

Therapeutic Class Overview Hereditary Angioedema Agents

Therapeutic Class

- Overview/Summary:** Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder resulting from an inherited deficiency or dysfunction of the C1 inhibitor, a primary component of the complement system. The two most common forms of HAE (types I and II) develop from either a deficiency (type I) or dysfunction (type II) of the C1 inhibitor; however, the exact mechanism(s) that lead to angioedema are not fully understood. The mediator bradykinin appears to be critical in the pathogenesis of HAE, and the C1 inhibitor is involved in regulating the production of bradykinin. HAE is characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin. Other mucosal tissues in the upper respiratory and gastrointestinal tracts may also be affected. The resulting swelling experienced by a patient is self-limiting; however, laryngeal involvement may cause fatal asphyxiation.¹ A diagnosis of HAE is commonly made in the second or third decade of life; however, symptoms often begin earlier. Mild trauma, including dental work, is a common trigger and will precipitate flares in many patients. Other triggers include *Helicobacter pylori* infection, stress, excitement, cold exposure, prolonged sitting or standing and ingestion of certain foods. HAE is distinguished from other forms of angioedema by its lack of response to other therapies such as antihistamines, steroids and/or epinephrine.¹

Treatment approaches include replacing C1 inhibitor (C1 inhibitor concentrate or fresh frozen plasma), increasing hepatic synthesis of C1 inhibitor (androgens), and inhibiting bradykinin formation and its receptor engagement. Included in this review are the injectable agents that are Food and Drug Administration (FDA)-approved for prophylaxis of HAE and/or treatment of acute HAE attacks. C1 esterase inhibitor (Berinert[®]), icatibant (Firazyr[®]) and ecallantide (Kalbitor[®]) are indicated to treat acute attacks of HAE, while C1 esterase inhibitor (Cinryze[®]) is the only injectable agent that is approved for prophylaxis against HAE attacks.²⁻⁷ None of these agents are currently available generically, and no head-to-head trials have been performed between the agents in this class.

Table 1. Current Medications Available in Therapeutic Class⁴⁻⁷

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
C1 esterase inhibitor (Berinert [®])	Treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema in adult and adolescent patients*	IV injection: 500 IU (single-use vial)	-
C1 esterase inhibitor (Cinryze [®])	Routine prophylaxis against angioedema attacks in adolescents and adult patients with hereditary angioedema	IV injection: 500 U (single-use vial)	-
Ecallantide (Kalbitor [®])	Treatment of acute attacks of hereditary angioedema [†]	SC injection: 10 mg/mL (1 mL single-use vial)	-
Icatibant (Firazyr [®])	Treatment of acute attacks of hereditary angioedema [‡]	SC injection: 10 mg/mL (3 mL single-use, prefilled syringe)	-

IV=intravenous, SC=subcutaneous

* Safety and efficacy for prophylactic therapy have not been established.

† In patients ≥16 years of age.

‡ In patients ≥18 years of age.

Evidence-based Medicine

- In patients ≥6 years of age with confirmed hereditary angioedema (HAE) and a history of ≥2 attacks per month, C1 esterase inhibitor (Cinryze[®]) significantly reduced the frequency of acute attacks compared to placebo.⁸

- Acute treatment with C1 esterase inhibitor (Berinert[®]) and icatibant demonstrate superiority compared to treatment with placebo in significantly shortening the time to first onset of symptom relief and total resolution of symptoms of an acute HAE attack.⁹⁻¹²
- Acute treatment with icatibant demonstrates superiority over treatment with tranexamic acid in significantly shortening the time to first onset of symptom relief and total resolution of symptoms of an acute HAE attack.¹¹
- Acute treatment with ecallantide significantly improves mean symptom complex severity scores and total outcome scores compared to placebo four hours after treatment administration and maintained for up to 24 hours.^{13,14}

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Short-term prophylaxis for minor surgical procedures is not recommended if plasma derived C1 inhibitor replacement therapy is immediately available; however, if replacement therapy is unavailable, prophylaxis for five days before and two to five days post event with 17- α -alkylated anabolic androgen or antifibrinolytic therapy is recommended.⁹
 - For invasive procedures, plasma derived C1 inhibitor replacement therapy should be considered, or if unavailable, short-term danazol is recommended.⁹
 - For major manipulations or intubation, plasma derived C1 inhibitor replacement therapy should be administered one to six hours prior to surgery. For long-term prophylaxis, antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy should be considered if more than one severe event per month occurs.⁹
 - Acute attacks should be treated as early as possible and first-line therapies include plasma derived C1 inhibitor replacement therapy, icatibant and ecallantide.⁹
- Other Key Facts:
 - Currently, Cinryze[®] is the only injectable hereditary angioedema (HAE) agent approved for prophylactic therapy of HAE attacks.⁴⁻⁷
 - Generic danazol capsules are also Food and Drug Administration-approved for the prevention of attacks of angioedema of all types in males and females; however, this agent is not included in the review.¹⁶
 - To date, head-to-head trials have not been conducted between the agents in the class.

References

1. Atkinson JP. Clinical manifestations and pathogenesis of hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
2. Atkinson JP. Treatment of acute attacks in hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
3. Atkinson JP. Prevention of attacks in hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
4. Berinert[®] [package insert]. Kankakee (IL): CSL Behring LLC; 2012 Jul.
5. Cinryze[®] [package insert]. Exton (PA): ViroPharma Biologics Inc.; 2010 Nov.
6. Firazyr[®] [package insert]. Lexington (MA): Shire Orphan Therapies, Inc.; 2011 Aug.
7. Kalbitor[®] [package insert]. Burlington (MA): Dyax Corp.; 2012 Feb.
8. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nano filtered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363:513-22.
9. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared to placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124(4):801-8.
10. Kunschak M, Engl W, Maritsch R, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion*. 1998;38:540-9.
11. Cicardi M, Banerji A, Brancho A, Rosenkranz MB, Bork RK, Lumry W, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363:532-41.
12. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Potter PC, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol*. 2011;107:529-37.
13. Levy RJ, Lumry WR, McNeil DL, Li HH, Champion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:523-9.
14. Cicardi M, Levy RJ, McNeil DL, Le HH, Sheffer AL, Champion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363:523-31.

15. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010 Jul 28;6(1):24.
16. Danazol [package insert]. Sellersville (PA): Teva Pharmaceuticals; 2012 Jan.

Therapeutic Class Review Hereditary Angioedema Agents

Overview/Summary

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder resulting from an inherited deficiency or dysfunction of the C1 inhibitor, a primary component of the complement system. The prevalence of HAE is estimated at one individual per 50,000, with reported ranges from 1:10,000 to 1:150,000. The two most common forms of HAE (types I and II) develop from either a deficiency (type I) or dysfunction (type II) of the C1 inhibitor; however, the exact mechanism(s) that lead to angioedema are not fully understood. The mediator bradykinin appears to be critical in the pathogenesis of HAE, and the C1 inhibitor is involved in regulating the production of bradykinin. HAE is characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin. Other mucosal tissues in the upper respiratory and gastrointestinal tracts may also be affected. The resulting swelling, experienced by a patient is self-limiting; however, laryngeal involvement may cause fatal asphyxiation.¹ A diagnosis of HAE is commonly made in the second or third decade of life; however, symptoms often begin earlier. Mild trauma, including dental work, is a common trigger and will precipitate flares in many patients. Other triggers include *Helicobacter pylori* infection, stress, excitement, cold exposure, prolonged sitting or standing and ingestion of certain foods. HAE is distinguished from other forms of angioedema by its lack of response to other therapies such as antihistamines, steroids and/or epinephrine.¹

Treatment approaches include replacing C1 inhibitor (C1 inhibitor concentrate or fresh frozen plasma), increasing hepatic synthesis of C1 inhibitor (androgens), and inhibiting bradykinin formation and its receptor engagement. Included in this review are the injectable agents Food and Drug Administration (FDA)-approved for prophylaxis of HAE and/or treatment of acute HAE attacks. C1 esterase inhibitor (Berinert[®]), ecallantide (Kalbitor[®]) and icatibant (Firazyr[®]) are indicated to treat acute HAE attacks, while C1 esterase inhibitor (Cinryze[®]) is the only injectable agent that is approved for prophylaxis against HAE attacks. Generic danazol capsules are also FDA-approved for the prevention of attacks of angioedema of all types in males and females; however, this agent is not included in the review.²⁻⁸

Short-term prophylaxis for minor surgical procedures is not recommended if plasma derived C1 inhibitor replacement therapy is immediately available; however, if replacement therapy is unavailable, prophylaxis for five days before and two to five days post event with 17- α -alkylated anabolic androgen or antifibrinolytic therapy is recommended. For invasive procedures, plasma derived C1 inhibitor replacement therapy should be considered, or if unavailable, short-term danazol is recommended. For major manipulations or intubation, plasma derived C1 inhibitor replacement therapy should be administered one to six hours prior to surgery. For long-term prophylaxis, antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy should be considered if more than one severe event per month occurs. Acute attacks should be treated as early as possible and first-line therapies include plasma derived C1 inhibitor replacement therapy, icatibant and ecallantide.⁹

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
C1 esterase inhibitor (Berinert [®])	Protein C1 inhibitor	-
C1 esterase inhibitor (Cinryze [®])	Protein C1 inhibitor	-
Ecallantide (Kalbitor [®])	Kallikrein inhibitor	-
Icatibant (Firazyr [®])	Bradykinin inhibitor	-

Indications**Table 2. Food and Drug Administration-Approved Indications⁴⁻⁷**

Indication	C1 Esterase Inhibitor (Berinert [®])	C1 Esterase Inhibitor (Cinryze [®])	Ecallantide	Icatibant
Routine prophylaxis against angioedema attacks in adolescents and adult patients with hereditary angioedema		✓		
Treatment of acute attacks of hereditary angioedema			✓ †	✓ ‡
Treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema in adult and adolescent patients	✓ *			

* Safety and efficacy for prophylactic therapy have not been established.

† In patients ≥16 years of age.

‡ In patients ≥18 years of age.

Pharmacokinetics**Table 3. Pharmacokinetics^{4-7,10}**

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
C1 esterase inhibitor (Berinert [®])	Not reported	Not reported	Not reported	Not reported	56±36
C1 esterase inhibitor (Cinryze [®])	Not reported	Not reported	<10	None	56±36
Ecallantide	Not reported	Not reported	Not reported	Not reported	2
Icatibant	97	Not reported	Not reported	Not reported	1.4

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the injectable hereditary angioedema (HAE) agents in their respective Food and Drug-Administration (FDA)-approved indications are outlined in Table 5.¹¹⁻²¹

Currently, C1 esterase inhibitor (Cinryze[®]) is the only injectable HAE agent approved for prophylactic therapy of HAE. In patients ≥6 years of age with confirmed HAE and a history of ≥2 attacks per month, C1 esterase inhibitor (Cinryze[®]) significantly reduced the frequency of acute attacks compared to placebo.¹¹ C1 esterase inhibitor (Berinert[®]), ecallantide and icatibant are all FDA-approved for the treatment of acute HAE attacks. Acute treatment with C1 esterase inhibitor (Berinert[®]) and icatibant demonstrate superiority compared to treatment with placebo in significantly shortening the time to first onset of symptom relief and total resolution of symptoms of an acute HAE attack.^{15,16,20,21} Acute treatment with icatibant demonstrates superiority over treatment with tranexamic acid for the same outcomes.²⁰

Acute treatment with ecallantide significantly improves mean symptom complex severity scores and total outcome scores compared to placebo four hours after treatment administration and maintained for up to 24 hours.^{17,18}

To date, head-to-head trials have not been conducted between the agents in the class.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
Prophylaxis of Hereditary Angioedema				
Zuraw et al ¹¹ C1-INH (Cinryze®) 100 U IV twice weekly vs placebo OL C1-INH injections were allowed as rescue therapy.	DB, PC, XO Patients ≥6 years of age with a confirmed diagnosis of HAE and history ≥2 attacks per month	N=22 24 weeks	Primary: Average number of attacks Secondary: Average severity of attacks, average duration of attacks, number of OL injections of C1-INH and total number of days of swelling	Primary: The average number of attacks was significantly lower with C1-INH compared to placebo (6.26 vs 12.73 attacks; treatment difference, 6.47 attacks; 95% CI, 4.21 to 8.73; <i>P</i> <0.0001). Secondary: The average score for severity (three point scale) of attacks was significantly lower with C1-INH compared to placebo (1.30±0.85 vs 1.90±0.36; <i>P</i> <0.0001). The total duration of attacks was significantly shorter with C1-INH compared to placebo (2.10±1.13 vs 3.40±1.39 days; <i>P</i> =0.002). A total of 11 and 22 patients receiving C1-INH and placebo, respectively, required OL rescue therapy. C1-INH therapy was associated with significantly fewer OL injections (4.70±8.66 vs 15.40±8.41 injections; <i>P</i> <0.001) and days of swelling (10.10±10.73 vs 29.6±16.9 days; <i>P</i> <0.001) compared to placebo.
Treatment of Acute Hereditary Angioedema				
Craig et al ¹² I.M.P.A.C.T.2 C1-INH (Berinert®) 20 U/kg administered as a single IV dose	ES, OL, PRO Patients ≥6 years of age with a confirmed C1-INH deficiency (type I or II HAE)	N=16 (39 laryngeal attacks) Single attack trial	Primary: Time to onset of symptom relief Secondary: Time to complete resolution of all symptoms	Primary: Median time to onset of symptom relief was 0.25 hours for the 30 attacks; all attacks were treated successfully. Median time to onset of relief for individual mean values per patient was 0.44 hours. Within one hour after administration, onset of relief was reported in ≥95% of all attacks, and the time to onset of relief was ≤0.75 hours in ≥85% of patients. Secondary: Median time to complete resolution of all symptoms was 8.25 hours when analyzed by attack and 5.87 hours when analyzed as the mean value per patient. Time to complete resolution of all symptoms was <16 hours in 75% of patients and <24 hours in 74% of attacks.
Craig et al ¹³ I.M.P.A.C.T.2	ES, OL, PRO Patients ≥6 years	N=57 (1,085 attacks)	Primary: Time to onset of symptom relief	Primary: Median time to onset of symptom relief was 0.46 hours. The individual average time was <1 hours in 89.5% of patients. Median times to onset of symptom relief were

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
C1-INH (Berinert®) 20 U/kg administered as a single IV dose	of age with a confirmed C1-INH deficiency (type I or II HAE)	Single attack trial (median duration, 24 months)	Secondary: Time to complete resolution of all symptoms	comparable for all types of attacks (range, 0.39 to 0.48 hours). Secondary: Median time to complete symptom resolution was 15.5 hours. The individual average time was <24 hours in 71.9% of patients. Median time to complete resolution of symptoms was shortest for laryngeal attacks. A single dose was effectively treated 1,073/1,085 (99%) HAE attacks. Additional doses were administered for 12 abdominal attacks in six patients for worsening of the attacks or because the patients felt the attack did not resolve quickly enough. None of the attacks treated with additional doses of C1-INH concentrate were associated with adverse drug reactions.
Bork et al ¹⁴ C1-INH (Berinert®) 500 to 1,000 U IV	Case report Patients with deficiency in C1-INH experiencing typical clinical symptoms of HAE	N=95 (193 laryngeal attacks) Patients were enrolled over a 20 year period	Primary: Time from injection to the first signs of symptom resolution Secondary: Time from injection to the end of symptom progression	Primary: The interval from injection to interruption in progress of symptoms ranged from 10 minutes to four hours (42.2±19.9 minutes). In all patients, difficulty breathing and fear of asphyxiation were the first symptoms that resolved. Dysphagia, the sensation of a lump in the throat and voice changes took longer to resolve completely. All patients experienced the onset of relief within four hours after C1-INH administration. Secondary: The duration of laryngeal edema was 15.3±9.3 hours in patients receiving C1-INH compared to 100.8±26.2 hours in patients who received no treatment (<i>P</i> <0.001).
Craig et al ¹⁵ I.M.P.A.C.T. 1 C1-INH (Berinert®) 10 to 20 U/kg administered as a single IV infusion vs	DB, MC, PC, RCT Patients ≥6 years of age with a confirmed diagnosis C1-INH deficiency (type I or II HAE)	N=124 24 hours	Primary: Time to onset of symptom relief Secondary: Time to complete HAE symptom resolution, proportion of	Primary: Median time to onset of symptom relief was significantly shorter with C1-INH 20 U/kg compared to placebo (0.5 vs 1.5 hours; <i>P</i> =0.0025). There was no significant difference between C1-INH 10 U/kg and placebo treatments (1.2 vs 1.5 hours; <i>P</i> =0.2731). Secondary: Median time to complete HAE symptom resolution was significantly shorter with C1-INH 20 U/kg compared to placebo (4.9 vs 7.8 hours; <i>P</i> =0.0237). The median time was longer with C1-INH 10 U/kg compared to placebo (<i>P</i> value not reported).

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>Patients were treated on presentation of acute moderate to severe abdominal or facial attack within five hours of the attack attaining moderate intensity.</p> <p>Patients, initially receiving C1-INH 10 U/kg or placebo who reported an inadequate response after four hours were eligible to receive another 10 U/kg dose (active group) or 20 U/kg dose (placebo group).</p>			<p>patients with worsened intensity of HAE symptoms between two and four hours after start of treatment, number of vomiting episodes within four hours of start of treatment and safety</p>	<p>The proportion of patients with worsened intensity of HAE symptoms between two and four hours after the start of treatment was significantly lower with C1-INH 20 U/kg compared to placebo (4.7 vs 31.0%; $P=0.0014$).</p> <p>The mean number of vomiting episodes within four hours after start of treatment was significantly lower with C1-INH 20 U/kg compared to placebo (0.1 vs 0.8; $P=0.0329$).</p> <p>The proportion of patients experiencing an adverse event within four hours of the start of treatment was lower with C1-INH 20 U/kg compared to placebo (19.6 vs 43.9%; P value not reported). The most frequently reported adverse events were nausea, diarrhea, abdominal pain and muscle spasms. The frequencies of these events were lower with C1-INH 20 U/kg compared to placebo.</p>
<p>Zuraw et al¹¹</p> <p>C1-INH (Cinryze[®]) 1,000 U administered IV once or twice</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients ≥6 years of age with confirmed diagnosis of HAE presenting within four hours of an acute attack</p>	<p>N=68</p> <p>Single attack trial</p>	<p>Primary: Time to onset of unequivocal relief</p> <p>Secondary: Proportion of patients who had an onset of unequivocal relief within four hours, time to complete</p>	<p>Primary: Time to onset of unequivocal relief was significantly shorter with C1-INH compared to placebo (two vs four hours; estimated success rate ratio, 2.41; 95% CI, 1.17 to 4.95; $P=0.02$).</p> <p>Secondary: There was no significant difference in the proportion of patients achieving onset of unequivocal relief within four hours between the C1-INH and placebo treatment groups (60 vs 44%, respectively; $P=0.06$). A second dose of blinded study drug was administered in 23 and 28 patients randomized to C1-INH and placebo, respectively.</p> <p>The median time to complete resolution of symptoms was significantly shorter with C1-INH compared to placebo (12.3 vs 25.0 hours; $P=0.004$), even though all</p>

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
			resolution of the attack and effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels	<p>patients who did not have substantial improvement by the end of the four hour assessment period were given OL C1-INH.</p> <p>Both antigenic and functional levels of C1 inhibitor increased significantly with C1-INH ($P<0.001$ for both). In contrast, C4 levels did not change and were not different between the two treatments ($P=0.86$).</p>
<p>Kunschak et al¹⁶</p> <p>C1-INH 25 PU/kg infusion</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with HAE presenting within five hours of an attack with a history ≥ 5 attacks during the 12 months preceding the study</p>	<p>N=23</p> <p>Single attack trial</p>	<p>Primary: Time to relief</p> <p>Secondary: Time to resolution</p>	<p>Primary: Time to relief was significantly shorter with C1-INH compared to placebo (7.62 vs 15.35 hours; $P=0.007$).</p> <p>Secondary: There was no significant difference between the two treatments with time to resolution of symptoms (23.98 vs 34.58 hours; $P=0.09$).</p>
<p>Levy et al¹⁷</p> <p>EDEMA4</p> <p>Ecallantide 30 mg SC</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients ≥ 10 years of age with documented evidence of type I or II HAE presenting within eight hours of a moderate to severe HAE attack affecting any anatomical location</p>	<p>N=96</p> <p>24 hours</p>	<p>Primary: Change in baseline mean symptom complex severity score four hours after treatment</p> <p>Secondary: Treatment outcome score four hours after treatment and</p>	<p>Primary: A significantly greater improvement in the mean symptom complex severity score was achieved with ecallantide compared to placebo (-0.8 ± 0.6 vs -0.4 ± 0.8; $P=0.01$).</p> <p>Secondary: A significantly greater improvement in total outcome score was achieved with ecallantide compared to placebo (53.1 ± 497.0 vs 8.1 ± 63.2; $P=0.003$).</p> <p>Twenty-four hours after dosing, the change from baseline mean symptom complex severity score was significantly greater with ecallantide compared to placebo (-1.5 ± 0.6 vs -1.1 ± 0.8; $P=0.04$). Similar results were observed for the treatment outcome score (88.8 ± 28.1 vs 55.1 ± 58.3; $P=0.03$). A significantly greater proportion of ecallantide-treated patients maintained significant overall improvement through 24 hours compared to placebo-treated patients (44 vs 21%; $P=0.02$).</p>

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
			maintenance of significant overall improvement through 24 hours	
Cicardi et al ¹⁸ Ecallantide 30 mg SC vs placebo	DB, PC, RCT Patients ≥10 years of age with documented diagnosis of HAE presenting within eight hours of a moderate to severe HAE attack	N=71 24 hours (plus 90 day follow-up)	Primary: Treatment outcome score four hours after treatment Secondary: Change in baseline mean symptom complex severity score four hours after treatment, time to significant improvement in overall response, treatment outcome score 24 hours after treatment and change in baseline mean symptom complex severity score 24 hours after	Primary: Median treatment outcome scores were significantly higher with ecallantide compared to placebo four hours after treatment (50.0 vs 0.0; <i>P</i> =0.004). Secondary: After four hours, the median change in baseline symptom complex severity score was significantly greater with ecallantide compared to placebo (-1.00 vs -0.50; <i>P</i> =0.01). There was no significant difference between ecallantide and placebo in the median time to significant improvement in overall response (165.0 and >240.0 minutes; <i>P</i> =0.14). After 24 hours, median treatment outcomes scores were significantly higher with ecallantide compared to placebo (75.0 vs 0.0; <i>P</i> =0.007). After 24 hours, the median change in baseline symptom complex severity score was significantly greater with ecallantide compared to placebo (-1.00 vs -0.50; <i>P</i> =0.04). The median time to sustained improvement in overall response was significantly shorter with ecallantide (67.0 vs 165.0 minutes; <i>P</i> =0.08) compared to placebo.

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
<p>Bork et al¹⁹</p> <p>Icatibant 0.4 mg/kg IV administered over two hours (Group 1)</p> <p>vs</p> <p>icatibant 0.4 mg/kg IV administered over 30 minutes (Group 2)</p> <p>vs</p> <p>icatibant 0.8 mg/kg IV administered over 30 minutes (Group 3)</p> <p>vs</p> <p>icatibant 30 mg SC (Group 4)</p> <p>vs</p> <p>icatibant 45 mg SC (Group 5)</p>	<p>Uncontrolled, pilot trial</p> <p>Patients 18 to 65 years of age with documented HAE and a recent attack frequency ≥ 1 every three months, with the current attack being of moderate to severe intensity at any location excluding laryngeal edema</p>	<p>N=15 (20 attacks)</p> <p>Single attack trial</p>	<p>treatment</p> <p>Primary: Efficacy</p> <p>Secondary: Safety</p>	<p>Primary: Median time to onset of symptom relief was 1.50, 1.42 and 1.13 hours with IV therapy (12 attacks) and 0.58 and 0.45 hour with SC therapy (eight attacks). Overall, treatment resulted in a time to onset of symptom relief of 1.16 ± 0.95 hours.</p> <p>Improvement of baseline symptoms after four hours was similar among the various groups, with median differences in the VAS scores of 5.31, 1.92 and 5.61 cm with IV therapy, and 3.15 and 4.31 cm with SC therapy. The median difference in the VAS score after four hours was 4.11 cm (95% CI, 1.72 to 6.07; $P < 0.01$) in all 15 patients.</p> <p>Historical data of a large number of attacks manifesting at the same location as the current attacks were available for all patients. Ten of 15 patients had >100 attacks before treatment. Unlike the short time to onset of symptom relief in all treated patients of 1.16 ± 0.95 hours, the untreated attacks had a long time to onset of symptom relief of 42.01 ± 14.1 hours. Treatment led to a 97% reduction concerning the time to relief.</p> <p>Secondary: Among the skin swellings treated, there were six facial swellings in five patients and 15 episodes of swellings in extremities in 12 patients. After onset of relief, there was no further increase or worsening of the skin swellings, and then the skin swelling continuously improved until it disappeared completely or until there was only a minimal residual swelling. The period between the maximum of skin swellings and the end of the swellings or the minimal residual swelling was 13.9 ± 12.3 hours (range, 0.5 to 45.2 hours) on average. All patients reported that all treated swellings were considerably shorter than usual.</p> <p>After SC administration, local reactions were noted in all patients, including itching, urticaria wheal, erythema and mild burning pain. Pain lasted for some minutes, itching urticaria wheal for some hours and residual erythema cleared within 24 hours. All symptoms resolved spontaneously and did not demand medical intervention. In none of the patients was the response severe enough that the patient would consider refusing therapy. One patient experienced moderate headache more</p>

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
				<p>than four hours after the infusion of icatibant. There were no other adverse events assessed as related to the study drug.</p> <p>Plasma bradykinin was consistently increased as much as 30-fold above normal levels. Four hours after infusion, median bradykinin was decreased from 48.5 to 18.0 pmol/L. Four hours after SC administration, there was a nonsignificant decrease in bradykinin from 75.0 to 30.5 pmol/L (<i>P</i> value not reported).</p>
<p>Cicardi et al²⁰ FAST-1 and -2</p> <p>Icatibant 30 mg SC administered as a single dose</p> <p>vs</p> <p>placebo (FAST-1) or tranexamic acid 3 g/day for two days (FAST-2)</p> <p>Patients with life-threatening laryngeal angioedema were also treated with OL icatibant.</p>	<p>2 DB, MC, PRO, RCT</p> <p>Patients ≥18 years of age with documented HAE presenting with cutaneous or abdominal attacks</p>	<p>N=130</p> <p>Single attack trial</p>	<p>Primary: Time to clinically significant relief of symptoms</p> <p>Secondary: Time to first symptom improvement according to the patient and according to the investigator, time to almost complete relief of symptoms, proportion of patients reaching the median time to clinically significant relief of the index symptom within four hours after the start of treatment, use</p>	<p>Primary: Median time to clinically significant symptom relief was not different with icatibant compared to placebo (2.5 vs 4.6 hours; <i>P</i>=0.14). The median time to clinically significant symptom relief was significantly shorter with icatibant compared to tranexamic acid (2.0 vs 12.0 hours; <i>P</i><0.001).</p> <p>Secondary: Median time to first symptom improvement was significantly shorter with icatibant compared to placebo, as assessed by patients (0.8 vs 16.9 hours; <i>P</i><0.001) and by investigators (1.0 vs 5.7 hours; <i>P</i><0.001). Similar results were observed with icatibant compared to tranexamic acid (0.8 vs 7.9 hours; <i>P</i><0.001 and 1.5 vs 6.9 hours; <i>P</i><0.001).</p> <p>Median time to almost complete relief of symptoms was not significantly different between icatibant and placebo (8.5 vs 19.4 hours; <i>P</i>=0.08); however, it was significantly shorter with icatibant compared to tranexamic acid (10.0 vs 51.0 hours; <i>P</i><0.001).</p> <p>The proportion of patients with clinically significant relief of the index symptom after four hours was not different between icatibant and placebo (67 vs 46%, respectively; <i>P</i>=0.18); however, it was significantly larger with icatibant compared to tranexamic acid (80 vs 31%; <i>P</i><0.001).</p> <p>Use of rescue medication within the first 12 hours was administered in 3/26 patients (11%) receiving icatibant compared to 13/29 patients (45%) receiving placebo, and within the first 48 hours in 6/26 (22%) and 15/29 (52%) patients, respectively. Similar results were observed with icatibant compared to tranexamic acid (0/36 [0%] vs 5/38</p>

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
			of rescue medication and safety	[13%] and 6/36 [17%] vs 11/38 [29%]; <i>P</i> values not reported). The most common adverse events were recurrent or worsening angioedema. Injection site reactions, which were recorded separately from the other adverse events, were reported by the majority of patients in each trial, and by more patients treated with icatibant (96 vs 28% and 97 vs 26%). In both trials, the proportions of patients reporting any adverse event were 44 vs 66% and 53 vs 42%. No serious adverse events occurred in FAST-1, while 11 vs 3% of patients reported a serious adverse event in FAST-2 (<i>P</i> values not reported).
Lumry et al ²¹ FAST-3 Icatibant 30 mg SC vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of HAE (type I or II) presenting within six to 12 hours after a mild to severely acute HAE attack	N=93 (non-laryngeal first attacks, n=88; laryngeal, n=5) Single attack trial	Primary: Time to 50% reduction in symptom severity of cutaneous and/or abdominal attacks Secondary: Time to onset of primary symptom relief, time to almost complete symptom relief, time to initial symptom improvement assessment by the patient and investigator, time to onset of symptom relief,	Primary: Median time to 50% reduction in symptom severity was significantly shorter with icatibant compared to placebo (2.0 vs 19.8 hours; <i>P</i> <0.001). The reduction in mean VAS score was significantly greater with icatibant compared to placebo from one hour following treatment (<i>P</i> =0.003), and was maintained for eight hours. Secondary: For non laryngeal attacks, icatibant was associated with a significantly shorter time to onset of primary symptom relief compared to placebo (1.5 vs 18.5 hours; <i>P</i> <0.001). For non laryngeal attacks, icatibant was associated with a significantly shorter time to almost complete symptom relief compared to placebo (8 vs 36 hours; <i>P</i> =0.012). For non laryngeal I attacks, icatibant was associated with a significantly shorter time to patient- (0.8 vs 3.5 hours; <i>P</i> <0.001) and investigator-assessed (0.8 vs 3.4 hours; <i>P</i> <0.001) initial symptom relief compared to placebo. For non laryngeal attacks, icatibant was associated with a significantly shorter time to onset of symptom relief for investigator-assessed composite symptom score (1.6 hours vs not reported; <i>P</i> <0.001) compared to placebo. For non laryngeal attacks, icatibant was associated with a significantly shorter time to onset of symptom relief for individual symptom VAS scores compared to placebo (skin swelling: 3.0 vs 22.3 hours; <i>P</i> <0.001; skin pain: 2 vs 8 hours; <i>P</i> =0.013;

Study and Drug Regimen	Study Design, Study Rating†, and Demographics	Sample Size and Study Duration	End Points	Results
			time to onset of symptom relief of individual symptoms, rescue medication	<p>abdominal pain: 1.8 vs 3.5 hours; $P=0.007$).</p> <p>For non laryngeal attacks, no patient treated with icatibant required rescue medication compared to 36% (16/45) of patients treated with placebo. Significance was achieved with icatibant for both use of rescue medications before the onset of symptom relief ($P<0.001$) and at any time point until attack resolution ($P<0.001$). More patients required rescue medications at any time during the attack and up to five days post-treatment with placebo (40%; 18/45) compared to icatibant (7%; 3/43).</p> <p>For laryngeal attacks, the median times to onset of symptom relief were 2.5 and 2.3 hours in patients who received DB and OL treatment with icatibant.</p>

Study abbreviations: CI=confidence interval, DB=double blind, ES=extension-study, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, XO=cross-over

Miscellaneous abbreviations: C1-INH=C1 esterase inhibitor, HAE=hereditary angioedema, IV=intravenous, PU=plasma units, SC=subcutaneous, U=units, VAS=visual analog scale

Special Populations**Table 5. Special Populations^{4-7,10}**

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
C1 esterase inhibitor (Berinert [®])	Safety and efficacy have not been established in the elderly.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
	Safety and efficacy have not been established in children <12 years of age.				
C1 esterase inhibitor (Cinryze [®])	Safety and efficacy have not been established in the elderly.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
	Safety and efficacy in neonates, infants, and children have not been established.				
Ecallantide	Safety and efficacy have not been established in the elderly.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
	Safety and efficacy have not been established in patients <16 years of age.				
Icatibant	Safety and efficacy have not been established in the elderly.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
	Safety and efficacy have not been established in patients <18 years of age.				

*Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Adverse Drug Events**Table 6. Adverse Drug Events^{4-7,10}**

Adverse Event(s)	C1 Esterase Inhibitor (Berinert [®])	C1 Esterase Inhibitor (Cinryze [®])	Ecallantide	Icatibant
Gastrointestinal				
Abdominal pain	4.7 to 7.0	-	-	-
Diarrhea	-	-	4.0 to 10.6	-
Nausea	7	-	5.0 to 12.9	-
Upper abdominal pain	-	-	5.1	-
Vomiting	2.3	-	5.5	-

Adverse Event(s)	C1 Esterase Inhibitor (Berinert®)	C1 Esterase Inhibitor (Cinryze®)	Ecallantide	Icatibant
General Disorders and Administration Site Conditions				
Anaphylaxis	-	-	3.9	-
Injection site reaction	-	-	3.0 to 7.4	97
Limb injury	-	8	-	-
Pruritus	-	8	5.1	-
Pyrexia	-	-	4.0 to 4.7	4
Rash	-	21	-	-
Investigations				
Transaminase increased	-	-	-	4
Nervous System Disorders				
Dizziness	-	-	-	3
Headache	7	17	8.0 to 16.1	-
Other				
Back pain	-	8	-	-
Bronchitis	-	8	-	-
Dysgeusia	4.7	-	-	-
Fatigue	-	-	11.8	-
Muscle spasms	2.3	-	-	-
Nasopharyngitis	-	-	3.0 to 5.9	-
Pain	2.3	-	-	-
Pain in extremity	-	8	-	-
Sinusitis	-	21	-	-
Upper respiratory tract infection	-	13	8.2	-
Viral upper respiratory tract infection	-	13	-	-

Contraindications**Table 7. Contraindications**^{4-7,10}

Contraindications	C1 Esterase Inhibitor (Berinert®)	C1 Esterase Inhibitor (Cinryze®)	Ecallantide	Icatibant
Hypersensitivity	✓	✓	✓	-

Boxed Warnings**Boxed Warning for Kalbitor® (ecallantide)**⁷

WARNING
Anaphylaxis has been reported after administration of Kalbitor®. Due to the risk of anaphylaxis, Kalbitor® should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer Kalbitor® to patients with known clinical hypersensitivity to Kalbitor®.

Warnings and Precautions**Table 8. Warnings and Precautions**^{4-7,10}

Warnings/Precautions	C1 Esterase Inhibitor (Berinert®)	C1 Esterase Inhibitor (Cinryze®)	Ecallantide	Icatibant
Laryngeal attacks; immediately seek medical attention if occur	✓	-	-	✓
Thrombotic events; have been reported and patients should be monitored	✓	✓	-	-
Transmission of infectious agents; made from human blood and may cause disease	✓	✓	-	-

Drug Interactions

No clinically significant drug interactions are reported for the injectable hereditary angioedema agents. In addition, no drug interaction studies have been conducted with either C1 esterase inhibitor.

Dosage and Administration**Table 9. Dosing and Administration**^{4-7,10}

Generic Name	Adult Dose	Pediatric Dose	Availability
C1 esterase inhibitor (Berinert®)	<u>Treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema in adult and adolescent patients:</u> IV injection, 20 IU/kg IV	Safety and efficacy have not been established in children <12 years of age.	IV injection: 500 IU (single-use vial)
C1 esterase inhibitor (Cinryze®)	<u>Routine prophylaxis against angioedema attacks in adolescents and adult patients with hereditary angioedema:</u> IV injection, 1,000 U IV every three or four days	Safety and efficacy in neonates, infants, and children have not been established.	IV injection: 500 U (single-use vial)
Ecallantide	<u>Treatment of acute attacks of hereditary angioedema:</u> SC injection, 30 mg SC; if the attack persists an additional 30 mg SC may be administered within a 24-hour period	Safety and efficacy have not been established in patients <16 years of age.	SC injection: 10 mg/mL (1 mL single-use vial)
Icatibant	<u>Treatment of acute attacks of hereditary angioedema:</u> Sc injection, 30 mg SC in the abdominal area; if response is inadequate or symptoms recur additional 30 mg SC injections may be administered at intervals ≥6 hours; maximum, three injections per 24 hours	Safety and efficacy have not been established in patients <18 years of age.	SC injection: 10 mg/mL (3 mL single-use, prefilled syringe)

IU=international units, IV=intravenous, SC=subcutaneous, U=units

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
<p>International Consensus Algorithm: International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema (2010)⁹</p>	<p><u>Short-term prophylaxis</u></p> <ul style="list-style-type: none"> • For minor manipulations (such as mild dental work), if plasma derived C1 inhibitor replacement therapy is immediately available, then no prophylaxis treatment is needed. If such manipulations have previously precipitated an attack in the patient, prophylaxis with plasma derived C1 replacement therapy should be considered. <ul style="list-style-type: none"> ○ If plasma derived C1 inhibitor replacement therapy is not available, then prophylaxis for five days before and two to five days post event with 17-α-alkylated anabolic androgen (danazol is the most widely used but also stanozolol and oxandrolone) or antifibrinolytic therapy (if available, tranexamic acid is preferred to epsilon aminocaproic acid) is recommended. • If considering more than mild manipulation, plasma derived C1 inhibitor replacement therapy should be considered. If plasma derived C1 inhibitor replacement therapy is not available, then short-term danazol is recommended. • Whenever possible, plasma derived C1 inhibitor replacement therapy should be immediately available. • For major manipulations or intubation, plasma derived C1 inhibitor replacement therapy administered one to six hours pre surgery is recommended. <ul style="list-style-type: none"> ○ If plasma derived C1 inhibitor replacement therapy is not available, then danazol or stanozolol are recommended. Solvent/detergent treated plasma is also an option one to six hours pre-surgery. <p><u>Long-term prophylaxis</u></p> <ul style="list-style-type: none"> • Consider prophylaxis with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy if more than one severe event per month occurs and if a treatment for acute attacks is not sufficiently effective or not available. • It should be noted that the number of events per year does not predict the severity of the next event or whether the first or next event will be an airway event. <p><u>Treatment of an acute attack</u></p> <ul style="list-style-type: none"> • It is recommended that all attacks be treated as early as possible. • Consider intubation early in progressive laryngeal edema. • First line therapies include plasma derived C1 inhibitor replacement therapy, icatibant and ecallantide.

Conclusions

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder resulting from an inherited deficiency or dysfunction of the C1 inhibitor and is characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin. Other mucosal tissues of the upper respiratory and gastrointestinal tracts may also be affected.¹ Currently, C1 esterase inhibitor (Cinryze[®]) is the only injectable HAE agent Food and Drug Administration (FDA)-approved for prophylactic therapy of HAE. C1 esterase inhibitor (Berinert[®]), ecallantide (Kalbitor[®]) and icatibant (Firazyr[®]) are all FDA-approved for the treatment of acute HAE attacks.⁴⁻⁷ Compared to placebo, prophylactic therapy with C1 esterase inhibitor (Cinryze[®]) significantly reduces the frequency of HAE attacks. Compared to placebo, acute treatment with C1 esterase inhibitor (Berinert[®]) and ecallantide significantly shortens the time to first onset of symptom relief and total resolution of symptoms.^{15,16,20,21} Acute treatment with ecallantide

demonstrates superiority over treatment with tranexamic acid in the same outcomes.²⁰ Compared to placebo, acute treatment with ecallantide significantly improves mean symptom complex severity scores and total outcome scores four hours after treatment administration. The significant improvements are maintained up to 24 hours.^{17,18} With regard to safety, no clinically significant differences between the HAE agents and placebo were observed within clinical trials.¹¹⁻²¹ Ecallantide is associated with a Black Box Warning regarding the risk of anaphylaxis.⁷

Treatment approaches include replacing C1 inhibitor (C1 inhibitor concentrate or fresh frozen plasma), increasing hepatic synthesis of C1 inhibitor (androgens), and inhibiting bradykinin formation and its receptor engagement.¹⁻³ For minor manipulations (e.g., mild dental work), if plasma derived C1 inhibitor therapy is immediately available short-term prophylaxis is not needed. If plasma derived C1 inhibitor therapy is not available, patients should receive short-term prophylaxis with, starting five days before and two to five days post event, with 17- α -alkylated anabolic androgen (danazol is the most widely used) or antifibrinolytic therapy (tranexamic acid is preferred). If patients experience more than one severe HAE event per month and if acute treatment is not sufficiently effective or available, then long-term prophylaxis with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy should be considered. Recommended treatments of an acute HAE attack include plasma derived C1 inhibitor replacement therapy, icatibant, or ecallantide.⁹

References

1. Atkinson JP. Clinical manifestations and pathogenesis of hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
2. Atkinson JP. Treatment of acute attacks in hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
3. Atkinson JP. Prevention of attacks in hereditary angioedema. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Nov 28]. Available from: <http://www.utdol.com/utd/index.do>.
4. Berinert[®] [package insert]. Kankakee (IL): CSL Behring LLC; 2012 Jul.
5. Cinryze[®] [package insert]. Exton (PA): ViroPharma Biologics Inc.; 2010 Nov.
6. Firazyr[®] [package insert]. Lexington (MA): Shire Orphan Therapies, Inc.; 2011 Aug.
7. Kalbitor[®] [package insert]. Burlington (MA): Dyax Corp.; 2012 Feb.
8. Danazol [package insert]. Sellersville (PA): Teva Pharmaceuticals; 2012 Jan.
9. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010 Jul 28;6(1):24.
10. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2012 Nov 28]. Available from: <http://www.thomsonhc.com/>.
11. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363:513-22.
12. Craig TJ, Wasserman RL, Levy RJ, Bewtra AK, Schneider L, Packer F, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol*. 2010;30:823-9.
13. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks-final results of the I.M.P.A.C.T.2 study. *Allergy*. 2011;66:1604-11.
14. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med*. 2001;161:714-8.
15. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared to placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124(4):801-8.
16. Kunschak M, Engl W, Maritsch R, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion*. 1998;38:540-9.
17. Levy RJ, Lumry WR, McNeil DL, Li HH, Champion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:523-9.
18. Cicardi M, Levy RJ, McNeil DL, Le HH, Sheffer AL, Champion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363:523-31.
19. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol*. 2007 Jun;119:1497-503.
20. Cicardi M, Banerji A, Brancho A, Rosenkranz MB, Bork RK, Lumry W, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363:532-41.
21. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Potter PC, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol*. 2011;107:529-37.