropriate medical support to manage anaphylaxis.[38]

There are 3 medications approved for long-term HAE prophylaxis that specifically address functional C1-INH deficiency or its consequences (Table 2). These include IV plasma-derived C1-INH (Cinryze; Shire, Lexington, MA), SC plasma-derived C1-INH (HAEGARDA; CSL Behring, Marburg, Germany), and an SC monoclonal antibody (TAKHZYRO [lanadelumab-flyo], Takeda [formerly Shire], Lexington, MA). In addition, short-term prophylaxis with C1-INH(IV) given immediately before events that might trigger an attack (eg, medical/surgical/dental procedures) is recommended for all HAE patients.[30]

The advent of C1-INH(IV) replacement therapy was a "game changer" in the treatment and prevention of HAE attacks. Human plasma-derived C1-INH(IV) was first available in Europe in the late 1970s and approved in the United States in 2008 for routine prevention and in 2009 for on-demand

## TABLE 2

## HAE-Specific Medications Used for Long-term Prophylaxis

| Product | FDA Approval | Indication | Recommended Dose and Schedule |
|---------|--------------|------------|-------------------------------|
| Human C1-INH, IV (Cinryze)[39] | 2008 | Routine prophylaxis to prevent angioedema attacks in children age 6 and above and adults with HAE | 1000 U every 3 or 4 d[a] ∼ 500 U/5 mL; infusion rate 1 mL/min |
| Human C1-INH, SC (HAEGARDA)[40] | 2017 | Routine prophylaxis to prevent HAE attacks in adolescents and adults | 60 IU/kg body weight twice weekly (500 IU/1 mL; inject SC slowly over ∼5 min[b]) |
| Lanadelumab, SC (TAKHZYRO)[41] | 2018 | Prophylaxis to prevent attacks of HAE in patients 12 y and older | 300 mg every 2 wk; dosing every 4 wk may be considered in some patients after 6 mo on every 2 wk |

[a]Doses up to 2500 U (but not exceeding 100 U/kg) may be considered based on individual patient response.
[b]Rate of administration should be adapted to the comfort level of the patient.
Abbreviations: C1-INH, C1 esterase inhibitor; d, days; FDA, US Food and Drug Administration; HAE, hereditary angioedema; IU, international units; IV, intravenous; min, minutes; mo, months; SC, subcutaneous; U, units; wk, weeks; y, years.

treatment of attacks. For the first time, a targeted approach was available to replace the missing C1-INH function, which results in the swelling attacks. Before C1-INH availability, fresh-frozen plasma, which contains C1-INH (1 IU/cc), was used as an on-demand treatment. Attenuated androgens (eg, danazol and stanozolol) were used for both short- and long-term prophylaxis. Although androgens are FDA-approved for HAE attack prevention, safety and efficacy limitations preclude their widespread use in today's environment, characterized by the availability of treatments that specifically address the deficiencies that cause the disease.[42]

Plasma-derived C1-INH(IV) (Cinryze) was approved for HAE prophylaxis in the United States in 2008. In a pivotal phase 3, double-blinded, crossover study with C1-INH(IV) for prophylaxis in patients with a history of at least 2 attacks per month, 1000 U administered intravenously every 3 to 4 days reduced the time-normalized rate of HAE attacks over 12 weeks by 51% (from 12.73 during the placebo phase to 6.26 attacks with C1-INH[IV] treatment).[39,43] These data established routine prophylaxis with IV C1-INH as an effective option for HAE management.

Lanadelumab-flyo (Takhzyro), a fully human monoclonal antibody, was FDA approved in 2018 for prevention of HAE attacks in patients ≥12 years of age with HAE. The approved dosing regimen is 300 mg SC every 2 weeks; dosing every 4 weeks can be considered after 6 months of every-2-weeks dosing if swelling attacks are controlled.[41] Lanadelumab acts by selectively binding to and inhibiting plasma kallikrein, preventing cleavage of bradykinin from high-molecular-weight kininogen,[44] thus attenuating bradykinin-mediated vascular permeability and edema formation. The clinical efficacy of lanadelumab was evaluated in the phase 3, double-blind, parallel-group, placebo-controlled HELP Study,[44] which compared attack frequencies among patients with HAE type 1 or 2 treated with lanadelumab 150 mg every 4 weeks (n = 28), lanadelumab 300 mg every 4 weeks (n = 29), lanadelumab 300 mg every 2 weeks (n = 27), or placebo (n = 41). Over 26 weeks of treatment, the mean number of attacks per month was significantly lower with lanadelumab 150 mg every 4

weeks (0.48 attacks per month), lanadelumab 300 mg every 4 weeks (0.53 attacks per month), and lanadelumab 300 mg every 2 weeks (0.26 attacks per month) compared with placebo (1.97 attacks per month; all $P < .001$ for differences versus placebo). The most common adverse event (AE) was injection site reactions reported by 52.4% of lanadelumab and 34.1% of placebo-treated patients.

## CLINICAL DEVELOPMENT OF C1-INH(SC)

The newest formulation of C1-INH is an SC product (C1-INH[SC]; HAEGARDA, CSL Behring) approved by the FDA in 2017 for routine prevention of swelling attacks in adolescents and adults with HAE at a recommended dose of 60 IU/kg administered subcutaneously every 3 or 4 days.[40] This formulation was developed in response to unmet needs that remained even after C1-INH(IV) became available. The burden of treatment with frequent IV administration is significant. Survey findings indicated that more than half of C1-INH(IV) users were not completely satisfied with ease of treatment administration, citing concerns about damaging veins, difficulties with IV self-infusion, and dissatisfaction with long infusion time with IV administration.[45] Some patients using C1-INH(IV) require placement of an indwelling SC port, which carries additional risks, such as thrombosis, sepsis, and other complications,[46–50] as well as a need for ongoing port maintenance and associated costs.[49] Finally, some patients experienced inadequate prevention of attacks with C1-INH(IV) prophylaxis,[46,51,52] although dose escalation up to 2500 IU every 3 to 4 days was subsequently found to improve attack prevention efficacy in a majority of patients not adequately controlled by lower doses.[53] The official prescribing recommendations allow consideration of doses up to this maximum if necessary (not to exceed 100 IU/kg).[40]

### Phase 1 Study

The SC administration of C1-INH was initially studied in a randomized, open-label, crossover study (NCT00748202)

involving 24 subjects with type 1 or 2 C1-INH-HAE.[54] Each subject received a single C1-INH 1000 IU dose by either IV infusion or SC injection during an attack-free period; after a washout period of at least 7 days, each subject received a single 1000 IU dose with the other administration technique (IV or SC), also during an attack-free period. Blood levels of C1-INH were measured after each treatment. This study demonstrated the bioavailability of C1-INH administered subcutaneously to be approximately 40% of that seen with IV administration.

## Phase 2 Study

A subsequent open-label, dose-ranging, crossover study (COMPACT phase 2; NCT01576523) was carried out in 18 patients with C1-INH-HAE type 1 or 2, each of whom received treatment with 2 of 3 fixed doses of C1-INH(SC) (1500, 3000, 6000 IU), each given twice weekly for 4 weeks.[51] For each subject, the 2 treatment periods were separated by a 4-week washout period. The data revealed a dose-dependent increase in mean trough C1-INH functional activity, with weight being the only associated variable; the 3000 and 6000 IU doses produced consistent functional C1-INH levels between doses that exceeded 40%, which is the level considered to be protective against attacks.

## Phase 3 Study

The pivotal clinical trial for C1-INH(SC) was the COMPACT phase 3 study (NCT01912456),[55] an international,

prospective, multicenter, randomized, double-blind, placebo-controlled, crossover study designed to test the hypothesis that twice-weekly C1-INH(SC) at 2 body weight–adjusted doses could reduce the frequency of HAE attacks. The crossover study design is particularly useful for studies in rare diseases, because each patient serves as his or her own control, reducing the number of confounding variables and allowing for robust statistical analysis. Study patients were 12 years of age or older with type 1 or 2 C1-INH-HAE. In addition, eligible patients had to have experienced 4 or more HAE attacks that required acute treatment or medical attention or that caused significant functional impairment over a 2-month period within the 3 months before screening and at least 2 attacks during a consecutive 4-week period during the run-in phase. Patients were randomly assigned to self-administer 1 of 2 C1-INH(SC) doses (40 IU/kg [n = 45] or 60 IU/kg [n = 45]) or placebo injections subcutaneously twice weekly for the first 16 weeks, followed by crossover treatment with C1-INH or placebo for 16 weeks. Other medications (eg, C1-INH[IV], icatibant, ecallantide, or fresh-frozen plasma) could be used as on-demand treatment of HAE attacks at any time during the study, including during the placebo period. Results for patients randomly assigned to C1-INH(SC) 60 IU/kg administered every 3 to 4 days, which is the FDA-approved dose, are reported below and in Table 3.

The study's primary end point was the mean number of time-normalized HAE attacks per month, which was

## TABLE 3

## Efficacy End Points in the COMPACT Study[a]

| | Patients in the C1-INH(SC) 60 IU/kg Treatment Sequence[b] | | | |
|---|---|---|---|---|
| | C1-INH(SC) 60 IU/kg (n = 43) | Placebo (n = 42) | Within Patient Difference | P Value |
| Primary Efficacy End Point | | | | |
| No. of time-normalized attacks per month (95% CI)[c] | 0.52 (0.00 to 1.04) | 4.03 (3.51 to 4.55) | -3.51 (-4.21 to -2.81) | < .001 |
| % Reduction in attacks vs placebo | | | | |
| Median | 95 | NA | | |
| Mean | 84 | NA | | |
| Secondary Efficacy End Points | | | | |
| Patients with a response, % (95% CI) | | | | |
| ≥50% reduction in attack vs placebo | 90 | NA | | |
| ≥70% reduction in attack vs placebo | 83 | NA | | |
| ≥90% reduction in attack vs placebo | 58 | NA | | |
| % Reduction in monthly rescue medication use vs placebo | | | | |
| Median | 100 | NA | | |
| Mean | 89 | NA | | |

[a]Data from Longhurst et al[55]
[b]Crossover design.
[c]Values in this category are least-squares means as estimated from a mixed model.
Abbreviations: C1-INH, C1 esterase inhibitor; CI, confidence interval; IU, international units; NA, not applicable; SC, subcutaneous.

significantly reduced with C1-INH(SC) 60 IU/kg compared with placebo (0.52 attacks per month vs 4.03 attacks per month; $P < .001$) (Table 3, Figure 4). An important secondary end point finding was the reduction in the use of rescue medication during the C1-INH(SC) 60 IU/kg treatment period as compared with during the placebo treatment period (0.32 vs 3.89 rescue medication uses per month) (Figure 4). Furthermore, there was a lower percentage of severe attacks during C1-INH(SC) use (9% of attacks were severe) compared with during placebo use (69% of attacks were severe) (Figure 5). The average number of days with angioedema symptoms per month was 1.61 days for C1-INH(SC) 60 IU/kg as compared with 7.51 days while using placebo. There were no potentially life-threatening laryngeal attacks during 16 weeks of C1-INH(SC) 60 IU/kg use.[55]

Pharmacokinetic and pharmacodynamic analysis found that C1-INH functional activity, C1-INH protein, and C4 protein were similar across treatment groups at screening; all 3 biomarkers showed a dose-dependent increase that reached steady state during the first 2 weeks of each C1-INH(SC) treatment period. The importance of increasing and maintaining the levels of C1-INH in patients with C1-INH-HAE cannot be overstated. As the level of functional C1-INH approaches normal, the risk of an angioedema attack decreases. During the COMPACT study, trough levels of C1-INH functional activity were well above the accepted threshold of ~40% for clinically relevant attack prevention in patients treated with C1-INH(SC) 60 IU/kg (Figure 6).[55]

Most AEs reported during the COMPACT phase 3 study were injection site reactions (most commonly pain and erythema)[57] that were reported by 31% of subjects during the C1-INH treatment phase and 24% during the placebo phase. Most of these reactions were mild in intensity (95%), and none were considered severe. Overall, C1-INH(SC) was shown to be safe and effective compared with placebo for routine prevention of attacks in patients with C1-INH-HAE.

## Treatment Satisfaction and HRQoL

Additional analyses from the COMPACT phase 3 study examined the impact of C1-INH(SC) on treatment satisfaction and HRQoL.[22] Investigator and patient assessment of response to treatment showed substantially better ratings during the use of C1-INH(SC) compared with placebo. A treatment satisfaction questionnaire for medication found that patients experienced greater effectiveness and overall satisfaction on C1-INH(SC). In a post hoc analysis, C1-INH(SC) was associated with subjective benefits versus placebo based on patient-reported outcome measures on widely used instruments such as the EQ-5D (standardized instrument for measuring generic health status), the Hospital Anxiety and Depression Scale (instrument for measuring anxiety and depression), and the Work Productivity and Impairment questionnaire. The mean EQ-5D scores at the end of 14 weeks of treatment with C1-INH(SC) was 0.92 (Figure 2). Substantial improvements in work "presenteeism" (health-related impairment in productivity while at work), work productivity, and daily activities were reported with C1-INH(SC) versus placebo. These subjective assessments are in line with the objective findings from the COMPACT studies, which show significant and clinically meaningful reductions in attack rate with C1-INH(SC).

## Long-Term Open-Label Extension Study

An open-label, randomized, parallel-arm extension of the COMPACT phase 3 study was conducted to evaluate the long-term safety and efficacy of C1-INH(SC) in patients ≥6 years of age with HAE type 1 or 2.[58] The study included previous COMPACT study participants, as well as C1-INH(SC)-naïve patients. Patients were randomized 1:1 to treatment with 40 or 60 IU/kg twice weekly. During the first 24-week treatment period, the C1-INH(SC) dose remained fixed, with the exception being that any patient experiencing 12 or more attacks during any 4-week evaluation period was eligible (at the discretion of the investigator) for
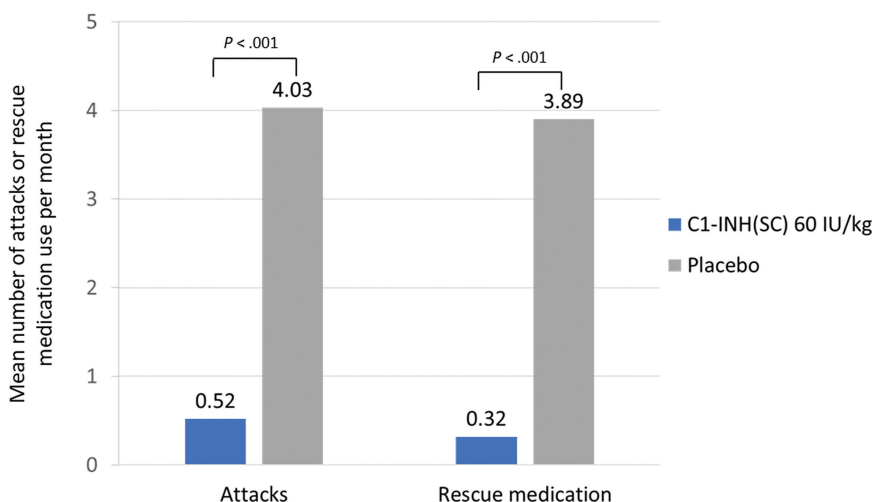
**Figure 4** Comparison of frequency of HAE attacks (primary end point) and rescue medication use for C1-INH(SC) 60 IU/kg vs placebo in the COMPACT phase 3 study.[55] *Abbreviations: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; IU, international units; SC, subcutaneous.*
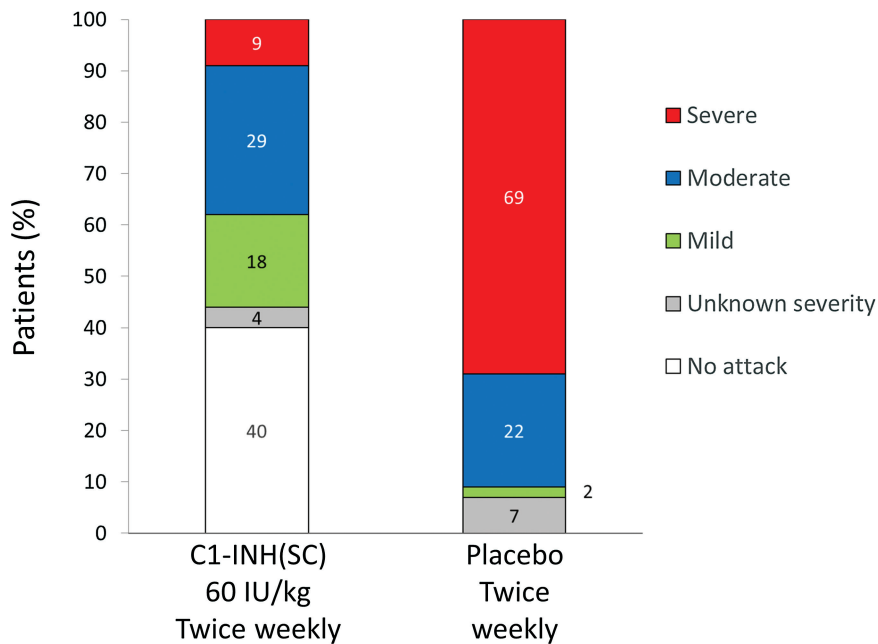
**Figure 5** Severity of HAE attacks experienced during the COMPACT study in 45 patients treated with 16 weeks each of C1-INH(SC) 60 IU/kg and placebo in crossover fashion.[a] Data from Longhurst et al.[55] [a]Patients categorized according to most severe attack during each study phase. *Abbreviations: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; IU, international units; SC, subcutaneous.*

incremental 20 IU/kg dose increases to a maximum dose of 80 IU/kg. The second treatment period was a 28-week dose adjustment period, during which dose increases were allowed for patients experiencing 3 or more attacks over 8 weeks. A protocol amendment allowed for an additional extension for patients in the United States to continue treatment for up to an additional 88 weeks. In total, 110 patients completed the study. The mean duration of C1-INH(SC) treatment was approximately 1.5 years; 35% of patients were treated for >2 years. There were no serious treatment-related events or any evidence of dose dependency with regard to AEs noted. Injection site reactions were reported in about half of patients but at a low incidence overall (0.08 [40 IU/kg] and 0.06 [60 IU/kg] events per injection). Median annualized attack rates were 1.3 (40 IU/kg group) and 1.0 (60 IU/kg group). Median

monthly rescue medication utilization rates were 0.3 uses per month, regardless of C1-INH(SC) dose. Post hoc analysis found an absence of rescue medication use in 50% of patients receiving 40 IU/kg and 62% of patients receiving 60 IU/kg throughout their entire study duration. The median time-normalized number of days with angioedema symptoms experienced was 0.2 and 0.1 d/mo for the 40 IU/kg and 60 IU/kg treatment groups, respectively. In the 60 IU/kg dosing arm (which is the approved dose), 83% of patients were attack free during the final observation period (US patients only, between 25 and 30 months; n = 23). Mean C1-INH functional activity in the 40 and 60 IU/kg treatment groups increased from baseline values of 30.4% and 28.3%, respectively, to 52.0% and 66.6% at the end of the study, both well above the assumed 40.0% attack protection threshold.[56]
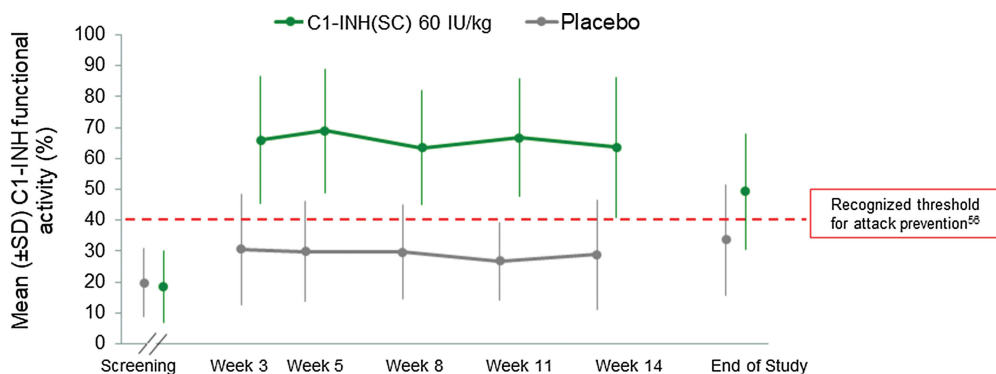


**Figure 6** C1-INH functional activity in a single group of patients during 14 weeks of treatment with C1-INH(SC) 60 IU/kg and placebo (crossover design) in the COMPACT study.[55] *Abbreviations: C1-INH, C1 esterase inhibitor; IU, international units; SC, subcutaneous; SD, standard deviation.*

## Nursing Perspectives

Nurses are important in the journey from diagnosis through treatment for patients who present with symptoms of angioedema or abdominal pain due to C1-INH-HAE. Nurses are often the first point of contact for patients presenting with undiagnosed HAE. An understanding of the unique characteristics of HAE allows a nurse to ask appropriate questions and be equipped to identify features of a patient's clinical picture as being suspicious for HAE (or not) during an intake interview. In the event that a patient presents with acute swelling, this differentiation is critical for implementation of effective treatment.

Many patients with HAE are already accustomed to using injectable medications, but for some, including newly diagnosed patients, IV or SC self-administration may be a new experience. Regardless, nursing support and guidance can be important factors in establishing patient confidence and proper technique to maximize the benefits of treatment and ensure the highest possible steady-state levels of functional C1-INH activity.

Nurses have a key role in providing patient instruction when initiating therapy with C1-INH(SC), as well as ensuring appropriate follow-up. It is important for nurses to check that drugs are properly prescribed before administration. C1-INH(SC) is available in 2000 and 3000 IU vials of lyophilized powder that requires reconstitution with sterile water (reconstituted solution = 500 IU/mL). The FDA-approved dose administered twice weekly (every 3 or 4 days) is 60 IU/kg, thus each patient's dose will be based on his or her body weight.[40] Although not part of official C1-INH(SC) dosing recommendations, in the COMPACT study,[55] the C1-INH(SC) dose was rounded up to the nearest full vial quantity to avoid wastage; nurses can consult with prescribing physicians to determine how whole-vial rounding may impact dosing for each patient. For example, the average patient weight in the COMPACT study was 82 kg; a 60 IU/kg dose equates to 4920 IU, which could be rounded to 5000 IU (one 2000 IU vial plus one 3000 IU vial, total of 10 mL).[59] To ensure maximum efficacy, every effort should be made to ensure that patients are receiving the recommended dosing (60 IU/kg body weight).

Steps for reconstitution and self-administration of C1-INH(SC) are provided in supplemental Tables 1 and 2 (http://links.lww.com/JIN/A98; http://links.lww.com/JIN/A99) and have been reviewed in detail in another publication.[59] A systematic training checklist of reconstitution and injection steps is a useful tool for patient training. Patients can be considered to have mastered self-administration once they can perform all necessary steps without prompting. The printed take-home materials can serve as a helpful reference to reinforce appropriate use. Patient support and resources can be found online at https://www.haegarda.com.

In terms of setting patient expectations regarding C1-INH(SC), it is important that patients are told about the potential for injection-site reactions, with such reactions being common, but generally mild and transient.[60] Local swelling at the injection site may occur, particularly when volumes >5 to 10 mL are injected into a single site; large doses may be split between 2 syringes. Needle lengths of 9 or 12 mm have been used for C1-INH(SC) administration, and choice may depend on patient preference or body type (thin versus overweight). During clinical trials, some patients indicated having fewer injection site reactions and less leakage with 12-mm needles versus shorter needles.[59]

Close contact with patients during the first few months of C1-INH(SC) is recommended. The type of follow-up (eg, phone, email, text) should be based on patient preference, and the frequency of follow-up (eg, weekly or less frequent) should be based on the patient's ability and skill level. Patients should be advised to record their C1-INH(SC) injections and to document any breakthrough HAE attacks.

## CONCLUSIONS

Patients who have C1-INH-HAE may have a considerable clinical burden and reduced HRQoL related to their disease. Newer treatments focus on the prevention of angioedema attacks through routine prophylaxis. SC administration may decrease the burden of treatment while improving treatment outcomes, including milder and less-frequent attacks and the potential to be attack free. C1-INH(SC), as demonstrated in the pivotal phase 3 COMPACT clinical trial, is a self-administered prophylaxis option that replaces the deficient or dysfunctional C1-INH protein. It has been shown to have a high degree of efficacy in preventing attacks and facilitating improvements in HRQoL with good safety and tolerability even after years of use. C1-INH(SC) meets unmet HAE management needs in patients who experience swelling attacks while on other prophylactic therapies. The SC route of administration is considered more convenient than IV administration and avoids venous access issues. Nurses have an important role across all aspects of HAE management from diagnosis through treatment and patient follow-up, beginning with the recognition of the various causes of "swelling" (angioedema) and consideration of HAE as a diagnostic possibility to facilitate proper diagnosis and timely management. Nurses are also instrumental in educating patients and families about HAE and training them to use HAE-specific therapies, including C1-INH(SC). Nursing vigilance and oversight of patients with HAE can provide vital details about disease and treatment-specific issues that can maximize treatment success.

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