REVIEW

# An evidence-based review of the potential role of icatibant in the treatment of acute attacks in hereditary angioedema type I and II

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**Introduction:** Icatibant, a first-in-class B2 bradykinin receptor antagonist, appears to have a favorable efficacy and safety profile for the treatment of acute attacks of hereditary angioedema in adults.

**Aims:** To update the evidence and provide an overview of the available data on icatibant.

**Evidence review:** Peer reviewed articles published and listed in Medline Search and published updated guidelines for the treatment of acute attacks in hereditary angioedema type I and II in adults were reviewed. The validity and quality of evidence were evaluated.

**Place in therapy:** Clinical evidence for the treatment of acute hereditary angioedema attacks with icatibant is strong. Approximately 10% of the patients require a second dose. No serious adverse reactions have been reported. The only significant side effects consistently registered by 90% of patients are transient local pain, swelling, and erythema at the local injection site.

**Conclusion:** Subcutaneously administered 30 mg icatibant has been shown to be a safe and efficacious treatment in clinical trials. It is the only specific treatment authorized for self-administration by the subcutaneous route offering increased patient independence.

**Keywords:** icatibant, hereditary angioedema, self-administration, acute attacks

**Core Evidence** Clinical impact summary for icatibant in acute attacks of hereditary angioedema type I and II

| Outcome measure | Evidence | Implications |
|---|---|---|
| Disease-oriented evidence | Demonstrates efficacy for the treatment of acute hereditary angioedema attacks, including cutaneous, abdominal, and laryngeal attacks.[19,29,31] No experience available in children. | Provides a complementary treatment to C1 inhibitor concentrate. According to international consensus patients may carry two doses of icatibant.[14–18] |
| Patient-oriented evidence | | |
| Self-administration | Patients are able to decide when to initiate a treatment, and they are able to safely self-administer icatibant earlier in their attacks.[23] | Potential to address a significant unmet need. |
| Quality of life | Not available. | |
| Economic evidence | Variations in prices and availability of and access to icatibant among countries.[54] | Co-payments can represent important barriers to patients.[55] |

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# Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency of functional C1 inhibitor (C1-INH). Bradykinin is the main mediator implicated in edema. It is a rare disorder characterized by recurrent episodes of non-pruritic, non-pitting, subcutaneous, or submucosal edema affecting the extremities, face, throat (tongue, larynx, and lips), trunk, genitalia, or bowels that are referred to as attacks. Swelling affecting the skin is usually painless. Abdominal attacks with diarrhea, vomiting, and pseudo-obstructive syndrome can result in unnecessary surgery and are very painful. All attacks localized over the shoulders must be considered severe and potentially life-threatening.[1,2] If undiagnosed and/or untreated, laryngeal edema can lead to the obstruction of the upper airways and death. Lifetime fatality rates have been estimated between 10% and 30%[3] in the absence of specific treatment, which is almost exclusively caused by laryngeal edema.[4–7] Edemas develop slowly over a period of up to 36 hours and resolve spontaneously within 3 to 4 days and do not cause residual effects. Edema can result in fearfulness, stress, social, and employment difficulties.

# Pathophysiology

C1-INH is a serine protease whose deficit promotes activation of the complement system. It inhibits C1r/s in the classical complement pathway, kallikrein, and factors Xa, XI, and XII of the contact pathway and plasmin of the thrombolytic pathway.

Two variants of HAE caused by genetic defects in chromosome 11 have been described: HAE type I with decreased C1-INH levels (85% of cases) and HAE type II with normal protein concentration but with a functional defect (15% of cases). Estrogens, trauma, minor infection, or psychological stress may precipitate attacks.[4,8]

Bradykinin is the key mediator of angioedema attacks. It is released following the activation of a cascade of proteases in the kallikrein–kinin pathway, which is activated by factor XII.[3] Vascular stress activates excessive contact-activated coagulation and leads to the release of large amounts of bradykinin.[9] Bradykinin binds to specific B2 vascular receptors, which will then open intercellular junctions and cause an increase in vascular permeability, plasma leakage, and edema.[8,10,11] Bradykinin B1 receptors also seem to be involved and probably mediate pain and possibly erythema.[12] Bradykinin is degraded by three enzymes: angiotensin-converting enzyme, aminopeptidase P, and carboxypeptidase enzymes.

# Treatment

The therapy goal is to normalize the lives of patients. International consensus conferences have been published and specific molecules have been developed in recent years for the treatment of acute attacks.[13–18]

Acute treatment aims to resolve angioedema symptoms as quickly as possible. Tranexamic acid is of very limited benefit and attenuated androgens are ineffective during acute attacks.[16,19] Currently, several specific treatments are available, but a guideline for proper treatment has not yet been established. In fact, the results of numerous Phase III clinical studies for these specific treatments cannot be directly compared because different treatment protocols were used. C1-INH concentrate (Berinert®) has been the first line therapy. Phase III clinical trials, with level one of evidence, have been published.[20,21] Until recently, it was the sole specific treatment for acute attacks. Ecallantide, a kallikrein inhibitor (Kalbitor®), recombinant C1-INH (Rhucin® and Ruconest™), and nanofiltered C1 inhibitor concentrate (Cinryze® and Cetor®) are specific treatments whose availability differ by country.

Icatibant (Firazyr®; Shire) is a synthetic antagonist of the bradykinin B2 receptor approved for the treatment of HAE in the European Union and the United States.[22,23]

# Icatibant: pharmacology

Icatibant is a synthetic decapeptide and a highly selective competitive antagonist of the bradykinin B2 receptor. It antagonizes the vasodilatory effect of excess bradykinin[24] and blocks edema formation. Icatibant has a similar structure to bradykinin but contains five nonproteinogenic amino acids and is resistant to degradation by bradykinin-cleaving enzymes.[25]

The affinity of icatibant for the B2 receptor is similar to that of bradykinin, while affinity for the B1 receptor is 100-fold lower. No binding to other receptors has been reported. Agonist activity is expressed at high concentrations (>3.2 mg/kg) and may explain the local injection site reactions.[26]

# Pharmacokinetics

Icatibant is rapidly absorbed from the subcutaneous injection site, and the peak concentration is reached in 20 to 30 minutes. Its bioavailability is excellent with low protein binding and a large distribution volume.[27] No differences were found in absorption between intravenous and subcutaneous formulations. Duration of action is not dose dependent, which allows a second injection rather than

increasing the dose when it has not been fully effective.[28] The elimination half-life is 1.2 to 1.5 hours. Icatibant is metabolized in the liver by cleavage to two smaller inactive peptides excreted in the urine, with less than 10% of the dose eliminated as unchanged drug. It has no effect on renal or hepatic function[27] and its clearance is reduced in the elderly.[22] Pharmacokinetics is independent of weight or gender. Icatibant has a poor diffusion in adipose tissue and does not cross the blood–brain barrier. Although there have been no studies in children or pregnant women, icatibant crosses the placenta and is excreted in breast milk in rats.[22]

## Pharmacodynamics

The optimum subcutaneous dose is 30 mg. The injection can be repeated at 6-hour intervals, up to three injections per day. The packaging is a 3 mL pre-filled syringe for subcutaneous injection. It is stable for up to 24 months at room temperature.

## Tolerance/side effects
### Injection-site reactions

In each study, injection-site reactions were reported by the majority of patients receiving with icatibant. Most commonly, there were erythema and/or swelling at the injection site that appeared 10 minutes after the injection. These were generally mild to moderate in severity and resolved spontaneously within 4 hours. Partial agonist activity explains the reaction.

### Adverse events

Since bradykinin has potential cardioprotective properties, icatibant could, in theory, impair cardiac function and decrease coronary blood flow. This has been described in animal models that developed myocardial infarction after icatibant treatment. It is not recommended for patients who present a cardiac or brain ischemia. Across all Phase III studies, 1076 icatibant doses were given to 225 patients for 987 attacks. In addition to exposure in clinical studies, over 8300 patient exposures to icatibant have occurred cumulatively in the post-marketing setting from EU regulatory approval.[23] The majority of adverse events appeared to be related to HAE attacks. The most common adverse events were recurrent or worsening angioedema. The incidence of adverse events was similar in icatibant and placebo-treated patients. No serious adverse events related to icatibant were reported.

No icatibant-treated patients experienced hypersensitivity reactions or developed anti-icatibant immunoglobulin G or E antibodies in a period of five weeks after treatment.[29]

The product is licensed in 37 countries, and in 2011, was granted approval for self-administration in the EU and US.

## Children, pregnancy, and breastfeeding

Currently, there is no experience with administration of icatibant in pregnant or breastfeeding women. A study to investigate the tolerability, safety, and pharmacokinetics of icatibant in pediatric patients with HAE is in progress (ClinicalTrials.gov identifier: NCT01386658).

## Aims

This review examines the evidence supporting the use of icatibant for the treatment of acute attacks of hereditary angioedema type I and II.

## Methods

A search of English-language scientific literature was carried out on PubMed and ClinicalTrials.gov using the following key words: hereditary angioedema and icatibant. Searches were last updated on February 28, 2012. Full-text articles were retrieved for the most relevant articles. Articles involving icatibant for the treatment of HAE were identified, with priority given to systematic reviews, double-blinded randomized placebo-controlled trials, and nonrandomized observational studies. We did not have any exclusion criteria, although abstracts of papers that seemed irrelevant were not retrieved. The validity and quality of evidence was evaluated using a methodology adapted from Clark and Mucklow.[30]

## Results

From the literature searches, 52 publications, including four international consensus statements,[14–18,28] were identified for inclusion in the following evaluation of the clinical evidence for icatibant in the treatment of HAE. Consensus statements prior to 2010 – published before the last trials and new treatments become available – were not analyzed. These new international consensus statements, published since icatibant became available, used an evidence-based approach. Currently, there are no specific studies available on laryngeal attack, rescue medication, self-administration, and recurrent attacks. To aid critical analysis of the studies included for assessment, each publication has been

assigned a quality of evidence rating: level I, one publication:[40] level II, 3 trials, 2 publications;[19,29] level III, 2 publications;[31,53] level IV, 2 publications;[46,54] level V, 45 publications.

## Clinical data

Clinical effectiveness was validated in an open study and in three double-blind randomized studies in patients with HAE type I or II.

In an uncontrolled pilot study (Phase II study), 15 patients with 20 attacks were treated with icatibant.[31] The treatment was administered either as a single intravenous (0.4 mg/kg over a period of 30 minutes or 2 hours or 0.8 mg/kg over a period of 30 minutes) or a single subcutaneous injection (30 or 45 mg). The median time to onset of symptom relief was longer in the intravenous groups (around 1 hour) than in the subcutaneous groups (30 minutes). Compared with untreated attacks, icatibant treatment reduced the mean time to onset of symptom relief by 97%. There were no differences between the doses (30 mg vs 45 mg). The 30-mg subcutaneous dose was chosen for the Phase III studies. This is the first report demonstrating the clinical usefulness of antagonizing bradykinin binding to the bradykinin B2 receptor for cutaneous and abdominal attacks in HAE.[31]

The clinical efficacy of icatibant in the treatment of acute HAE attacks was investigated in the controlled For Angioedema Subcutaneous Treatment (FAST-1, and FAST-2) and FAST-3 Phase III clinical studies.[19,29] FAST-1 and FAST-2 involved all types of attack, except for laryngeal attacks included in an open-label study. In FAST-3, patients with mild laryngeal attack were included. Patients with severe laryngeal symptoms were treated in an open-label study. All studies were followed by an open-label extension (data not published). In all trials, the treatment was administered no later than 6 hours after an acute attack became moderate in severity, or mild for laryngeal attacks in FAST-3.

In FAST-1 and FAST-3, the comparator was a placebo, while in FAST-2, it was oral tranexamic acid (3 g daily for 2 days). In all trials, outcomes were measured using a 100-mm visual analog scale (VAS) and additional outcome assessments were measured using a five- or seven-point symptom score described by the physician and the patient. In FAST-1 and FAST-2, the primary endpoint was the time to clinically significant relief of symptoms, defined by a minimum decrease of 30% in the index symptom score on VAS sustained for three consecutive measurements. One of the three main symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) was defined in each patient as the index symptom for the purpose of assessing the primary endpoint. Secondary endpoints included time to the first improvement of the index symptom according to the patient and the investigator, time to almost complete relief of symptoms, response rate at 4 hours after injection, global assessment and overall patient improvement, and a patient satisfaction questionnaire at week 24. In FAST-3, the primary endpoint was subject-assessed time to 50% reduction in symptom severity in the index symptom score on VAS. Secondary endpoints included time to the onset of primary symptom relief, time to almost complete symptom relief, time to initial symptom improvement assessed by the subject and investigator, time to the onset of symptom relief (50% reduction in composite score), and global assessment.

The FAST-1, -2, and -3 trials were randomized, double-blind controlled multicenter studies.[19,29] During the controlled phase of FAST-1, a total of 56 patients were randomized where 27 patients received icatibant and 29 patients received placebo in the US, Canada, Argentina, and Australia. During the controlled phase of FAST-2, a total of 74 patients were randomized where 36 patients received icatibant and 38 patients received tranexamic acid in the EU and Israel. Demographic data are shown in Table 1. The primary endpoint was reached in 2.5 hours with icatibant versus

**Table 1** Characteristics of the study patients in the FAST-1, -2 and -3 trials

| | FAST-1 | | FAST-2 | | FAST-3 (nonlaryngeal population) | | FAST-3 (laryngeal population) | |
|---|---|---|---|---|---|---|---|---|
| | Icatibant (n = 27) | Placebo (n = 29) | Icatibant (n = 36) | Tranexamic acid (n = 38) | Icatibant (n = 43) | Placebo (n = 45) | Icatibant (n = 3) | Placebo (n = 2) |
| Age (years) | 34.8 ± 9.8 | 34.9 ± 11.4 | 40.4 ± 13.6 | 41.9 ± 12.4 | 36.1± 3.7 | 36.6 ± 11.2 | 40.3 ± 6.7 | 50 ± 22.6 |
| Female/male | 16/11 | 21/8 | 24/12 | 23/15 | 27/16 | 29/16 | 2/1 | 1/1 |
| Weight (kg) | 80.3 ± 21.1 | 76 ± 21.9 | 80.1 ± 16.1 | 74.2 ± 15.6 | 81.7 ± 25.1 | 80.7 ± 20.9 | 86.6 ± 33.4 | 70.3 ± 5 |
| Primary attacks, n (%) | | | | | | | | |
| Cutaneous | 14 (51.8) | 13 (44.8) | 24 (66.7) | 23 (60.5) | 26 (60.5) | 26 (57.8) | | |
| Abdominal | 13 (48.2) | 16 (55.2) | 12 (33.3) | 15 (39.5) | 17 (39.5) | 19 (42.2) | | |

**Note:** Values are expressed as mean ± SD or number (%).

4.6 hours with the placebo in the FAST-1 trial ($P = 0.14$) and in 2 hours versus 12 hours with tranexamic acid in the FAST-2 study ($P < 0.001$) (Table 2). In FAST-2, icatibant significantly improved patients at a faster rate, while in FAST-1, the difference was not significant. The improvement was significant for all endpoints in FAST-2, but not in FAST-1 (Table 2). The primary endpoint for both FAST-1 and FAST-2 was a secondary endpoint in FAST-3. Significant benefit was observed in FAST-1 and FAST-2 when these studies were analyzed according to the primary endpoint as defined in FAST-3 (Table 2). Results showed a time to relief of the index symptom of 2.5 hours with icatibant versus 7 hours with the placebo ($P = 0.02$) in FAST-1, and 2 hours with icatibant versus 15 hours with tranexamic acid ($P < 0.001$) in FAST-2. The median time to almost complete relief of symptoms was 8.5 hours with icatibant and 19.4 hours with the placebo ($P = 0.08$) in FAST-1 (Table 2), and 10 hours with icatibant and 51 hours with tranexamic acid ($P < 0.001$) in FAST-2. The median time to first improvement of the index symptom was significantly shorter with icatibant than with the placebo in FAST-1, as assessed by the patient (0.8 vs 16.9 hours; $P < 0.001$) or by the investigator (1.0 vs 5.7 hours; $P < 0.001$). Similarly, the median time to first improvement of the index symptom was significantly shorter with icatibant than with tranexamic acid in FAST-2, as assessed by the patient (0.8 vs 7.9 hours; $P < 0.001$) or by the investigator (1.5 hours vs 6.9 hours; $P < 0.001$) (Table 2).

The results of these studies led to the authorization of icatibant in the EU for the treatment of HAE attacks in adults. Because of differences in effectiveness, FAST-3 was performed to obtain additional data.

The FAST-3 study is a randomized, double-blind, placebo-controlled study using the same design as FAST-1. During the controlled phase of FAST-3, a total of 88 patients were randomized where 43 patients received icatibant and 45 patients received placebo in eleven countries.[29] Demographics data are shown in Table 1. The primary endpoint was subject-assessed time to 50% reduction in symptom severity in the index symptom score on VAS. Results demonstrated that icatibant was effective in the treatment of attacks. Time to 50% reduction in symptom severity was 2 hours with icatibant versus 19.8 hours with the placebo ($P < 0.001$) (Table 2). Improvement was also significant for all secondary endpoints (Table 2). Overall, efficacy findings in FAST-3 were consistent with other studies. Time to first symptom improvement according to patients was 0.8 hours for the icatibant group in FAST-1, -2, and -3, which is

**Table 2** Time to symptom improvement in the FAST-1, -2 and -3 trials

| | FAST-1 | | | FAST-2 | | | FAST-3 (nonlaryngeal population) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Icatibant (n = 27) | Placebo (n = 29) | P value | Icatibant (n = 36) | Tranexamic acid (n = 38) | P value | Icatibant (n = 43) | Placebo (n = 45) | P value |
| Time to first symptom improvement (according to patient) (hours) | 0.8 (0.5–2) | 16.9 (3.2–NA) | <0.001 | 0.8 (0.4–1.4) | 7.9 (1.1–NA) | <0.001 | 0.8 (0.5–1) | 3.5 (1.9–5.4) | <0.001 |
| Time to first symptom improvement (according to investigator) (hours) | 1 (0.8–2) | 5.7 (2–11.2) | <0.001 | 1.5 (0.7–3) | 6.9 (4–13.8) | <0.001 | 0.8 (0.6–1.3) | 3.4 (2.6–6) | <0.001 |
| Time to 30% reduction in symptom severity (hours)* | 2.5 (1.1–6) | 4.6 (1.8–10.2) | 0.14 | 2 (1–3.5) | 12 (3.5–25.4) | <0.001 | NA | NA | |
| Time to 50% reduction in symptom severity (hours)** | 2.5 (NA) | 7 (NA) | 0.02 | 2 (NA) | 15 (NA) | <0.001 | 2 (1.5–3) | 19.8 (6.1–26.3) | <0.001 |
| Time to almost complete symptom relief (hours) | 8.5 (2.5–31.5) | 19.4 (10.2–55.7) | 0.08 | 10 (2.8–23.2) | 51 (12–79.5) | <0.001 | 8 (5–42.5) | 36 (29–50.9) | 0.012 |

**Notes:** *Primary endpoint in FAST-1 and -2 studies; **primary endpoint in FAST-3 study. Values are expressed as median (interquartile range).
**Abbreviation:** NA, not available.

significantly shorter than that of patients in the placebo or tranexamic acid group. In addition, FAST-3 confirmed a significant reduction in time to almost complete symptom relief with icatibant (Table 2).

Some case reports have been published on the treatment of acute attacks in HAE type I and II.[32–35] In a prospective study, nine patients were treated for 16 attacks with icatibant administered at home by health care professionals (HCPs).[36] Median times to onset of symptom relief improvement were 0.83 hours for cutaneous attacks, 0.50 hours for upper airway attacks, and 0.57 hours for abdominal attacks. This study demonstrated that icatibant administered by HCPs at home has a similar efficacy and tolerability profile as icatibant administered in clinical settings.

## Laryngeal attacks

Forty-five laryngeal attacks were treated with icatibant.[37] A total of eight patients in FAST-1 and three patients in FAST-2 received open-label icatibant for laryngeal attacks.[19,29] In FAST-2, one patient required intubation 5 minutes after icatibant administration. In these trials, the time to first symptom improvement according to the patient was 0.6 hours and 1.0 hours, respectively (Table 3). As reported by the investigator, nine of the eleven patients had no symptoms at 4 hours after icatibant administration. The remaining patient had mild symptoms at 4 hours.

In FAST-3, ten patients were treated, with five patients included in the double-blind trial (three patients with icatibant and two patients with a placebo) and the other five patients receiving open-label icatibant.[29] The two patients randomized to the placebo received icatibant (post-hoc analysis). Time to first improvement according to the patients was 1 hour with icatibant versus 2.1 hours with the placebo in the double-blind trial. The median times to 50% reduction in symptom severity were 2.5 hours in the double-blind trial and 2.3 hours in open-label

icatibant (Table 3). Time to first symptom improvement for laryngeal attacks in the icatibant population (ranging from 0.6 hours to 1 hours) was similar to that seen in the icatibant group for the non-laryngeal population in FAST-1, -2, and -3 (median 0.8 hours each). Currently no other studies are available.

## Rescue medication

Rescue medication, such as C1 inhibitor concentrate, narcotic, analgesics, and anti-emetics, was administered to patients receiving the placebo or acid tranexamic (Table 4). As shown in Table 1, a larger proportion of the placebo patients in FAST-1 had abdominal attacks than in FAST-3. Abdominal attacks are painful and often difficult to tolerate without pharmacological intervention. The need for additional rescue medication suggested inferior symptom control in the comparator arm, and therefore, may explain the lack of significance in FAST-1. Post-hoc analysis in FAST-1 showed that the primary end-point adjusted for rescue medication was 2.5 hours with icatibant and 9 hours with the placebo ($P = 0.02$). The fact that rescue medications before the onset of symptom relief were not required in FAST-3 supports the clinical efficacy of icatibant.

## Self-administration

An open-label FAST-4 trial (or Evaluation of the Safety of Self-administration with Icatibant [EASSI]) was conducted to evaluate the safety of self-administered injections. EASSI addressed the safety in 56 patients self-administering icatibant during an acute attack. Health care professionals administered second and/or third doses if needed. Median time to 50% reduction in symptom severity was 2.6 hours (2 to 4). The study has not yet been published, but its results are similar to previous Phase III trials when icatibant was administered by an HCP.[23] The European Commission and US Food and Drug Administration approved icatibant as a self-administered injection in 2011.

**Table 3** Time to symptom improvement in laryngeal attack

| | Open label | | | Double-blind (FAST-3) | |
| --- | --- | --- | --- | --- | --- |
| | **FAST-1** (n = 8) | **FAST-2** (n = 3) | **FAST-3** (n = 5) | **Icatibant** (n = 3) | **Placebo** (n = 2) |
| Time to first symptom improvement (according to patient) (hours) | 0.6 (NA) | 1 (NA) | 0.2 (NA) | 1 (0.6–2.5) | 2.1 (0.5–3.9) |
| Time to 50% reduction in symptom severity (hours) | NA | NA | 2.3 (1.5–4) | 2.5 (1.3–3) | 3.2 (1–5.4) |

**Note:** Values are expressed as median (interquartile range).
**Abbreviation:** NA, not available.

**Table 4** Use of rescue medication

| Subjects receiving rescue medications, n (%) | FAST-1 | | FAST-2 | | FAST-3 (nonlaryngeal population) | | |
|---|---|---|---|---|---|---|---|
| | Icatibant (n = 27) | Placebo (n = 29) | Icatibant (n = 36) | Tranexamic acid (n = 38) | Icatibant (n = 43) | Placebo (n = 45) | P value |
| In the first 12 h | 3 (11) | 13 (45) | 0 | 5 (13) | | | |
| In the first 48 h | 6 (22) | 15 (52) | 6 (17) | 11 (29) | | | |
| Before 50% reduction in symptom severity | | | | | 0 | 16 (36) | <0.001 |
| At any time during the attack and up to 5 days | | | | | 3 (7) | 18 (40) | <0.001 |

**Note:** Values are expressed as number (%).

## Recurrent attacks

Approximately 10% of patients require a second dose for re-emergent symptoms, usually 10–27 hours after the initial treatment and a third dose is required in 1% of patients.[38] The short half-life of icatibant may be responsible for recurrent attacks. Patients must be informed of the possibility and may carry two doses of icatibant.[15]

Repeated use of icatibant over time after up to 110 treatments in 118 patients produces a consistent response at each attack, with no diminution of efficacy.[23] A case report on the treatment of 141 attacks of HAE in a patient with icatibant has been published.[39] Its efficacy was not impaired by repeated administrations over a 3-year period.

## Discussion

Icatibant is a first-in-class B2 bradykinin receptor antagonist indicated for the treatment of acute HAE attacks in adults. Treatment of acute attacks of HAE has been revolutionized over the last years by new drugs. There have been multiple Phase III clinical trials and other studies published on HAE therapy. C1-INH concentrate has been the first line therapy for several decades. Evidence suggests that the C1-INH concentrates, plasma-derived (Berinert®, Cinryze®, and Cetor®) and recombinant (Rhucin® and Ruconest™), kallikrein inhibitor ecallantide (Kalbitor®), and bradykinin B2 receptor antagonist icatibant (Firazyr®) are suitable for the acute treatment of HAE. Four international consensus guidelines were established in 2010, before FAST-3 results were published. All recommended early treatment with a specific molecule, including icatibant, during an acute attack of HAE with strong evidence.[14–18] There are no head-to-head trials comparing icatibant with C1-INH concentrates or other treatments. No superiority or lack of inferiority head-to-head trials between the five licensed therapies have been conducted to date. Tranexamic acid has been demonstrated

to be a relatively ineffective therapy and danazol is only used as a prophylactic drug.

The efficacy and safety of icatibant for the treatment of acute attacks of HAE in adults have been studied in three double-blind Phase III studies and in repeated open-labels. In multiple end-points in these controlled studies, icatibant has been shown to be a safe and efficacious treatment for acute attacks, as demonstrated by reproducible and consistent efficacy. Icatibant showed a significant benefit in the FAST-2 trial with tranexamic acid and in the FAST-3 with a placebo, while in the FAST-1 trial, there was no significant difference. In order to explain these results, we can discuss the treatment method of the attacks in the control group. In FAST-1, 45% of the placebo group received treatments such as analgesics, anti-emetics, opiates, or even C1-INH concentrate, compared with only 13% of patients in FAST-2. The inferior results in FAST-1 may, therefore, be explained by the increased use of back-up treatments. The results of FAST-1 become significant when adjusting for rescue medication. The early use of rescue medication led to a type II error.[38,40,41] As for other new drugs, there are little published data on the open-label phase of the studies, particularly on the outcome of laryngeal attacks. Based on the available reports, icatibant shortens time to resolution for laryngeal attacks.

Treatment of acute HAE is most effective when given early.[42] Berinert® is approved for patient self-administration by intravenous infusion after proper training by an HCP in the US and EU. Intravenous administration can result in a delay in the initiation of treatment and requires practice and motivation. Ecallantide is only approved for administration in a supervised setting due to the risk of hypersensitivity reaction. Icatibant is the first and only subcutaneous treatment for HAE attacks licensed for self-administration. The EASSI study showed that self-administration of icatibant

for acute attacks of HAE was generally well tolerated. The results demonstrated that patients were able to decide when the initiation of treatment was appropriate, and they were able to safely self-administer icatibant earlier in their attacks. Time to icatibant administration tended to be shorter for patients who were able to self-administer in the EASSI study than for those in the controlled Phase III studies who had to travel to a clinical site to receive treatment. Therefore, self-administration of icatibant provides patients the option of early access to treatment. The major application of icatibant seems likely to be in self-administration. Patients and physicians can evaluate the appropriateness of self-administration based on a patient's knowledge of disease and ability to self-treat. Finally, international treatment guidelines recommend that every patient with HAE must be considered for self-administration. Also, the availability of an effective treatment that, after training, patients will be able to administer at the onset of an attack will minimize the impact of this condition on patients' lives, and will reduce the need for repeated attendances in emergency departments.[14–16]

Direct medical costs are represented by treatment of HAE attacks and long term care. It is also necessary to take into account quality of life, education, and career, which contribute to the economic burden. Because of the low incidence of the disease, little is known about the humanistic and economic burden of HAE on patients, caregivers, and health care systems.[43] Wilson et al have studied the substantial economic costs associated with both acute attacks and the ongoing chronic nature of the disease.[44] The total annual per-patient costs were estimated at $42,000 for the average HAE patient. Costs increased considerably with increasing attack severity: $14,000 for patients with mild attacks and up to $96,000 for patients with severe attacks. They also described high rates of work absences, lower productivity, and lower income, contributing to indirect annual costs of $16,000 for the average patient. This study showed that HAE resulted in an economic burden, but this survey was conducted before the approval of C1-INH therapy and icatibant in the US. In another study based on the current prices in Germany, the cost of one dose of icatibant (30 mg) is equal to the cost of one dose of 20 U/kg of Berinert® for a standard 70 kg patient.[45] For a 100 kg patient receiving a dose of 20 U/kg of Berinert®, it is more expensive compared to icatibant. Some humanistic burdens are not easily quantifiable but have a tangible financial impact and the indirect costs may be underestimated. Lumry et al showed that patients reported significantly impaired health and mental quality of life, education, career and work productivity as well as substantial economic burdens.[46] For the first time, a self-administered specific agent offers the possibility of effective acute therapy to reduce the morbidity, mortality, and disability associated with HAE attacks. Future cost-effectiveness studies are needed.

There are many types of bradykinin-mediated angioedema. In addition to HAE type I and II (associated to C1-INH deficiency), there are also HAE type III (no C1-INH deficiency), acquired angioedema associated with C1-INH deficiency, and angioedema associated with angiotensin converting enzyme inhibitors or angiotensin II antagonists.[1,2] To date, there has been no prospective study using icatibant in patients with other types of angioedema. The pathophysiology of these diseases and the mechanism of the action of icatibant seem to suggest that icatibant could be used.[41] Several case reports have been published.[47–52] Bas et al reported the efficacy of icatibant in eight patients with acute angiotensin converting enzyme inhibitors angioedema.[53] First symptom improvement occurred at a mean time of $50.6 \pm 21$ minutes after icatibant injection and complete relief of symptoms at $4.4 \pm 0.8$ hours. A randomized study to evaluate the effectiveness of icatibant in patients with angiotensin converting enzyme inhibitor-associated angioedema is in progress (ClinicalTrails.gov identifier: NCT01574248).

Blankart et al showed variations in prices and availability of and access to icatibant between countries.[54] Substantial co-payments can represent important barriers to patient access to treatment.[54,55]

## Conclusion

To date, there is a strong evidence of the applicability of icatibant in the treatment of acute HAE attacks in adults. There are international consensus guidelines and recommendations for acute treatment. It was emphasized that all patients should carry two doses of a specific treatment. Incorporating the knowledge that early treatment is more effective, it was agreed that all patients should be trained for self-administration and that the attacks should be treated as soon as they are recognized. Icatibant has the advantage that it can be self-administered by the subcutaneous route, offering increased patient independence. Patients can have rapid access to effective treatment, regardless of geographic location, which offers the possibility of normalizing the lives of patients affected by HAE. However, it is important to conduct rigorous Phase IV clinical trials and head-to-head studies.

# Disclosure

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