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Clinical Review

NOVEL THERAPIES FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA: A SYSTEMATIC REVIEW OF CURRENT EVIDENCE

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Abstract—Background: Angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema can occur at any point during therapy and, when severe, can require mechanical ventilation. Standard agents for anaphylactic reactions have limited efficacy for bradykinin-mediated angioedema and, therefore, agents approved for hereditary angioedema are increasingly prescribed for these patients. **Objective of the Review:** This systematic review critically evaluates evidence describing the off-label use of fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), complement 1 esterase inhibitor (C1-INH), icatibant, and ecallantide for treatment of ACEI-induced angioedema. **Discussion:** A PubMed search was conducted and articles were cross-referenced for additional citations. All full-text clinical trials, case series, and case reports published in the English language describing pharmacologic treatment of ACEI-induced angioedema were included. Thirty-seven publications detailing FFP, PCC, and regimens approved for hereditary angioedema, including icatibant, ecallantide, and C1-INH, are reviewed extensively. **Conclusions:** While findings of decreased time to symptom resolution or a cessation in symptom progression have been reported with each of these therapies, additional data showing clinically relevant implications, such as reduced intensive care unit length of stay or avoidance of mechanical ventilation, are warranted, especially when taking cost into consideration. FFP has limited evidence demonstrating a benefit for treatment of ACEI-induced angioedema without

consistent dosing strategies. However, given its wide availability and low potential for adverse reactions, FFP therapy may be reasonable. Of the novel agents traditionally used for hereditary angioedema, icatibant has the highest level of evidence and has been reported to be successful in limiting the progression of angioedema. © 2017 Elsevier Inc. All rights reserved.

Keywords—angiotensin converting enzyme inhibitor; angioedema; C1-esterase inhibitor; ecallantide; emergency medicine; icatibant; intubation

INTRODUCTION

Angioedema is characterized by sudden, self-limited swelling of the dermis, subcutaneous, and submucosal tissues (1,2). Approximately 15–25% of the general population will experience angioedema, with women affected more frequently (2,3). While different forms of angioedema exist, all exhibit nonpitting edema as a result of increased permeability of post-capillary venules (3). Most commonly, swelling is noted in the periorbital area, lips, tongue, larynx, and pharynx (1,2). However, other areas of involvement may include the extremities, gastrointestinal tract, and genitalia (1). Although rare, of most concern is airway swelling and compromise,

which can lead to complications such as intubation, tracheostomy, and mortality (4).

Angioedema can be broken down further into two main categories: histamine-mediated and bradykinin-mediated, the latter including hereditary angioedema (HAE), acquired angioedema, and angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema. Differentiation based on symptoms alone may be difficult. A thorough medical history including familial history or previous episodes of similar symptoms, current medications, exposure to any known allergens, and timing of the episode plus a physical examination can often assist in distinguishing between forms (3).

Bradykinin-mediated angioedema occurs as a result of a proteolytic cascade of events more complex than allergic or immunoglobulin E-mediated angioedema. Kinins are pharmacologically active peptides released after enzymatic activity of kallikreins on kininogens (2). The kallikrein-kinin cascade begins with activation of factor XII through binding to damaged tissue. Factor XIIa converts prekallikrein to plasma kallikrein, and through a positive-feedback loop, the proteins continue to autoactivate each other (2). The final step involves the cleavage of bradykinin from high-molecular-weight kininogen (HMWK) by plasma kallikrein. Bradykinin is then available to bind to receptors (bradykinin β_2) to cause vasodilation with subsequent vascular permeability leading to angioedema.

Hereditary Angioedema

HAE is a rare condition affecting approximately 1 in 50–100,000 individuals (5,6). The autosomal-dominant disorder results from C1 esterase inhibitor (C1-INH) deficiency. C1-INH regulates several inflammatory pathways and physiologic reactions (5,6). In healthy individuals, these include inhibition of factor XII and prekallikrein activation, plasmin breakdown of fibrin, and conversion of HMWK to bradykinin (6). Because C1-INH plays a key role in the inhibition of three enzymes within the kallikrein-kinin cascade (factor XIIa, factor XII_f, plasma kallikrein), any deficiency or dysfunction will result in uncontrolled activation and subsequent bradykinin accumulation. Edema seen with HAE commonly affects the gastrointestinal tract, and gastrointestinal symptoms are apparent in up to 93% of cases (6). Airway edema occurs in 50–60% of patients with hereditary angioedema. Symptoms generally worsen over a period of up to 36 h with resolution occurring over 48–72 h (6).

Acquired Angioedema

Acquired angioedema is more uncommon than HAE, with prevalence believed to be 1 in 100–500,000 cases

(2). This disorder, primarily affecting older adults, is associated with lymphoproliferative diseases (2,3). It also results from C1-INH deficiency, however, is not related to a genetic mutation.

Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema

ACEI-induced angioedema is the focus of the remainder of this review. While occurring in only 0.3–0.68% of patients on ACEI therapy, widespread use of ACEIs allows this otherwise small percentage to become significant (7). Angioedema, like cough, is a class effect, and possible with any single agent. Therefore, if ACE-I angioedema occurs, the offending drug should be discontinued and it should be considered a contraindication to substitute with a different agent in the same pharmaceutical class.

While the incidence is highest within the first month of therapy, angioedema can occur at any point throughout therapy; cases occurring after several years of therapy are well documented (3,8). ACEI-induced angioedema rarely manifests with urticaria and most commonly involves swelling of the lips and tongue (2). African Americans are four to five times more likely than Caucasians to experience angioedema, largely due to a genetic polymorphism in a critical enzyme necessary for ACEI metabolism (2). Other risk factors identified for ACEI-induced angioedema include age >65 years, chronic heart failure or coronary artery disease, female sex, tobacco use, or history of any drug rash (9).

In addition to the inhibition of the conversion of angiotensin I to angiotensin II, ACE (kininase II) is the enzyme responsible for bradykinin degradation. Thus, through ACE inhibition, the half-life of bradykinin is prolonged and can result in accumulation and increase in activity over time (7). Although the exact mechanism of ACEI-associated angioedema is yet to be fully elucidated, this physiologic relationship is clearly implicated.

DISCUSSION

Due to the potential for ACEI-induced angioedema to cause life-threatening airway edema and its strong similarity in symptoms of histamine-mediated angioedema, standard initial management strategies typically include airway stabilization, antihistamine therapy, glucocorticoids, and epinephrine rescue. A retrospective analysis of 228 patients characterizing ACEI-induced angioedema found that of 12 patients who required intubation and had available chart records, those given histamine-1 (H1) receptor antagonists ($n = 7$) were extubated sooner than patients without this therapy (mean 34 h vs. 62 h, respectively; $p = 0.05$) (10). It must be noted that the baseline characteristics of this small sample size were not

recorded and possible confounding variables limit the clinical application of these results. Unfortunately, a prospective trial to confirm these findings would be considered largely unethical, and clinical success with limiting angioedema progression to avoid intubation is not documented.

Knowledge surrounding the pathophysiology behind ACEI-induced angioedema in addition to clinical experience of minimal improvement after administration of standard initial management strategies has led emergency physicians to a search for other therapies to aid in clinical resolution of angioedema and avoidance of an emergent and complicated intubation or cricothyrotomy. This review focuses on several newer therapies that have been shown to be effective in HAE to determine whether they are also effective for ACEI-induced angioedema, particularly because the pathophysiologic mechanisms for both are similar.

METHODS

A study protocol was completed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and after registration in the PROSPERO (International Prospective Register of Systematic Review) database (CRD42016034035) (11). Articles were identified to address the following PICOS (patient, intervention, comparator, outcome, and study design) question: Among patients with ACEI-induced angioedema (P), does administration of novel agents for HAE such as icatibant, C1-INH, ecallantide or fresh frozen plasma (FFP) (I) compared to standard therapy (eg, histamine receptor blockers, steroids, epinephrine) or a different novel agent for HAE (C) cause symptomatic improvement or resolution of angioedema (O)?

Selection Criteria

We included randomized controlled trials, cohort studies, case-control studies, and case reports that describe the treatment of ACEI angioedema with FFP, icatibant, ecallantide, C1-INH, and prothrombin complex concentrate (PCC). Full-text literature published in the English language was included for review. Abstracts were excluded. Studies were not restricted to any specific outcomes.

Literature Search

We searched Medline from 1966 to October 2016 using the following MeSH (medical subject heading) terms together with ACE inhibitor: *angioedema*, *icatibant*, *ecallantide*, *complement 1 esterase inhibitor*, and *fresh frozen plasma*. This search was repeated in Embase with limitations of human studies only applied. A

detailed outline of the search process is included in Fig. 1. Titles, abstracts, and full-text articles were independently reviewed by two authors for inclusion using a standard data extraction form, with any disagreement reviewed by a third author. References of included articles were also reviewed to obtain additional articles. Given that case reports and case series are mainly included in this review, a formal grade of evidence was not performed.

Results and Literature Analysis

Fresh frozen plasma. As an alternative to conventional therapy, FFP has been used successfully to halt the progression of ACEI-induced angioedema. Although commonly used for hemostasis, FFP additionally contains C1-INH and kininase II (12). FFP has effectively treated acute HAE and is used as a preventive measure against acute HAE attacks before surgical procedures (6).

Nine publications were found detailing 16 cases of ACEI-induced angioedema where FFP was utilized (Table 1) (12–20). Thirteen patients experienced either symptom resolution or cessation of progression within 4 h of FFP (12–16,19). One patient did not have symptom improvement within 4 h, and subsequently received C1-INH (17). Another patient received FFP approximately 58 h after symptom onset, but had a cardiac arrest before completion (20).

Although the majority of cases with reported success with FFP utilize 1–4 U, patient weights were often not reported (21). Therefore, the optimal dosing strategy is yet to be determined and a specific dosing recommendation cannot be made based on the available literature. The rate of administration of FFP is also not discussed in the literature, therefore, clinical judgment should be used. Common concerns about FFP include its volume for administration (200–300 mL/units) and potential for viral transmission (12). However, the possibility of causing edema is low if only several units are administered and rigorous blood screening processes render a minimal risk for viral transmission (22). ACEI use can unmask HAE, and although there is a theoretical concern that FFP can worsen HAE, there are no reports to date describing such outcomes (12,23,24). As with any clinical situation, these concerns must be weighed against the potential to avoid airway compromise.

Unfortunately, there are no clinical trials evaluating FFP for ACEI-induced angioedema and these benefits of therapy are only seen in reported cases, thus increasing the risk of publication bias in the literature. In two of the cases where FFP was not successful, administration was > 48 h after presentation (18,20). Thus, early administration of FFP may be required for success, but this needs to be studied further. In the successful cases

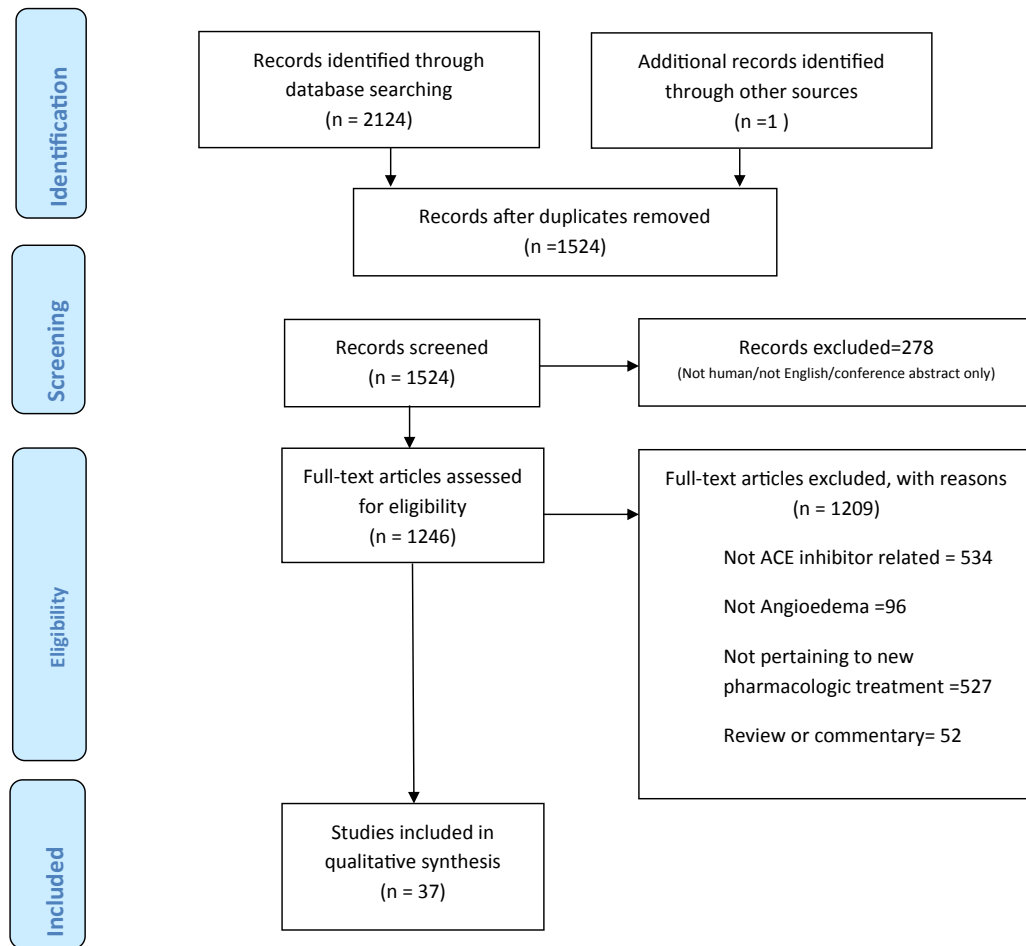


Fig. 1. PRISMA literature search and inclusion strategy. ACE = angiotensin-converting enzyme.

described, there is a temporal relationship with partial or full resolution of symptoms within 2–4 h of FFP administration. Clinicians can consider FFP for treatment of ACEI angioedema if used early after symptom onset; however, its use may rely on rapid availability and administration.

Prothrombin complex concentrate. PCC was effective in treating ACEI-angioedema in one case report (25). A 67-year-old man presented with his third episode of laryngeal edema and dyspnea. In addition to ACEI use, he was prescribed a vitamin K antagonist and sitagliptin, a dipeptidylpeptidase inhibitor also implicated in angioedema. There was no symptom improvement with inhaled epinephrine, methylprednisolone, and chlorpheniramine, thus, four-factor PCC (Kanokad[®]) was administered for vitamin K antagonist reversal in anticipation of a difficult airway. After administration of 1500 units, symptoms began improving within 20 min and resolved within 8 h. Complement levels before PCC administration were within normal limits. This four-factor PCC contains

C1-INH and, according to the authors, the patient ultimately received a 50-mg dose (a previously reported conversion is approximately 8 units/mg protein) (26). KCENTRA[®] (four-factor PCC; CSL Behring) contains 0.02 IU/mL C1-INH (personal communication, CSL Behring, August 26, 2016). This is the only published case where PCC has been used for ACEI-induced angioedema, therefore, its routine use cannot be recommended at this time.

Complement-1 esterase inhibitor. C1-INH (Berinert[®] and Ruconest[®]) is approved for acute HAE, administered as 20 IU/kg i.v. An alternative formulation (Cinryze[®]) is marketed for prevention of HAE attacks, however, it is not approved for acute resolution. Two formulations, Berinert[®] and Cinryze[®], are produced from pooled human plasma, whereas Ruconest[®] is produced through recombinant technology. These products supplement C1 esterase to inhibit plasma kallikrein and factor XIIa to ultimately reduce serum bradykinin (26). The data for its utilization in HAE stem from the IMPACT (International

Table 1. Cases of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Fresh Frozen Plasma Was Utilized

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Fresh Frozen Plasma	Resolution
Hassen, 2013 (12)	49-year-old female with right lower lip swelling, itching, and diarrhea. Started metformin the day before	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart after swelling progression	2 U 7 h after second set of conventional therapy	No further progression of symptoms
	64-year-old male with upper and lower lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 4 h apart after swelling progression	3 U 7 h after second set of conventional therapy	Progression stopped within 4 h
	58-year-old male with upper and lower lip swelling and shortness of breath	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart	2 U 2.5 h after second set of conventional therapy	Progression stopped within 3 h
	62-year-old male with facial and lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2.5 h apart	2 U 5 h after second set of conventional therapy	Progression stopped within 2 h
	51-year-old female with lip swelling, also ate crab and lobster the previous night for the first time	Not obtained	Methylprednisolone, diphenhydramine, and famotidine	2 U 3 h after conventional therapy	Progression stopped, time unknown
	73-year-old male with face and tongue swelling	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 3 h apart	2 U at 2 h after second set of conventional therapy	Progression stopped within 2 h
Karim, 2002 (13)	75-year-old male with tongue swelling	Complement levels WNL	i.v. chlorpheniramine, hydrocortisone and i.m. epinephrine, 2 nd round after intubation	4 U 24 h after intubation	Symptom improvement within 2 h
	45-year-old male with lip swelling	Complement levels WNL	i.m. epinephrine, methylprednisolone, diphenhydramine and famotidine	1 U 3 h after initial therapy	Symptom improvement and progression cessation within 2 h

(Continued)

Table 1. Continued

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Fresh Frozen Plasma	Resolution
Warrier, 2004 (14)	43-year-old female with lip swelling and tongue edema	Complement levels WNL	4 days of antihistamines, corticosteroids, epinephrine, cyclosporine and i.v. immunoglobulin	2 U at hospital day 4	Full resolution after 2–4 h
Bolton, 2012 (15)	76-year-old male with tongue and sublingual edema progressing to oropharynx. He was intubated earlier that day for an outpatient procedure	Not obtained	Antihistamines and corticosteroids	2 U at time not discussed	Full resolution after 2 h
Stewart, 2012 (16)	52-year-old male with tongue swelling	Not obtained	Hydrocortisone	2 U 3 h after conventional therapy failed	Full resolution during infusion of 2 nd unit
	79-year-old male with tongue swelling	Not obtained	No other therapy given	2 U 3 h after arrival	Full resolution after 4 h
Lipski, 2015 (17)	77-year-old female with edema of tongue, lips, mouth, and neck	C3 complement slightly increased and others WNL	s.c. methylprednisolone and epinephrine	Not specified	No improvement after 4 h
Tharayil, 2014 (18)	60-year-old male with edema from base of the tongue up to the cricoid cartilage and snugly fitting endotracheal tube with no peritubal air	Complement levels WNL	i.v. hydrocortisone and antihistamines	2 U at > 48 h after intubation	Patient got tracheostomy due to persistent airway edema on day 11
Shiber, 2014 (19)	67-year-old female with edema of the tongue	Not reported	i.v. diphenhydramine and methylprednisolone Nebulized racemic epinephrine	4 U after nasal intubation	Symptoms improved over the next 6 h and was extubated the next morning
Atalay, 2015 (20)	77-year-old female with dysphagia, bilateral orbital edema, edema of the tongue, laryngeal face of the epiglottis, left aryepiglottic fold and left arytenoid	Not reported	i.v. methylprednisone, diphenhydramine, subcutaneous epinephrine, and inhaled epinephrine	1 U approximately 58 h after symptom onset	Tracheotomy and cardiac arrest before completion of FFP infusion

FFP = fresh frozen plasma; i.m. = intramuscular; s.c. = subcutaneous; WNL = within normal limits; i.v. = intravenous; U = units.

Multi-centre Prospective Angioedema C1-Inhibitor Trial) 1 and 2 trials (27). A post-hoc analysis of 83 patients from these studies found that administering 20 IU/kg C1-INH within 6 h of HAE onset was associated with a faster onset of symptom relief (hazard ratio [HR] = 3.36; 95% confidence interval [CI] 1.69–6.68) and complete resolution compared to placebo (HR = 4.30; 95% CI 2.09–8.82) (27). The time to complete resolution of symptoms in patients receiving 20 IU/kg C1 INH within 6 h of onset was 2.78 h (range 0.83–52.00 h) compared to 8.04 h (range 0.33–76.98 h) with placebo in the IMPACT1 trial.

Eight publications, including one multicenter prospective observational study, one prospective case series with a historical control, and six case reports, were found detailing 27 reports of ACEI-induced angioedema treated with C1-INH (Table 2) (17,28–34). Time from administration to first improvement in symptoms occurred within a median of 0.5 h in one prospective observational study, the first hour in four case reports, a mean of 88 min in one case series, and 5 h in one case report (28–33). Complete resolution of symptoms was noted within 1 h in 1 case report, 2 h in 1 case report, and a mean of 10.1 h in 1 case series (17,29,31). One case reported the requirement of icatibant to avoid tracheostomy after worsening of angioedema despite administration of a C1-INH, although neither dose nor time to treatment failure was reported (34).

Greve et al. completed a prospective case series including 10 patients with angioedema of the tongue (n = 5), larynx (n = 3), lips/face (n = 1), and right cheek (n = 1) who were treated with a fixed dose of 1000 units i.v. C1-INH (29). This group was compared to a historical control group (n = 47) treated with methylprednisolone and clemastine. Administration of corticosteroids, antihistamines, or epinephrine in the C1-INH group was not reported. The mean time to first improvement was 88 ± 39 min, but was not assessed in historical controls. Mean time to complete symptom resolution was shorter with C1-INH compared to historical controls (10.1 ± 3 h vs. 33.1 ± 19 h, respectively). No patients treated with C1-INH were intubated or had a tracheostomy compared to 2 and 3 patients, respectively, in the control. This difference between the groups, however, may be limited due to the small number of patients evaluated and sample size difference between groups.

Javaud et al. performed a multicenter prospective observational study evaluating ACEI-induced angioedema involving the upper lip (55%), tongue (44%), cheeks (42%), lower lip (40%), larynx (24%), or uvula (5%) and were treated with 20 U/kg C1-INH (n = 11) or icatibant 30 mg subcutaneous (s.c.) (n = 30) or neither (n = 21) (28). Patients arrived a median of 5.8 h after

the initiation of swelling and received antihistamines (70%), corticosteroids (56%), and epinephrine (8%). Baseline characteristics were not described. Treatment with C1-INH or icatibant was associated with a quicker median time to onset of symptom relief compared to no treatment (0.5 h vs. 3.9 h, respectively; $p < 0.0001$). No significant differences in onset of symptom relief were observed between icatibant and C1-INH administration groups, although time from arrival to treatment was faster with icatibant compared to C1-INH (median 1 h vs. 2 h, respectively; $p = 0.02$). There was also no difference observed between admitted and discharged patients with regard to those who received C1-INH compared to either group. In addition to the sample size limitation, a greater benefit of reduced hospitalizations with C1-INH administration may not have been seen due to the non-randomized design. Therefore, it is possible that treatment bias occurred, where patients who were treated were more severe and more likely to be hospitalized.

Reported doses of C1-INH vary and include weight-based doses ranging from 11 U/kg to 20 U/kg, as well as fixed doses ranging from 1000 U to 2000 U (17,28–33). Although studied in a small population, C1-INH has been associated with decreased time to symptom resolution and onset of symptom relief compared to conventional therapy, and may decrease the duration of mechanical ventilation when given early (28,29,33). C1-INH does not seem to be beneficial in all patients, however, and prevention of intubation may be limited by the time it takes to prepare and deliver the medication to the patient (28,33,34). Adverse effects were more common with C1-INH than placebo, however, these were mild in severity and did not result in death or drug discontinuation (29,35). Strong evidence for efficacy of C1-INH in ACEI-induced angioedema is lacking, but hopefully will be provided by a randomized, double-blind, multicenter phase 3 trial, which is currently recruiting patients, comparing Berinert® to placebo use in conjunction with a corticosteroid plus antihistamine in ACEI-induced angioedema (ClinicalTrials.gov number: NCT01843530).

Ecallantide. Ecallantide (Kalbitor®) is a kallikrein inhibitor approved for the treatment of HAE as a 30-mg s.c. injection that can be repeated once in 24 h. It lowers bradykinin serum concentration by selectively inhibiting plasma kallikrein. The largest trial describing use of ecallantide for HAE comes from the EDEMA4 (Efficacy Study of DX-88 [Ecallantide] to Treat Acute Attacks of Hereditary Angioedema) study: a phase 3, randomized, double-blind study consisting of 89 patients (36). The investigators uncovered a greater decrease in mean symptom complex severity from baseline to 4 h

Table 2. Cases of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Complement-1 Esterase Inhibitor Was Utilized

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of C1 Esterase Inhibitor	Resolution
Lipski, 2015 (17)	77-year-old female with edema of tongue, lips, mouth, and neck	C3 complement slightly increased and others WNL	s.c. methylprednisolone and epinephrine FFP (no dose specified)	i.v. 2000 U (20 U/kg) after no improvement 4 h after FFP given	Swelling resolved within 1 h
Nielsen, 2016 (30)	61-year-old female with edema of the tongue and arytenoids	C1-INH value WNL	i.v. hydrocortisone and dexchlorpheniramine s.c. epinephrine	i.v. 1500 U over 8 h after hospital arrival and initial treatment	Over 20 min stridor subsided, patient calmed and was able to talk
Rasmussen, 2013 (31)	63-year-old male with edema of tongue, uvula, floor of mouth, and soft palate	Not reported	Epinephrine, antihistamine, and corticosteroid	i.v. 1000 U (11 U/kg), within 20 min of arrival	Significant regression within 20 min and resolution after 2 h
Hermanrud, 2016 (32)	56-year-old male with edema of tongue, uvula, right palate-pharyngeal arch, right side of the lingual tonsil and hypopharynx, piriform sinus, right aryepiglottic fold, and right ventricular fold	Not performed in acute phase	i.v. methylprednisolone	i.v. 2000 U (18 U/kg), on arrival (did not wait for methylprednisolone to have an effect)	Patient reported rapid decrease in symptoms. Severity of swelling decreased upon fiber-optic reassessment 5 h after
Urnoski, 2015 (33)	41-year-old male with edema of the lip, tongue, and airway swelling	Not reported	i.v. diphenhydramine, methylprednisolone, and ranitidine	i.v. 1500 U (17 U/kg) after intubation and 1.5 h after arrival	Swelling decreased within 1 h and extubation occurred within 16.5 h of presentation
Schmidt, 2010 (34)	42-year-old white male with edema of neck, tongue and larynx	C4 level WNL	i.v. methylprednisolone, diphenhydramine Nebulized epinephrine	Dose not specified, time not discussed	Did not resolve symptoms, patient required icatibant injection rescue therapy

C1-INH = complement 1 esterase inhibitor; FFP = fresh frozen plasma; s.c. = subcutaneous; WNL = within normal limits; i.v. = intravenous.

after treatment with ecallantide than with placebo (-0.8 ± 0.6 vs. -0.4 ± 0.8 , respectively; $p = 0.01$).

Literature was reviewed and two randomized controlled trials were included evaluating 84 patients treated with ecallantide (37,38). The first publication, a double-blind, phase 2 study randomized patients presenting within 12 h of symptom onset to receive placebo ($n = 18$) or ecallantide at doses of 10 mg ($n = 20$), 30 mg ($n = 19$), and 60 mg ($n = 19$) (37). Patients were excluded if imminent intubation or tracheostomy was required. The majority of patients were also treated with corticosteroids (86%), H1 blockers (86%), H2 blockers (67%), and adrenergic agonists (18%). Patients included had mostly mild (45%) or moderate (42%) and Ishoo stage I (lip or facial edema and rash; 45%) or Ishoo stage III (tongue edema; 41%) angioedema. The primary outcome was meeting six predetermined discharge criteria ≤ 6 h after ecallantide administration. The study was prematurely discontinued after an interim analysis did not demonstrate a difference in the primary outcome between the combined ecallantide arms vs. placebo (88% and 72% respectively; $p > 0.05$). There were no differences in adverse events between ecallantide and placebo. A larger percentage of patients who received 30 mg and 60 mg doses compared to placebo and ecallantide 10-mg doses experienced a treatment-emergent adverse reaction (respectively, 42% and 37% vs. 22% and 25%), although statistics were not reported.

The second publication was a multicenter, triple-blind, phase 2 randomized controlled trial comparing three s.c. injections of 10 mg ecallantide ($n = 26$; total 30 mg) to placebo ($n = 24$) in patients presenting within 12 h of symptom onset who did not improve or worsened after antihistamines and corticosteroids (38). If during observation the patient was at risk of severe upper-airway compromise or had worsening symptoms 2 h after blinded treatment, an open-label ecallantide 30-mg dose could be given. A second open-label 30-mg ecallantide dose could be repeated after an additional 2 h. The primary outcome was meeting discharge criteria within 4 h of treatment. Those who required open-label ecallantide were deemed treatment failures. Patients had mostly moderate (62.5% in placebo and 69.2% in ecallantide) and severe (20.8% in placebo and 19.2% in ecallantide) angioedema at baseline and an Ishoo grading of I (indicating face and lip swelling, 62.5% in placebo and 50% in ecallantide) or III (tongue swelling, 20.8% in placebo and 34.6% in ecallantide). There was no difference in the primary outcome (31% ecallantide vs. 21% placebo; 95% CI -14% to 34%). Open-label ecallantide was administered more often in the placebo group vs. the ecallantide group (54% vs. 42%, respectively; no statistics reported). A second open-label dose was required in 2

patients in the placebo group and no patients in the ecallantide group. Ecallantide was well tolerated compared to placebo, with no adverse events or serious adverse events occurring related to the drug.

Overall, the data are insufficient to make a conclusion on the efficacy of ecallantide in ACEI-induced angioedema. Two phase 2 trials have found non-statistically significant increases in discharges from the emergency department (ED) in 4 h and 6 h with ecallantide vs. placebo, respectively (37,38). Our literature search did not reveal any published case reports or case series. Statistically significant differences may not have been seen due to the small patient populations included in these studies thus far. In addition, these studies had a limited number of patients with severe angioedema, who would be in the position to benefit most from this additional treatment (37,38). It is also still unknown whether administration of ecallantide changes clinically relevant outcomes, such as the rates of intubation, tracheostomy, or mortality. Ecallantide is considered to be relatively safe with mild adverse events, such as injection site pain, headache, nausea, and pruritus (37,38). There are reports of anaphylaxis ($<1\%$) with administration, thus it is necessary to administer a test dose under observation by a health care professional (39).

Icatibant. Icatibant (Firazyr[®]) is a novel bradykinin receptor antagonist that stops bradykinin from binding to β_2 receptors, preventing its activation that leads to angioedema. It is administered as a 30-mg s.c. injection that may be repeated once in 6 h if HAE symptoms persist. Icatibant received its approval for HAE attacks from the FAST (For Angioedema Subcutaneous Treatment) 1 ($n = 56$) and FAST 2 trials ($n = 74$), which compared icatibant to placebo and tranexamic acid, respectively (40). In the FAST 1 trial, there was no difference in median time to clinical resolution (2.5 h with icatibant vs. 4.6 h with placebo; $p = 0.14$). In the FAST 2 trial, icatibant produced a shorter time to resolution of symptoms (2.0 h vs. 14.0 h with tranexamic acid; $p < 0.001$). Both trials had a shorter time to first symptom improvement with icatibant as assessed by the investigator and patient.

Seventeen publications were identified evaluating 95 patients and 99 episodes of ACEI-induced angioedema treated with s.c. icatibant (Table 3). This was composed of 10 case reports, 5 case series reporting 42 cases, 1 randomized controlled trial reporting 13 cases, and 1 prospective observational study reporting 30 cases (28,34,41,49–55). Most patients received 30 mg s.c. icatibant, with no report of a dose provided for 3 patients (46,49,52). One patient received 60 mg total, and 1 patient received 90 mg total (43,54). Time from drug administration to first improvement ranged from

Table 3. Case Reports and Case Series of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Icatibant Was Utilized

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Icatibant	Resolution
Schmidt, 2010 (34)	42-year-old male with edema of neck, tongue, and larynx	C4 levels WNL	i.v. methylprednisolone and diphenhydramine Nebulized epinephrine C1 esterase inhibitor (dose not specified)	s.c. 30 mg, time not discussed	Symptoms began to improve in 10–15 min
Bartal, 2015 (41)	76-year-old female with edema of tongue, lips, and face	Not reported	s.c. epinephrine ×2, i.v. methylprednisolone, ranitidine, and promethazine	s.c. 30 mg, time after initial therapy not discussed	Dyspnea relieved in min, swelling almost resolved in 30 min
Charmillon, 2014 (42)	65-year-old female with edema of the face, tongue, and macroglossia	Not reported	No other pharmacologic agents reported	s.c. 30 mg, after emergent tracheostomy, time not discussed	Almost total regression of angioedema in 1 h Decanulated 3 days later
Crooks, 2014 (43)	75-year-old female with edema of the tongue and lips	Not reported	i.v. hydrocortisone, dexamethasone, and chlorphenamine i.m. epinephrine	s.c. 30 mg, after intubation on ICU day 4, then two more doses 8 h apart	Significant decrease in tongue swelling within 30 min Resolution within the first few hours of icatibant Extubation 36 h after first icatibant dose (delayed due to development of ventilator-associated pneumonia) Mild erythema around the injection site 10 h after swelling had resolved almost completely and the patient was discharged
Gallitelli, 2012 (44)	76-year-old male with edema of left side of his face	C4 levels WNL	None	s.c. 30 mg, time not discussed	No immediate benefit with progressive upper airway edema, drooling, and inability to speak Patient intubated Slow resolution was seen over 48 h was extubated Symptoms resolved in h
Illing, 2012 (45)	62-year-old male with edema of the tongue and epiglottis	C1 esterase levels WNL	Hydrocortisone and chlorphenamine Nebulized epinephrine	s.c. 30 mg, time not discussed	
Mahajan, 2015 (46)	40-year-old female with edema of soft palate	Not reported	No other pharmacologic agents reported	Dose not specified Patient intubated, time not discussed	
Manders, 2012 (47)	45-year-old female with edema of tongue	Not reported	i.m. epinephrine and clemastine i.v. Di-Adreson-F (corticosteroid)	s.c. 30 mg, after progressive swelling for several hours	Symptoms started to resolve within min.

Pucar, 2015 (48)	65-year-old female with edema of the tongue, epiglottis and left arytenoid	C4 and C1 esterase inhibitor WNL	Epinephrine, i.v. dexamethasone and glycopyrrolate i.m. promethazine	s.c. 30 mg, 5 h after progression of symptoms	Improvement after 10 min, complete resolution within 5 h No development of injection site reactions
Kaeslin, 2012 (49)	56-year-old with edema of the tongue, face, cords and larynx	C1 esterase inhibitor and C4 WNL	No other pharmacologic agents reported	Dose not specified, time not discussed	Significant decrease in symptoms by 2 h
Bas, 2010 (50)	91-year-old male with edema of larynx/pharynx	All cases had no C1 esterase inhibitor deficiency. Other complement levels not reported.	None	s.c. 30 mg, on arrival	Mean time after icatibant to first symptom improvement and complete relief: 50.6 min (SD 21 min) and 4.4 h (SD 0.8 h; range 3–5.5 h) No required intubation or tracheostomy All developed local site reactions that spontaneously resolved in ~2 h
	61-year-old male with edema of the tongue		None	s.c. 30 mg, on arrival	
	67-year-old female with edema of the tongue		None	s.c. 30 mg, on arrival	
	72-year-old male with edema of larynx/pharynx		None	s.c. 30 mg, on arrival	
	81-year-old male with edema of the tongue		None	s.c. 30 mg, on arrival	
	58-year-old male with edema of larynx/pharynx		None	s.c. 30 mg, on arrival	
	82-year-old female with edema of the tongue		None	s.c. 30 mg, on arrival	
Bova, 2015 (51)	84-year-old female with edema of larynx/pharynx and tongue		None	s.c. 30 mg, on arrival	
	82-year-old male with edema of neck, sublingual and pharyngeal mucosa	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 5 h after symptom onset	25 min to symptom relief and 8 h to complete resolution
	63-year-old male with edema of face, lips, tongue, and oropharynx	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 4 h after symptom onset	30 min to symptom relief and 4 h to complete resolution
	52-year-old male with edema of tongue	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 3 h after symptom onset	35 min to symptom relief and 4 h to complete resolution
	69-year-old male with edema of lips, tongue, uvula and possibly supralaryngeal	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 7 h after symptom onset	45 min to symptom relief and 2 h to complete resolution
	80-year-old male with edema of lips and tongue	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 3 h after symptom onset	30 min to symptom relief and 2 h to complete resolution
	85-year-old male with edema of left side of face and lips	WNL	Corticosteroid	s.c. 30 mg, 3 h after symptom onset	25 min to symptom relief and 4 h to complete resolution
	69-year-old male with edema of tongue	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 3 h after symptom onset	15 min to symptom relief and 9 h to complete resolution
	81-year-old male with edema of the tongue	WNL	Corticosteroid	s.c. 30 mg, 2 h after symptom onset	30 min to symptom relief and 10 h to complete resolution

(Continued)

Table 3. Continued

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Icatibant	Resolution
Jacob, 2015 (52)	75-year-old female with edema of lips, tongue and epiglottis	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 8 h after symptom onset	50 min to symptom relief and 5 h to complete resolution
	86-year-old female with edema of face and tongue	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 6 h after symptom onset	30 min to symptom relief and 5 h to complete resolution
	67-year-old female with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 5 h to complete resolution
	71-year-old male with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 6 h to complete resolution
	74-year-old male with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 6 h to complete resolution
	4 male and 2 female with 10 episodes	Not reported	Epinephrine corticosteroids and antihistamines in all cases	NA, time not discussed	Resolution of symptoms within 12 h for all cases
	Mean age 69 years 4 tongue and lips, 3 tongue, lips, and face, 3 tongue only				No serious adverse effects
Volans, 2013 (53)	Male in 70s with edema of submental area, tongue, lower lip, neck, and supraglottis area	Not measured	i.v. chlorpheniramine and steroids	s.c. 30 mg, 10 h after symptom onset	Symptoms began to resolve at 20 min and symptom-free by 4 h
	86-year-old female with edema of the tongue and supraglottis area	Not measured	i.v. chlorpheniramine, tranexamic acid Nebulized epinephrine	s.c. 30 mg, 10 h after symptom onset	Intubation avoided Symptoms began to resolve at 20 min and symptom-free by 4 h.
Fok, 2015 (54)	75-year-old female with edema of lip, tongue, aryepiglottic folds with mucosa prolapsing onto airway, and piriform fossa	C4 WNL	11 received epinephrine and corticosteroid. 2 patients received no other therapy	s.c. 30 mg, 70 h after intubation and 73 h after symptom onset	First symptom resolution after 7 h
	49-year-old male with edema of the face and soft palate	C4 WNL		s.c. 30 mg, at same time as intubation and 26 h after symptom onset	First symptom resolution after 3 h
	40-year-old female with edema of base of tongue and postnasal space	C4 WNL		s.c. 30 mg, 1 h after intubation and 8 h after symptom onset	First symptom resolution after 3 h
	62-year-old female with edema of submental and tongue	C4 WNL		s.c. 30 mg, at same time as intubation and 16 h after symptom onset	First symptom resolution after 2 h
	70-year-old female with edema of tongue	C4 WNL		s.c. 30 mg, 8 h after symptom onset	First symptom resolution after 0.5 h

76-year-old male with edema of tongue and face	C4 WNL	s.c. 30 mg, 15 h after symptom onset	First symptom resolution after icatibant: 2 h
87-year-old male with edema of tongue, submandibular, and lip	C4 WNL	s.c. 30 mg, 4 h after symptom onset	First symptom resolution after icatibant: 1 h
38-year-old female with edema of tongue	C4 WNL	s.c. 30 mg, 9 h after symptom onset	First symptom resolution after icatibant: 0.5 h
59-year-old female with edema of submandibular, tongue, and floor of mouth	C4 WNL	s.c. 30 mg, 5.5 h after symptom onset	First symptom resolution after icatibant: 3.5 h
68-year-old male with edema of tongue, soft palate, uvula, epiglottis, and false cords	C4 WNL	s.c. 30 mg, 11 h after symptom onset; received second icatibant dose 2 h after first dose due to continued edema and symptoms consisting of loud inspiratory stridor and moist cough	First symptom resolution after second dose of icatibant: 2 h
81-year-old male with edema of lip and tongue	C4 WNL	s.c. 30 mg, 10 h after symptom onset	First symptom resolution after icatibant: 0.25 h
81-year-old female with edema of tongue, floor of mouth, and neck	C4 WNL	s.c. 30 mg, 83 h after symptom onset	First symptom resolution after icatibant: 3 h
80-year-old male with edema of tongue	C4 WNL	s.c. 30 mg, 4.5 h after symptom onset	First symptom resolution after icatibant: 4 h

ICU = intensive care unit; s.c. = subcutaneous; SD = standard deviation; WNL = within normal limits; i.m. = intramuscular; i.v. = intravenous.

minutes to 7 h; of those that reported individual patients who responded to the first dose of icatibant and time to symptom improvement was provided, 50% ($n = 17$) improved within 30 min, 15% ($n = 5$) improved between 31 min and 1 h, 18% ($n = 6$) improved between 1.5 and 2 h, and 18% ($n = 6$) improved after 2 h (28,34,41–43,47–51,53,54). Time to almost complete symptom resolution or total symptom resolution ranged from 30 min to > 16 h, with 40% ($n = 18$) of cases having resolution in ≤ 4 h (41–44,46,48,50–53,55). One must use caution in interpreting this information, however, because these studies and cases assessed patients at different time intervals, some retrospectively, and with different criteria for what was considered an improvement or complete resolution. Intubation was not required in several high-acuity angioedema cases after use of icatibant in a single case in one study and 4 cases in others (34,41,48,53). Worsening of angioedema was reported in 1 patient, despite administration of icatibant, who subsequently required intubation for 48 h (45).

A case series by Bas et al. prospectively evaluated 8 adult patients who received icatibant 30 mg s.c. for ACEI-induced angioedema and compared them to 47 historical controls who received methylprednisolone and clemastine (50). The severity of illness was not assessed directly. The mean time to first symptom improvement with icatibant was 50.6 min (standard deviation [SD] 21 min); mean time to complete symptom relief was 4.4 h (SD 0.8 h) compared to 33 h (SD 19.4 h) in historical controls. Time to first symptom improvement with the historical control was not available. No additional interventions were required in icatibant-treated cases, whereas in the historical control, additional interventions included tracheotomy ($n = 3$), intubation ($n = 2$), and additional i.v. steroids ($n = 12$). The small sample size in the icatibant group compared to the historical controls limits this assessment and may lead to a type II error. Furthermore, the lack of treatment in half of the historical controls may have confounded the results observed. Transient local injection-site reactions, including erythema and itching, occurred in all 8 icatibant-treated patients, which all resolved within 2 h.

Another case series by Bova et al. evaluated 13 patients with ACEI-induced angioedema who received icatibant 30 mg s.c. after not responding to standard therapy including corticosteroids ($n = 13$), antihistamines ($n = 10$), and epinephrine ($n = 7$) (51). Ten patients cumulatively experienced 27 previous angioedema episodes and served as an historical control. Half of the historical attacks were treated with corticosteroids, only one with antihistamines, and the remainder were not treated. The median time from symptom onset to relief of symptoms and complete resolution was shorter with icatibant

compared to the historical controls (3 h $\pm$ 30 min vs. 11 h, respectively; $p = 0.0088$ and 3 h $\pm$ 5 h vs. 54 h, respectively; $p = 0.002$). No patients who experienced angioedema of the upper airways required intubation, tracheotomy, repeat dosing of icatibant, or additional drugs, and all patients were discharged within 24 h. No adverse events were reported except for 1 patient who developed mild, transient pain at the injection site.

As detailed earlier, Javaud et al. performed a multicenter prospective observational study comparing C1-INH ($n = 11$), icatibant 30 mg s.c. ($n = 30$), or neither ($n = 21$) (28). Specific treatment with icatibant or C1-INH was associated with a quicker median time to onset of symptom relief compared to the untreated group (0.5 h vs. 3.9 h, respectively; $p < 0.0001$) and no difference was seen between icatibant or C1-INH treatment. Icatibant did not have a significant effect on whether patients were admitted or discharged.

Most recently, a multicenter, double-blind, double-dummy, randomized phase 2 study comparing icatibant to placebo was conducted, providing the majority of evidence for its use in ACEI-induced angioedema (55). This trial included 27 patients with edema of the face (23% in icatibant and 21% in placebo), floor of mouth (46% and 64%, respectively), lips (23% and 29%, respectively), cheeks (23% and 14%, respectively), tongue (62% and 71%, respectively), soft palate and pharynx (31% and 36%, respectively), and larynx (46% and 50%, respectively), who were randomized to receive 30 mg of s.c. icatibant ($n = 13$) or standard of care ($n = 14$) consisting of prednisolone and clemastine within 10 h of symptom onset. Patients could receive an additional 30 mg of icatibant and prednisolone if there was no symptom reduction by 6 h post-treatment. The majority of patients were male (69% in icatibant and 57% in placebo groups), with a mean age of 62.4 ± 9.7 and 69.4 ± 16.6 years, respectively, had a median time from symptom onset to treatment of 6.1 h (range 3–10 h) and 5.1 h (range 2–9.3 h), respectively, and were classified by the investigator to have mild angioedema (mean score 1.1 ± 0.2 in both groups; score of zero represents no angioedema and 4 represents severe angioedema, and was calculated as the average of four symptom scores). A shorter median time to complete edema resolution was observed with icatibant compared to placebo as evaluated by both the patient and investigator (8 vs. 27.1 h, respectively; $p = 0.002$). Also, a shorter time to onset of symptom relief was observed according to investigator-assessed symptom scores (2.0 h vs. 11.7 h, respectively; $p = 0.03$). There was no difference in the onset to patient reported symptom relief (2.0 h vs. 7.9 h, respectively; $p = 0.36$), however, a greater percentage of icatibant group patients had complete resolution of edema at 4 h post-treatment (38% vs. 0%, respectively). Finally, 3 patients required

rescue therapy and 1 patient required tracheotomy in the standard therapy group, whereas no patients in the icatibant group required either intervention. Injection site reactions including redness (80% vs. 27%, respectively), swelling (53% vs. 20%, respectively), pain (47% vs. 13%, respectively), itching (27% vs. 7%, respectively), and sensation of warmth (27% vs. 0%, respectively) were common with icatibant vs. placebo. These reactions were transient and resolved within 4 h.

In studies, including one randomized controlled trial, icatibant decreased time to symptom resolution and onset of symptom relief compared to standard therapy in ACEI-induced angioedema (28,50,51,55). However, the randomized controlled trial is limited due to the majority of patients having mild angioedema. It has also been observed to be associated with limiting angioedema progression and avoidance of intubation and tracheostomy per author opinions in case reports, although certainly difficult to objectively prove (34,41,48,53). However, 1 patient was reported to have clinical worsening of symptoms despite icatibant administration necessitating intubation, thus further research needs to be done to elucidate who would benefit from this treatment (45). Injection-site reactions seem common with icatibant, although these have been reported to be minor, resolve quickly, and have not resulted in death or discontinuation of drug (40,50,54,55).

CONCLUSIONS

Treatment of ACEI-induced angioedema has historically been similar to that of histamine-mediated angioedema, with β -2 agonists, epinephrine, steroids, and histamine antagonists given in the majority of patients. As stated previously, cases of ACEI-induced angioedema can be refractory to this standard treatment regimen, as it does not inhibit pathophysiologic mechanisms responsible for symptoms. Because both HAE and ACEI-induced angioedema involve accumulation of bradykinin, treatments for HAE are being explored for their efficacy in ACEI-induced angioedema, with varying reports of success. A recent consensus statement delivered on behalf of the French Reference Centre for Angioedema (CREAK) provides recommendations for the diagnostic and therapeutic strategy for angioedema of the upper airways in adult ED patients (56). For bradykinin-mediated angioedema, it is recommended that all attacks above the shoulder be treated (strong agreement). The agents of choice per the CREAK group include treatment of all upper angioedema with antihistamines and epinephrine in the absence of a precise diagnosis, and icatibant 30 mg or plasma-derived C1-INH concentrates utilizing weight-based dosing of 20 U/kg; ecallantide is not available in Europe and recombinant C1-INH is not adapted to

emergency use. They further recommend that effectiveness of treatment should be judged in the hour after administration. Should therapy be ineffective, or the attack progresses after elimination of another etiology or complication, the CREAK group recommends via expert opinion to switch drugs rather than readminister the same one.

The purpose of this systematic review is to further evaluate published literature concerning the treatment of ACEI-induced angioedema with these novel agents. Despite recent consensus statements, a limitation of this review is that the overall quality of available evidence is low, consisting of mostly case reports and case series; conference abstracts and non-English literature were not included. Furthermore, of the available literature included, there is wide heterogeneity on the severity of patients included, outcomes assessed and reported clinical end points. Many of these studies and case reports use outcomes, such as time to discharge and time to onset of symptom relief, to evaluate drug efficacy (28,37,38,50,51). More pertinent clinical end points such as peak severity of symptoms, need for intubation or tracheostomy, duration of mechanical ventilation, or requirement for hospital admission have not been evaluated. The clinical end points mentioned would be of most interest and value to an emergency physician when evaluating these different treatment options. One of the major challenges that arises when assessing treatment options for ACEI-induced angioedema is the large variety in assessment scales used during each case and trial. Investigator-based Likert scales, Ishoo staging, visual analogue scale, and mean symptom complex severity, have each been used to assess angioedema severity and treatment response, complicating efficacy comparisons between trials. Additionally, the majority of literature available describing treatment of ACEI-induced angioedema is susceptible to publication bias, as reports of negative trials or case reports may be limited.

The choice of which treatment to administer depends not only on efficacy, but institutional availability. While FFP may be readily available at most health care systems and carries the lowest cost, controlled trials evaluating its efficacy do not exist and the optimal dose is yet to be elucidated. However, risks of FFP are relatively minimal, so a trial of FFP in severe refractory ACEI-induced angioedema may be reasonable. Time to administration remains an important consideration, however, and the need to thaw FFP may contribute to delays. The greatest amount of published literature surrounds icatibant use; however, the data are heterogeneous. There is great variability with regard to severity of angioedema, time to treatment, dose, and outcome measures. Additionally, the inclusion of mild angioedema in the large randomized controlled trial evaluating icatibant makes the results

difficult to generalize to patients in the ED for whom it would likely be cost effective to use: patients with severe angioedema who need therapy to avoid progression to intubation or tracheostomy or to shorten their course, if possible (55). Icatibant is supplied as a ready-to-use product, which may improve time to administration over other agents. C1-INH also has limited evidence to support routine use in ACEI-induced angioedema and, similar to FFP, doses used in published literature are widely varied. This poses a challenge in extrapolating data for clinical decision-making. C1-INH also needs to be prepared and delivered to the patient, and thus would not be the preferred option. Two randomized controlled trials evaluated ecallantide use and found no differences in the primary outcome. Additionally, 42% of patients in one of the trials who received ecallantide required a second open-label dose due to lack of efficacy (2,37,38). Without additional evidence available, ecallantide cannot be recommended at this time for treatment of ACEI-induced angioedema.

The potential benefit of these medications must be weighed against their high cost (icatibant: \$11,328 per 30-mg injection; ecallantide: \$5049 per 10-mg injection; and C1-INH: \$3222 per 500-U injection) (57). If complications of ACEI-induced angioedema, such as mechanical ventilation or tracheotomy, could be avoided or durations shortened, the costs would be further justified. However, at this time, there is limited evidence evaluating these clinical end points. The most evidence, while still limited, includes case reports that demonstrate the avoidance of angioedema progression requiring intubation after icatibant administration. Icatibant cases also are described in which there was symptomatic improvement within 30 min, a time frame that may allow for prevention of intubation. However, it is important to note that first, more pertinent clinical outcomes, such as the need for intubation or tracheostomy or intensive care unit (ICU) admission, were not evaluated. Also, the mild angioedema seen in the majority of the patients prevents extrapolating these findings to patients in whom emergency physicians would likely find it to be a cost-effective therapy. Future study of FFP and novel agents for ACEI-induced angioedema should focus on standardizing symptom scales, dosing schematics, and utilizing clinical end points that would allow for sufficient cost analysis. Trials evaluating patients with more severe angioedema, as well as assessment of duration of mechanical ventilation, need for tracheostomy, or ICU length of stay are warranted before recommending widespread use.

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ARTICLE SUMMARY

1. Why is this topic important?

Angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema can cause life-threatening airway compromise requiring airway stabilization. Due to the large percentage of patients now on chronic ACEI therapy, a thorough assessment of therapies approved for use in hereditary angioedema is warranted because of the potential to alleviate symptoms and possibly avoid intubation.

2. What does this review attempt to show?

Therapies used off-label for ACEI-induced angioedema are assessed and include fresh frozen plasma, prothrombin complex concentrate, icatibant, ecallantide, and complement-1 esterase inhibitor. This systematic review describes the published available evidence surrounding the efficacy of these therapies.

3. What are the key findings?

There is a wide heterogeneity within the literature for each studied medication with respect to the severity of cases included in the study, clinical outcomes assessed, and measurement tools for angioedema severity. Icatibant has the highest-quality evidence for use in ACEI-induced angioedema, though it is suboptimal; however, fresh frozen plasma may be more readily available at most institutions.

4. How is patient care impacted?

Through this review, bedside emergency physicians will be able to assess the large body of evidence to determine which therapy is most appropriate for their patient and what clinical outcomes are anticipated.