Hereditary angioedema: epidemiology, management, and role of icatibant

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Abstract: Hereditary angioedema (HAE) is an autosomal dominant, potentially life-threatening condition, manifesting as recurrent and self-limiting episodes of facial, laryngeal, genital, or peripheral swelling with abdominal pain secondary to intra-abdominal edema. The estimated prevalence of HAE in the general population is one individual per 50,000, with reported ranges from 1:10,000 to 1:150,000, without major sex or ethnic differences. Various treatment options for acute attacks and prophylaxis of HAE are authorized and available in the market, including plasma-derived (Berinert®, Cinryze®, and Cetor®) and recombinant (Rhucin® and Ruconest™) C1 inhibitors, kallikrein inhibitor-ecallantide (Kalbitor®), and bradykinin B2 receptor antagonist-icatibant (Firazyr®). Some of these drugs are used only to treat HAE attacks, whereas others are only approved for prophylactic therapies and all of them have improved disease outcomes due to their different mechanisms of action. Bradykinin and its binding to B2 receptor have been demonstrated to be responsible for most of the symptoms of HAE. Thus icatibant (Firazyr®), a bradykinin B2 receptor antagonist, has proven to be an effective and more targeted treatment option and has been approved for the treatment of acute attacks of HAE. Rapid and stable relief from symptoms of cutaneous, abdominal, or laryngeal HAE attacks has been demonstrated by 30 mg of icatibant in Phase III clinical trials. Self-resolving mild to moderate local site reactions after subcutaneous injection of icatibant were observed. Icatibant is a new, safe, and effective treatment for acute attacks of HAE. HAE has been reported to result in enormous humanistic burden to patients, affecting both physical and mental health, with a negative impact on education, career, and work productivity, and with substantial economic burdens. The timely and proper use of disease-specific treatments could improve patients' quality of life, reduce the disease-specific morbidity and mortality, and, last but not least, reduce costs associated with hospitalizations and emergency room visits. Therefore, the paradigm of HAE treatment has the potential to evolve significantly, thereby exponentially improving a patient's quality of life.

Keywords: hereditary angioedema, icatibant, C1 inhibitor, bradykinin

Introduction

Angioedema is a transient, intense, and most often disfiguring swelling of a localized body area involving the skin, mucosa, and subcutaneous tissues. The most commonly involved areas include the face, lips, tongue, pharynx, and supraglottic area and, uncommonly, the subglottic area.[1] Angioedema may also involve the hands and feet, as well as the gastrointestinal mucous membranes and the genitalia.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder, characterized by recurrent attacks of angioedema resulting from a deficiency of C1 inhibitor enzyme. Historically, two types of HAE have been described.[1] Type 1 HAE, which is more

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common than type 2, is caused by the decreased production of C1-inhibitor (C1-INH), thereby resulting in decreased C1-INH activity both in tissues and in blood; however, in type 2 HAE, normal or supranormal quantities of functionally impaired C1-INH are produced. A variant type of HAE has been recently described,[2] in which C1-INH levels and function are normal. All three types are symptomatically indistinguishable.

The primary biological role of C1-INH is to regulate activation of the complement system, the contact system (Hageman factor and plasma kallikrein), and the intrinsic coagulation system. Thus, in HAE, due to decreasing levels of C1-INH, there is unchecked activation of complement and contact system, causing the complement levels to fall and release of increased quantities of bradykinin respectively.[1] Bradykinin, in turn, has been shown to be the primary mediator responsible for capillary leakage and the consequent edema in HAE.[3]

Natural history, epidemiology, pathophysiology, and diagnosis of HAE
History
J L Milton was the first to describe HAE, in 1876,[4] and Quincke was the first to assign the name "angioneurotic edema" to the disease, in 1882.[5] Mental stress was observed to have an effect on exacerbations of the disease, thus the word "neurotic" was used as part of its name. Sir William Osler, in 1888, was the first to provide a detailed description of HAE over five generations, thus noting the hereditary component of this disease.[6] The biochemical basis for hereditary angioneurotic edema – the absence of C1-INH – was discovered several decades later and first published by Donaldson and Evans in 1963.[7] Since that study, a plethora of information regarding the genetic basis, pathophysiology, clinical manifestation, and management of HAE has been discovered and published.

Epidemiology
The estimated prevalence of HAE is 1 in 50,000, with reported ranges from 1:10,000 to 1:150,000.[1,8,9,19] HAE has been reported in all races and sexes. Type 1 is estimated to occur in 80% to 85% of HAE patients and type 2 in the remaining 15% to 20%. HAE can present as a cutaneous swelling in almost three-fourths of patients and as severe abdominal attacks in approximately one-fourth.[1,10] In one series of patients, recurrent abdominal pain and facial/upper airway edema occurred in 52% and 36%, respectively.[11] In 39% of these cases, patients could attribute their first episode to an identifiable traumatic event.[11]

Episodes of laryngeal edema are the least frequent, but are the primary cause of mortality in patients with HAE because they may progress to asphyxiation. Those episodes usually evolve over a period of hours however at times can progress expeditiously.

Abdominal attacks, caused by intestinal edema, can be very debilitating. They usually manifest as dramatic abdominal spasms, and almost 80% of patients with HAE will experience a gastrointestinal attack.[11]

The frequency of attacks in most symptomatic untreated patients ranges from weekly to less than a year. Each attack typically lasts for a few days before spontaneous resolution, thus it is estimated that the average patient with HAE has the potential to be debilitated by their symptoms for 20 to 100 days per year.[4]

Pathophysiology and clinical manifestations
HAE results from mutations in the *C1-INH* gene on chromosome 11, inherited in almost three-quarters of HAE patients with autosomal dominant mode; in one-fourth of HAE patients, the mutation appears de novo. Thus the diagnosis of HAE should not be ruled out in the absence of family history.[1,12] This mutation leads to either decreased (HAE-1) or dysfunctional (HAE-2) production of C1-INH, which is responsible for inhibition of the first complement system component; inactivation of coagulation factors XIIa, XIIf, and XIa; and direct inhibition of activated kallikrein.[13]

HAE type 3 is no longer considered to be an X-linked disease, since it has been associated with a gain-of-function mutation in the coagulation factor XII, inherited in an autosomal dominant pattern. Other unidentified mutations are likely to exist that could affect regulation of the kinin–kallikrein system.[14] Furthermore, hormone replacement therapy or estrogen-containing oral contraceptives, which may influence the kinin pathway, have also been thought to be associated with this type of HAE.[14]

Within the complement system, the biological role of C1-INH is to prevent the autoactivation of C1 by dissociating C1q subunit and binding to C1r and C1s. This binding forms an inactive $C1r_2-Cs_2-(C1-INH)_2$ complex which is unable to cleave and activate complement factors C2 and C4, keeping the Classical pathway dormant.[1] Therefore, in HAE, with decreased or absent C1-INH, there is unchecked activation of the early complement cascade (C1, C2, and C4) even before other inhibitors (C4-binding protein and factor I) can abort the pathway, resulting in consumption of the complement factors (C4) and increased formation of anaphylatoxins (C3a, C5a) and chemotaxins (C3b), perpetuating the inflammation,

local edema of skin and visceral organs, ascites, and intra-vascular volume depletion.[1]

The C1-INH plays a pivotal role in inactivation of coagulation factors XIIa and its metabolite XIIf as well as causes direct inhibition of activated kallikrein. A decrease in CI-INH level and activity allows generation of significantly increased quantities of factors XIIa and XIIf. Factor XIIa activates factor XII, which in turn activates further molecules of factor XIIa. The unopposed enhancement of this positive feedback loop contributes to the significant increase in factor XIIa levels. Factor XIIa also cleaves prekallikrein to the active enzyme kallikrein, which, in turn, cleaves high-molecular-weight plasma kininogens, resulting in excessive release of bradykinin. Moreover, decreased C1-INH activity also results in loss of its direct inhibitory effect on kallikrein activity, which, as stated earlier, cleaves high-molecular-weight plasma kininogens to release bradykinin, thus further promoting bradykinin generation.[1] Hence, in the absence of normal production of CI-INH in HAE, there is unchecked generation of the contact system mediator, the bradykinin, which binds to Bradykinin type 2 receptors on endothelial cells, causing increased vascular permeability (edema, swelling, and ascites), vasodilation (congestion, erythema, and hypotension), and contraction of nonvascular smooth muscle (cramps, spasms, and pain) (see Figure 1).

HAE is characterized by episodes of marked, diffuse, and recurrent edema, which usually follow a typical pattern of gradual progressive swelling over the first 24 hours, followed by slow resolution of symptoms over the next 48–72 hours, although there can be a high degree of inter- and intra-individual symptom variability among HAE patients. The swelling involves all skin layers as well as layers of the walls of hollow visceral organs and solid organs. The cutaneous edema is non-pitting, non-urticarial, with ill-defined margins, and most commonly involves areas of the face, extremities, and genitals. Facial swelling occurs in approximately 80% of patients, involving lips, tongue, oropharynx, and periorbital tissues. Extremity swelling is also quite common and can emerge in an asymmetric fashion, progressing over hours or days, to affect large areas of the arms or legs. Patients can experience considerable discomfort if the swelling is moderate-to-severe in sensitive regions such as the face or urogenital areas.[15]

The gastrointestinal tract is also commonly involved in HAE, causing bowel angioedema which, in turn, can be extremely painful and can mimic an acute abdomen as it can be unaccompanied by cutaneous symptoms. It is usually accompanied by nausea and vomiting and, less frequently, by diarrhea. This myriad of acute abdominal symptoms can be a cause of frequent emergency room visits and, at times, may lead to unnecessary surgical abdominal explorations, cholecystectomies, and appendectomies.

Laryngeal edema, although significantly less common than cutaneous or abdominal involvement, can be a primary cause of mortality in HAE due to the potential for
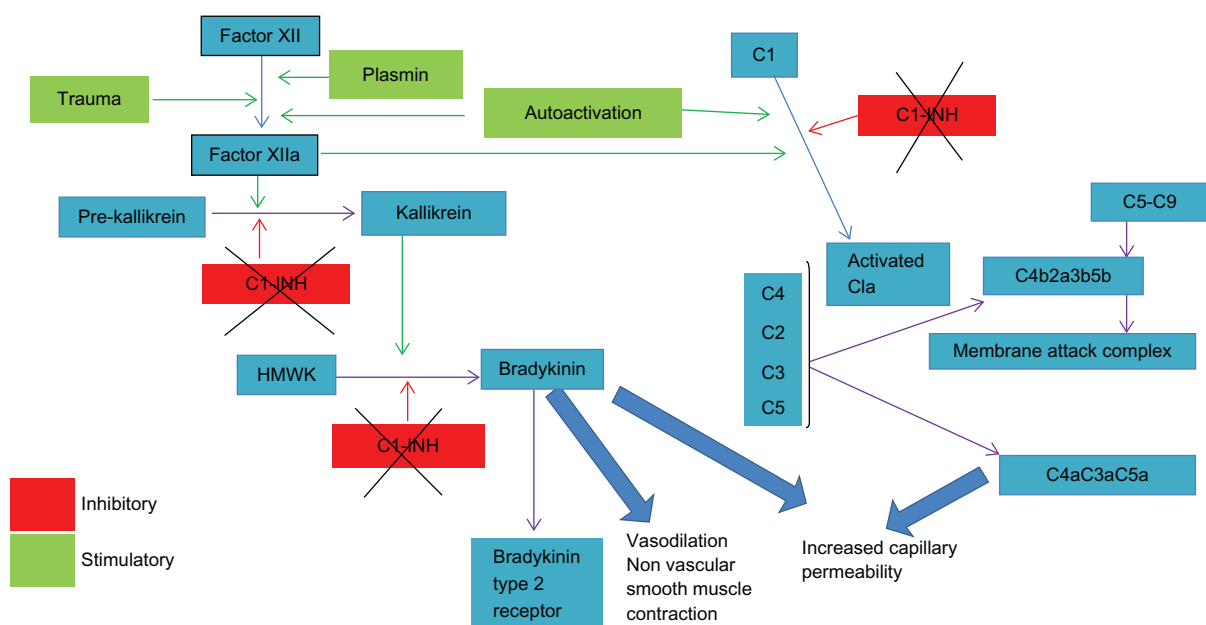

Figure 1 In the absence of normal production of C1-INH in HAE, there is unchecked generation of the bradykinin that binds to B2 receptors on endothelial cells, causing increased vascular permeability, vasodilatation, and smooth muscle contraction.
Abbreviations: C1-INH, C1-inhibitor; HAE, Hereditary angioedema; HMWK, high-molecular-weight plasma kininogens.

asphyxiation secondary to upper-airway obstruction. In undiagnosed cases, mortality can be as high as 30% to 40%.[16,17] The early presenting symptoms can be sensation of tightness or a "lump" in the throat, subtle voice changes, or dysphagia, which can potentially progress to dyspnea due to airway obstruction. Episodes of HAE-associated laryngeal edema usually evolve gradually over a period of several hours; however, more rapid progression from onset to airway obstruction cannot be ruled out.

HAE attacks are usually spontaneous without a clear triggering factor, although local tissue trauma (eg, dental and medical procedures), emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors can trigger attacks.[18,19] Furthermore, HAE attacks are highly variable and unpredictable, which can be a cause of significant anxiety and concern among patients and caregivers.

Diagnosis

It is essential to make an accurate and an early diagnosis of HAE, to avoid encumbrance due to inappropriate medical care and to reduce the mortality associated with undiagnosed cases of HAE, respectively. A detailed history and physical examination is as vital as are the confirmatory laboratory diagnostic tests. In patients with HAE types 1 and 2, laboratory tests indicate markedly decreased C1-INH activity and C4 levels but normal C1q levels, with decreased (type 1), normal, or supranormal but dysfunctional (type 2) levels of C1-INH; however, in type 3, these levels are within normal limits. Some patients with acquired angioedema will also show a marked decrease in C1-INH activity, but with decreased C1q levels.[1] All tests should be carried out on a serum sample that is fresh (drawn less than 4 hours before) or freshly frozen. C4 and C1-INH protein antigen are routine laboratory tests assessed by immunochemistry, but C1-INH functional assays are specialized laboratory tests only done in reference laboratories.[19,20] Both the chromogenic or C1s-binding enzyme-linked immunosorbent assay (ELISA) may be used for C1-INH functional assays; however, the C1s ELISA assay performance may be poor if the manufacturer's normal range (>67%) is used instead of the higher cut-off (84%). Thus, it is necessary that the reference laboratory determines the normal range locally with receiver-operating characteristic (ROC) analysis.[20,22]

Management options

The management of HAE is directed towards treating acute attacks and/or preventing further attacks. Multiple drugs have been available for both approaches since 1970, but, due to the sparsity of controlled studies, consensus guidelines were, until recently, primarily based on observational studies and expert opinions instead of evidence-based recommendations.[19,21,22]

The management guidelines for HAE have been revitalized enormously in the past decade by the emergence of three new drugs and two plasma-derived C1-INH concentrates in the market, after they underwent controlled trials. An evidence-based consensus guideline was reframed by 58 HAE expert physicians named as HAWK (Hereditary Angioedema International Working Group) in an International conference held in Gargnano del Garda, Italy, in September 2010 and published in February 2012.[23] The recommendations, based on high-quality double-blind, randomized, placebo-controlled trials for the treatment of acute attacks "on demand" in all patients (even if asymptomatic) with HAE owing to C1-INH deficiency, indicated that plasma-derived (Berinert®; CSL Behring, King of Prussia, PA, USA; Cinryze®; ViroPharma Incorporated, Exton, PA, USA; Cetor®; San Quin, Amsterdam, Netherlands) and recombinant C1-INH concentrates (Rhucin®in USA, Santarus, Inc, San Diego, CA, USA, /Ruconest™ in Europe; Pharming NV, Leiden, Netherlands), Kallikrein inhibitor ecallantide (Kalbitor®; Dyax Corporation, Cambridge, MA, USA), or bradykinin B2 receptor antagonist icatibant (Firazyr®; Shire Human Genetic Therapies AB, Lund, Sweden) are appropriate and efficacious.[24–28,41] Moreover, it is highly desirable that one of these medications should be made accessible to patients with HAE patients.[23]

The HAWK group also conferred[23] that long-term prophylactic (LTP) treatment was appropriate for patients in whom on-demand acute treatment was not adequate; however, due to lack of evidence-based trials, there was no unanimity about the circumstances under which on-demand treatment would be deemed inadequate and LTP treatment would have a net benefit. There was a marginal consensus recommending LTP treatment if the demand treatment was inadequate only if the expert physician deemed it appropriate for that particular patient; however, many others were of the opinion that inadequate treatment be defined based on an objective criteria such as having more than 24 attacks (including mild ones) per year or more than 12 severe acute attacks per year.[23] For long term-prophylaxis in HAE, two classes of drugs, namely attenuated androgens and plasma-derived C1-INH concentrates, were recommended based on their proven efficacy in clinical trials and practice, with the caveat, however, that 17-alpha androgens should be given

neither to patients under 16 years of age nor to pregnant or lactating women.[23] As far as antifibrinolytic therapy for LTP is concerned, they have been traditionally limited to LTP of patients under 16 years of age in whom other prophylactic agents especially androgens could not be used.[21–23] Moreover, there have been no trials confirming the efficacy in the general patient population, thus this class of medications was not discussed.[23,29]

The HAWK group did not recommend any changes made to the already established consensus guidelines regarding short-term prophylaxis in patients with HAE because of the unavailability of further studies.[23] Prophylactic administration of fresh frozen plasma, C1-INH concentrate, or oral 17-α alkylated androgens before any major surgical or dental procedure is necessary to prevent an acute episode of HAE.[22,30]

Severe upper airway compromise from laryngeal edema necessitates intubation and ventilator support to establish an airway until the resolution of an acute attack. Typically, HAE does not respond to administration of antihistamines, glucocorticoids, or epinephrine.

Icatibant and its role in the management of HAE

Bradykinin, the key element responsible for manifestations of HAE, mediates its effects through a bradykinin B2 receptor, which is constitutively expressed by vascular endothelial and smooth muscle cells. The binding of bradykinin to the B2 receptor on the vascular endothelium results in the generation of various inflammatory mediators, including nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor.[31] It has been shown that local bradykinin concentrations are elevated in patients during an HAE attack.[32,33] Icatibant has demonstrated the reversal of increased vascular permeability in C1-INH-knockout mice. It was also established that mice deficient in the bradykinin B2 receptor as well as C1-INH exhibited lesser vascular permeability compared with the mice that were only deficient in C1-INH.[34] Therefore, the inhibition of receptor binding of bradykinin represents a feasible approach to treating acute attacks of HAE. This has been accomplished by icatibant, a selective and potent bradykinin B2 receptor antagonist that provides a targeted as well as more specific treatment than other currently available treatment options, including replacement therapy with C1-INH, kallikrein inhibitors, or attenuated androgens.[35]

Currently, icatibant injection (Firazyr®) is licensed in 37 countries, and approval was also granted for its self-administration in the EU and US in 2011.[23,40]

Pharmacology, efficacy, and safety/tolerability of icatibant
Pharmacology
Chemistry
Icatibant is a synthetic decapeptide (H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH) with a similar structure to bradykinin except with five non-proteinogenic amino acids.[36] Icatibant has a relatively long shelf life; it retains its stability for up to 6 months at 25°C and up to 24 months at 5°C. Icatibant injections are supplied as 3 mL pre-filled syringes for subcutaneous use.

Preclinical pharmacological assays
Icatibant has been tested in several in vitro and in vivo pharmacological assays. It was shown to be a highly active bradykinin 2 receptor antagonist by displaying high-affinity binding in crude membrane preparations of guinea pig ileum.[36] Compared to other bradykinin antagonists, icatibant was found to be 70 times more potent in smooth muscle preparations.[36] The drug further established its selectivity to bradykinin 2 receptors by demonstrating inactivity in isolated rabbit aorta, which contains the bradykinin 1 receptor type.[36]

Wirth et al tested the potency, duration of action, and tolerability of icatibant in different in vivo models and compared it with the well-known bradykinin antagonist D-Arg-[Hyp2, Thi5,8, D-Phe7] bradykinin.[37] It established itself as highly potent and long-acting inhibitor of bradykinin-induced hypotensive responses in rats. After 4 hours of subcutaneous administration of 20 nmol kg^{-1} of icatibant, significant inhibition was demonstrated by icatibant as compared to D-Arg-[Hyp2, Thi5,8, D-Phe7] bradykinin. Furthermore, it strongly inhibited the bradykinin-induced bronchoconstriction in guinea pigs, which confirmed the findings obtained in the blood pressure experiments in rats.[37] At intravenous doses between 0.1 and 1 mg kg^{-1} of icatibant, carrageenin-induced inflammatory edema of the rat paw was considerably inhibited. Moreover, it demonstrated a very good tolerability in conscious dogs at intravenous doses of 0.01 and 0.1 mg kg^{-1}.[37]

Pharmacokinetics
Icatibant is a highly selective competitive antagonist of the bradykinin B2 receptor with a similar B2 receptor affinity to that of bradykinin, although 100-fold lower for B1 receptor. At higher concentrations (>3.2 mg/kg), agonist activity has been reported, which could explain the local injection-site reactions.[38]

Icatibant has an excellent bioavailability profile with low protein binding and a large distribution volume. Absorption from the local injection site is rapid, reaching its peak concentration in 20 to 30 minutes.[39] Intravenous and subcutaneous formulations were found to have a similar pharmacokinetic profile; however, the subcutaneous route was considered more convenient. Icatibant has demonstrated a poor distribution in adipose tissue and does not appear to cross the blood–brain barrier; however, it crosses the placenta and is excreted in breast milk in rats.[40]

Icatibant is metabolized in the liver and the cleavage products (90% metabolites and 10% intact icatibant) are excreted in the urine.[39] The elimination half-life is 1.2 to 1.5 hours. Liver and renal dysfunction do not affect the pharmacokinetics, nor do weight and sex;[39] however, the clearance of icatibant is reduced in the elderly.[40]

Pharmacodynamics

In Phase III clinical trials, doses of intravenous 0.4 mg/kg icatibant were given as a single dose and subcutaneous doses of 30–45 mg up to three times/day with 6 hours between the doses, which was based on the pharmacological data from the Phase II studies.[40–42] From these data, the optimum calculated subcutaneous dose of 30 mg given up to three times daily was proposed in accordance to the half-life of icatibant and the margin up to the dose levels where agonist reactions may occur.[40] Furthermore, if indicated, administration of a second or third 30 mg dose is favored over a higher single dose, because the duration of action of icatibant is not dose dependent.[40]

At supratherapeutic doses of 3.2 mg/kg or higher, partial bradykinin agonist activity was demonstrated in animal studies, which could explain the local injection-site reactions.[40]

Side effects

Mild-to-moderate local injection-site reactions to icatibant have been reported by patients in Phase III clinical studies.[41,42] Partial agonist activity is implicated as the reason for those local transient injection-site reactions.[41,42] Based on all Phase III trials as well as the data collected from the cumulative exposures of icatibant in the post-marketing setting, the majority of the adverse events reported have appeared to be related to the HAE itself.[40–43] The adverse event rate was found to be similar in icatibant and the placebo group.[41–43] Most commonly reported adverse events were recurrent or worsening angioedema.

Bradykinin is thought to play a cardioprotective role, thus icatibant could potentially impair cardiac function.[44]

This has been demonstrated in animal studies, therefore it is recommended not to use icatibant in patients with acute cardiac or brain ischemia. Bradykinin antagonism could theoretically increase blood pressure; however, intermittent use of icatibant is not considered to be a long-term risk factor for hypertension because of its short duration of action. The concept of bradykinin antagonism could also translate into a decreased antihypertensive effect of ACE inhibitors.[45] It is noteworthy that clinical trials so far have excluded patients on ACE inhibitors.

Special patient populations

To the authors' knowledge, there are, as yet, no available studies on icatibant use in pregnant or lactating mothers; however, a study involving a pediatric patient population is in progress, which will be investigating the pharmacokinetics, tolerability, and safety of icatibant in children with HAE.[46]

Icatibant has demonstrated a satisfactory tolerance in a trial for resistant ascites in liver cirrhosis, wherein patients with severe liver and renal impairment were included.[40]

Efficacy, safety, and tolerability

Based on data from recently conducted high-quality studies,[35,41,42] icatibant has been deemed clinically efficacious for the treatment of acute HAE in the latest international consensus guidelines.[23] In a Phase II, open-label, uncontrolled pilot study, icatibant was administered either as a single subcutaneous (30 or 45 mg) or 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) injection to 15 patients who had experienced 20 attacks.[35] The median time to onset of symptom relief was 1.50, 1.42, and 1.13 hours in the intravenous groups and 0.58 and 0.45 hours in the subcutaneous groups, respectively. In contrast to the untreated attacks, icatibant treatment reduced the mean time to onset of symptom relief by 97%. There were no differences between the 30 mg and 45 mg doses. Median bradykinin concentration was elevated to 48.5 pmol/L (seven times normal) during acute attacks, which, after 4 hours of icatibant administration, decreased to 18.0 pmol/L. This is the first report validating the clinical efficacy of icatibant for cutaneous and abdominal attacks in HAE.[35]

Three Phase III controlled, double-blind, randomized multicenter studies (For Angioedema Subcutaneous Treatment [FAST] trials) have been done to investigate the clinical efficacy and safety of icatibant in the treatment of acute HAE attacks.[41,42] In all three similarly designed studies (FAST-1, -2 and -3), the inclusion criteria were adults above the age of 18 who had a documented diagnosis of HAE type 1 or type 2.

The exclusion criteria included a diagnosis other than HAE type 1 or type 2, concomitant serious illness, pregnancy, and lactating mothers. The FAST-3 trial included additional exclusion criteria, including treatment with angiotensin-converting enzyme inhibitors or any pain medications and previous treatment with icatibant. Furthermore, in both the FAST-1 and -2 trials, patients with potentially life-threatening laryngeal angioedema were treated with open-label icatibant. Additionally, any patient who had a subsequent severe attack in the course of the study, necessitating treatment was included in an open-label extension phase. In FAST-3, patients with mild laryngeal attack were included, but patients with severe laryngeal symptoms were treated in an open-label study. In all three 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. Moreover, in all three trials, response to therapy was measured by visual analog scale as well as the patient/physician-reported symptoms.[41,42]

In the FAST-1 trial[41], 56 patients were randomized to receive either icatibant (n = 27) or placebo (n = 29), whereas in the FAST-2 trial, 74 patients were randomized to receive either icatibant (n = 36) or tranexamic acid (n = 38). A total of eleven patients had laryngeal symptoms and received open-label icatibant in the FAST-1 and -2 trials. Rescue therapy was permitted, but withheld until 8 or 9 hours after study-drug administration.[41]

The primary endpoint was the time to onset of significant relief of index symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) defined by sustained improvement of at least 30% on the visual analog scale for three consecutive measurements. Secondary endpoints included response rate at 4 hours after injection, time to onset of improvement of the index symptom according to the patient and the investigator, time to relief of all symptoms, global assessment and overall patient improvement, and a patient satisfaction questionnaire at week 24.[41]

The primary endpoint was reached in 2.5 hours with icatibant as compared with 4.6 hours with the placebo ($P = 0.14$) and in 2 hours as compared with 12 hours with tranexamic acid in the FAST-2 study ($P < 0.001$). Thus, a statistically significant benefit of icatibant, with regard to the primary endpoint as compared to tranexamic acid, was found in the FAST-2 trial, which was not seen in the placebo-controlled FAST-1 trial. For the secondary endpoints, improvement was significant in FAST-2, whereas a nonsignificant trend to improvement was seen in FAST-1. After post hoc analysis, early use of rescue medications was identified as a reason for

obscuring the benefit of icatibant in FAST-1. There were no reports of icatibant-associated serious adverse events.[41]

In the FAST-3 trial,[42] subjects with moderate-to-severe cutaneous or abdominal symptoms received icatibant (n = 43) or placebo (n = 45). Five subjects with laryngeal (mild-to-moderate) first attacks received icatibant (n = 3) or placebo (n = 2) and five subjects with severe laryngeal first attacks received open-label icatibant. For cutaneous or abdominal attacks, icatibant, in comparison to placebo, significantly reduced time to 50% reduction in symptom severity (2.0 vs 19.8 hours; $P < 0.001$, primary endpoint), onset of primary symptom relief (1.5 vs 18.5 hours; $P < 0.001$, key secondary endpoint), or almost-complete symptom relief (8.0 vs 36.0 hours; $P = 0.012$) and demonstrated a shorter time to initial symptom relief (0.8 vs 3.5 hours; $P < 0.001$). For laryngeal attacks, median time to 50% or more reduction in symptom severity was 2.5 hours with icatibant versus 3.2 hours with placebo. No icatibant-treated subject required rescue medication before symptom relief occurred. The incidence of adverse events was similar in icatibant- and placebo-treated subjects (41% and 52%, respectively). All icatibant-treated subjects experienced injection-site reactions, but none reported clinically relevant changes in safety parameters or serious adverse events.[42]

This study achieved its primary endpoint (statistically significant shorter time to symptom relief) as well as the secondary endpoint (statistically significant shorter time to onset of primary symptom relief). The efficacy results were similar for laryngeal and cutaneous/abdominal attacks. The incidence of adverse events was similar in both the treatment and placebo group. There were no reports of serious adverse events or any clinically significant alterations in safety parameters, except transient local injection-site reactions with icatibant. Overall, this study reaffirmed the efficacy of subcutaneously administered icatibant in the treatment of acute attacks of type 1 and type 2 HAE. Furthermore, the rescue medications were not required before the onset of symptoms in the treatment group, thus establishing the statistical significance that could not be achieved in the FAST-1 trial.[42]

Laryngeal attacks

Eight patients in FAST-1 and three patients in FAST-2 received open-label icatibant for laryngeal attacks and the time to first symptom improvement according to the patient was 0.6 hours and 1.0 hour, respectively. At 4 hours after icatibant administration, nine of the eleven patients were symptom free and the remaining two had mild symptoms.[41]

In the FAST-3 trial, after post hoc analysis, a total of 21 subjects with 21 first laryngeal attacks had received icatibant, including three in the laryngeal attack arm randomized to the double-blind treatment with icatibant and 18 subjects who received open-label icatibant (two in the laryngeal attack arm initially randomized to placebo but who eventually received icatibant, five with severe laryngeal attacks, and eleven from the abdominal and/or cutaneous attack arm treated with open-label extension phase). The median time to 50% or more reduction in symptom severity was 2.5 hours with icatibant versus 3.2 hours with placebo. Time to first symptom improvement was similar for laryngeal attacks in the icatibant population and the icatibant group for the non-laryngeal population in the FAST-1, -2, and -3 trials.[42]

Rescue medication

A larger proportion of the placebo patients in FAST-1 needed rescue medications than in FAST-3, which was suggestive of inferior symptom control in the comparator arm, explaining the lack of significance in the FAST-1 trial and supporting the clinical efficacy of icatibant in FAST-3. In FAST-1, post hoc analysis demonstrated that the primary endpoint adjusted for rescue medication was 2.5 hours with icatibant and 9 hours with the placebo ($P = 0.02$).[41,42]

Self-administration

Since acute attacks of HAE are unpredictable and can be potentially life-threatening if appropriate treatment is not timely, self-administration of medications at home at the onset of the attack could reduce the mortality associated with this disease. This was recommended at the consensus report of the HAWK Group at the international conference,[23] but with a low level of evidence because it is based on observational studies. Nevertheless, a larger prospective, open-label Phase III-b (Evaluation of the Safety of Self-administration with Icatibant [EASSI]) study has recently been conducted to evaluate the safety of self-administration injections. In this study, 56 patients were evaluated for safety and efficacy of self-administering icatibant during an acute attack. If needed, health care professionals administered second and/or third doses. Overall, the study demonstrated that self-administration of icatibant for an acute attack of HAE was generally well tolerated and safe. The times to symptom relief were consistent with the Phase III studies and were similar whether self-administered or administered by a health care professional.[43]

Patient-focused perspectives such as quality of life, patient satisfaction, and acceptability

Quality of life

The debilitating nature of HAE has a life-altering impact on health-related quality of life. However, little is known about the humanistic and economic burden of HAE on patients, caregivers, and health care systems because of the low incidence of the disease.[47] Lumry et al published the first comprehensive study to look at the quality of life of patients with HAE and assess its humanistic burden.[48] It is a web-based survey of patients that entailed collecting information on attack characterization, treatment, side effects, pain, and functional and emotional burden of disease management. A significantly poorer health-related quality of life versus population norms was reported by the patients. HAE patients also demonstrated a higher incidence of depression. A 34% overall work impairment was seen, thus impacting productivity. Workers lost a mean of 3.3 days and students a mean of 1.9 days due to their most recent HAE attack. Thus, it was concluded that HAE results in enormous humanistic burden to patients, affecting both physical and mental health; negative impact on education, career, and work productivity; and substantial economic burdens.[48]

Both acute attacks and the chronic nature of the disease contribute to the substantial economic costs associated with this disease. Before the approval of C1-INH therapy and icatibant in the US, Wilson et al conducted a survey that demonstrated the economic burden associated with HAE.[49] They estimated the total annual per-patient costs at US$42,000 for the average HAE patient. Furthermore, costs increased considerably with increasing attack severity: US$14,000 for patients with mild attacks and up to US$96,000 for patients with severe attacks. High rates of work absence, lower productivity, and lower income were also reported, which in turn contributed to indirect annual costs of US$16,000 for the average patient.[49]

Patient satisfaction and acceptability

Patient satisfaction with health care professional-administered icatibant and their level of interest in self-administration was assessed as part of the open-label extension phases of the FAST-1 and -2 clinical trials in adults by use of a short questionnaire completed by the patients at the 24-week follow-up visit. A total of 94 patients (74.6%; 53 patients in FAST-1 and 41 patients in FAST-2) responded to the questionnaire.[50]

Overall, favorable experiences following treatment with health care professional-administered icatibant were reported by subjects in the FAST-1 and FAST-2 open-label extension phases who responded to the questionnaire. In comparison with their usual therapies for HAE attacks, most patients were more or much more satisfied with the way icatibant relieved their symptoms and were more likely to continue using icatibant upon completion of the study. Furthermore, self-administration of icatibant at home was preferred by the majority of patients.[50]

Conclusion and place in therapy

HAE can be a disfiguring and debilitating illness, thus accurate and timely diagnosis is crucial to decrease the morbidity and mortality associated with it. Over the last few years, there has been a renaissance in the pharmacologic treatment options for HAE, prompted by an improved understanding of pathophysiologic processes. This advent of innovative treatment options has made a positive impact on physical, mental, and social health domains. According to the recently revised international HAWK group consensus guidelines[23] for HAE treatment, 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®) have been deemed suitable for the acute treatment of HAE; however, no head-to-head trials between the five licensed therapies have been conducted to date. Attenuated androgens and plasma-derived C1-INH concentrates were conferred as options for prophylaxis for HAE attacks.

Multiple double-blind Phase III studies and repeated open-label administrations have demonstrated the efficacy and safety of icatibant for the treatment of acute attacks of HAE with considerable reproducibility and consistency, thereby establishing robust evidence for the utility of icatibant in the treatment of acute HAE attacks in adults. The international HAWK group consensus guidelines[23] recommend icatibant as one of the prime options for the acute treatment of HAE. Furthermore, it was emphasized that all patients should carry two doses of a specific treatment and that all patients should be trained for self-administration since the attacks should be treated as soon as they are recognized.

Icatibant is the foremost and the only subcutaneous treatment option for all acute HAE attacks that is licensed for self-administration, therefore, it offers increased patient independence and early effective treatment. It has the advantage of being readily available, offering timely access to effective treatment and thus positively impacting the quality of life of patients affected by HAE and will reduce the need for repeated attendances in emergency departments.[22,23,51] The other drug that is approved for patient self-administration in the US (to treat acute facial and abdominal attacks) and EU (to treat all acute attacks) is Berinert®. The route of administration, however, is only by intravenous infusion after proper training by a health care professional which can delay the initiation of treatment and requires practice and drive on the patient's part. Ecallantide, on the other hand, is only approved for administration in a supervised setting due to the risk of hypersensitivity reactions.[52] Moreover, icatibant is less expensive than ecallantide and has an equivalent cost profile to that of the C1-INH Berinert®.[53] It is important to conduct head-to-head comparisons of recently approved alternatives for treatment of acute attacks, and more cost-effectiveness studies are also required. Of note, Blankart et al analyzed the availability of and access to orphan drugs, which included icatibant, ecallantide, and two complement C1-INHs, and showed substantial copayments can represent important barriers to patient access to treatment.[54] Pricing and reimbursement of orphan drugs have been issues of significant concern. Simoens conducted a literature review to gain more understanding of those issues and established that there is a need for a transparent and evidence-based approach towards orphan drug pricing and reimbursement.[55]

Recently, a study has been published demonstrating the beneficial effect of early on-demand icatibant treatment of HAE attacks.[56] This study could very well strengthen the earlier weak recommendation of the HAWK consensus to treat HAE type 1 and 2 attacks early, regardless of the location and ideally before visible or disabling symptoms occur.[23]

Other than HAE type 1 and 2, there are other types of bradykinin-mediated angioedema, including HAE type 3, acquired angioedema associated with C1-INH deficiency, and angioedema associated with angiotensin-converting enzyme inhibitors,[57,58] wherein icatibant has therapeutic potential given its mechanism of action.[59] A number of case reports have been published.[60–65] The efficacy of icatibant with acute angiotensin-converting enzyme inhibitor angioedema has been reported by Bas et al in a case series of eight patients.[66] After icatibant injection, first symptom improvement was reported at a mean time of 50.6 ± 21 minutes and complete relief of symptoms at 4.4 ± 0.8 hours.[66] A randomized study to evaluate the effectiveness of icatibant in patients with angiotensin-converting enzyme inhibitor-associated angioedema is in progress in the US.[67] Prospective studies

using icatibant in patients with other types of angioedema are much needed.

Disclosure

The authors report no conflicts of interest in this work.

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