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REVIEW

Icatibant in the Treatment of Acute Attacks of Hereditary Angioedema (HAE) in Adults

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Abstract:

Introduction: Hereditary Angioedema (HAE) is a potentially life-threatening condition consisting of recurrent episodes of limb, abdominal, genital, facial or laryngeal swelling. Unregulated bradykinin activity is known to be the main driving mechanism for the characteristic edema flares in HAE. Thus, a bradykinin receptor antagonist is a sensible treatment for acute attacks of HAE.

Methods: A Pubmed literature search was conducted from 2005-present using the search terms *icatibant, HOE 140, angioedema,* and *hereditary angioedema* singly and in combination. Non-English articles were excluded.

Results: Overall, there have been a total of 116 patients (314 attacks) treated with icatibant. Of these attacks, the majority reported the onset of symptom relief within two hours and the resolution of symptoms within 12–24 hours. Thirty patients (9.6%) had recurrent symptoms; five were treated with rescue Berinert, seven were treated with an additional dose of icatibant, and the remainder 18 were given either C1-INH concentrate, anti-emetics, or opiates. The most reported adverse effect from icatibant was a local reaction (swelling, burning, erythema, and itching). Icatibant use has also been reported with ACE-inhibitor induced, acquired, and HAE type III angioedema as well as in one case as prophylaxis.

Conclusion: The numerable new treatments for HAE now gaining favor, including icatibant, provide an exciting opportunity for both patients and providers to take swift control of this disease process.

Keywords: hereditary angioedema, HAE, icatibant

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Introduction

Hereditary Angioedema (HAE) is a potentially life-threatening condition consisting of recurrent episodes of limb, abdominal, genital, facial or laryngeal swelling. The pathophysiology of this inherited condition has been linked to the deficiency (type I) or dysfunction (type II) of C1-inhibitor (C1-INH), an important regulator of the contact-kinin system, resulting in the over-production of bradykinin. Unregulated bradykinin activity is known to be the main driving mechanism for the characteristic edema flares in hereditary angioedema.[1,2] Thus, a bradykinin receptor antagonist is a sensible treatment for acute attacks of HAE.

Bradykinin is produced by the breakdown of high-molecular-weight-kinin (HMWK) through the action of kallikrein (typically inhibited by C1-INH), and, although bradykinin has a very short plasma half-life of approximately 15–30 seconds,[3] patients with HAE have significantly higher levels of plasma bradykinin during an acute attack compared to times of "remission".[1] Bradykinin is primarily degraded by kininase II/angiotensin-converting enzyme (ACE) but can also be degraded by endopeptidase, carboxypeptidase N/kininase I, or carboxypeptidase M and U.[3] There are two identified bradykinin receptors, one constitutively expressed receptor (BR2) and one inducible receptor (BR1); both are located on chromosome 14.[2] The final products of BR2 activation are vasodilatory prostaglandins while the complete function of BR1 is yet to be elicited.[4] BR2 activation leads to the formation of inositol 1,4,5-triphosphate and diacylglycerol with a resultant increase in intracellular calcium. This rise in intracellular calcium activates both endothelial nitric oxide synthase (eNOS) and phospholipase A2, leading to the production of vasoactive nitric acid (NO) and PGI2, respectively.[2] The bradykinin BR2 antagonist, icatibant or HOE 140, has been shown to selectively mitigate the vasodilatory and permeability effects of BR2 activation both in vitro and in vivo.[4–8]

The use of icatibant in the treatment of acute attacks of HAE is gaining clinical support. Overall, there have been a total of 116 patients (314 attacks) treated with icatibant reported in the literature that we were able to identify through a Pubmed search from 2005-present using the search terms icatibant, angioedema, hereditary angioedema, and HOE 140 singly and in combination. Of these attacks, the majority reported the onset of symptom relief within two hours and the resolution of symptoms within 12–24 hours (to be discussed further below). Thirty patients (9.6%) had recurrent symptoms; five of these were treated with rescue Berinert, and seven were treated with an additional dose of icatibant. The 18 recurrences in the For Angioedema Subcutaneous Treatment (FAST) 1 and 2 trials were treated with C1-INH concentrate, anti-emetics, or opiates, and, so, it is not clear how many received additional product administration versus symptomatic management. The most reported adverse effect from icatibant was a local reaction (swelling, burning, erythema, and itching). In the future, it is possible that the use of icatibant may also be expanded to asthma, refractory ascites, allergic rhinitis, pancreatitis, and traumatic brain injury.[3]

Supporting Evidence

Clinical trials

Bork et al was the first to report a phase II dose-finding series of 15 patients (ages 20–61) with 20 attacks, excluding laryngeal attacks, in 2007.[8] Bork's study evaluated symptom relief following either intravenous or subcutaneous administration of icatibant within 10 hours (ranging from 1.9 to 10.3 hours) of the onset of an attack. Improvement following icatibant administration was assessed by the validated visual analog scale (VAS) and later compared to previously untreated attacks experienced by the same patient population. Adverse effects were recorded up to five days following icatibant dosing and included local reactions following subcutaneous injection (all resolved within 24 hours) and headache in one patient four hours after IV infusion.

Patients in Borks' study[8] received icatibant 1.9 to 10.3 hours after the onset of symptoms. The onset of symptom improvement was reported within 30 minutes in 6/20 attacks (30%), within 1 hour for 15/20 attacks (75%), and within 2 hours for 18/20 attacks (90%); the remainder 2/20 (10%) experienced the onset of relief within 5 hours following drug administration. Complete resolution of an attack (with minimal swelling remaining) ranged from 1.5 to 46 hours, with 13/20 attacks (65%) completely resolving within 12 hours and 17/20 attacks (85%) completely resolving by 24 hours. Five of these attacks

had recurrence of symptoms (from 14 to 27 hours after icatibant administration) that were successfully treated with rescue Berinert.

Cicardi et al recently completed two subsequent phase III trials, FAST-1 and FAST-2, comprised of 56 and 74 patients, respectively, presenting within six hours of the onset of abdominal or cutaneous attacks, again excluding laryngeal attacks.[9] Subcutaneous icatibant (30 mg) was compared to placebo in FAST-1 and to tranexamic acid (3 g daily for 2 days) in FAST-2. Cicardi's primary endpoint was sustainable VAS symptom improvement of at least 30% following drug or placebo administration, using intent-to-treat analysis even if rescue therapy or symptomatic treatment (opiates, anti-emetics) was required. Additional data were collected with respect to patient and provider report of the onset of symptom relief as well as the complete resolution of symptoms per VAS scoring. Adverse events were recorded up to at least five days after drug administration and included local reactions, abnormal LFTs, dizziness, and nasal congestion in FAST-1 and local reactions, abdominal pain, nausea, worsening of the acute HAE attack (in one patient), asthenia, and rash in FAST-2. 9/27 (33%) patients in FAST-1 and 6/36 (17%) patients in FAST-2 received rescue medication (C1-INH concentrate, anti-emetic agents, or opiates) within 48-hours of icatibant administration.

Patients enrolled in FAST-1 and FAST-2 ranged in age from 23–45 years-old and 27–53 years-old, respectively. Although the FAST-1 trial did not reach statistical significance when comparing the primary endpoint of icatibant and placebo (2.5 hours versus 4.6 hours, $P = 0.14$), FAST-2 did show superiority of icatibant over tranexamic acid (2 hours versus 12 hours, $P < 0.001$). Both studies demonstrated a trend toward improvement in time to the onset of symptom relief and time to complete resolution (secondary endpoints) when using icatibant. There was significant improvement in time to the onset of symptom relief at 0.8 hours for icatibant-treated attacks versus 16.9 hours for placebo ($P < 0.001$) in FAST-1 and at 0.8 hours for icatibant-treated attacks versus 7.9 hours for tranexamic acid ($P < 0.001$) in FAST-2. Time to complete resolution took 8.5 hours in icatibant-treated attacks versus 19.4 hours for placebo ($P = 0.08$) in FAST-1 and 10 hours for icatibant-treated attacks versus 51 hours for tranexamic acid ($P < 0.001$) in FAST-2.[9]

Although a total of 11 laryngeal attacks were excluded from FAST-1 and FAST-2 trials, these patients also received open-label icatibant and reported onset of symptom improvement at a median time of 0.6 and 1 hours, respectively. Nine of these patients (82%) were reportedly symptom-free at four hours following icatibant administration. Three patients later received additional rescue medication (C1-INH, antiemetics, or opiates) for recurrent symptoms within 24 hours of the initial icatibant administration.[9]

Case reports

Additional case reports have also demonstrated the effectiveness of icatibant for acute attacks. These have included 2 presentations of a 53-year-old woman with type II HAE whose first presentation included GI symptoms that resolved within 30 minutes of being given icatibant 30 mg subcutaneously and whose second presentation included facial swelling that resolved within 2 hours of being given the same dose of icatibant.[10] One 46-year-old woman is reported to have had recurrent attacks (unknown number but previously experiencing about 25 attacks a year) treated with icatibant 30 mg subcutaneously since 2009 after failing prophylaxis with tranexamic acid and not tolerating prophylaxis with androgens.[11] In another report, a 59-year-old patient was treated successfully (although noting local irritation with burning and erythema) with icatibant 30 mg subcutaneously for a total of 38 acute attacks (9 facial, 19 abdominal, 2 limb, 4 genital, and 4 laryngeal) over the course of about 1 year; with respect to laryngeal attacks, the patient reported improvement within 2 hours and complete recovery within 4 hours.[12] Another 34-year-old woman who experienced 12 attacks of acute edema (facial, abdominal, cutaneous, genital) treated with icatibant 30 mg subcutaneously noted symptom improvement in 1 hour and resolution in 24 hours for the majority of attacks; she required a second dose of icatibant in one attack 24 hours after her first dose and experienced local reaction as her only side effect.[13]

Two small case series are also available. In one case series, 5 patients ranging in age from 23–64 were treated with a single dose of subcutaneous icatibant with symptom improvement at 10 minutes-2 hours (median 30 minutes) and significant improvement at 30 minutes-18 hours (median 1 hour); there was 1

Table 1. Therapies for acute attacks of HAE.

Drug name and dosing	Class	Half-life	Negative attributes	Advantages
Icatibant 30 mg SQ	Bradykinin receptor 2 antagonist	1.2–4 h	Short half-life Local injection site reaction Rebound attack	SQ administration Stable at room temperature
Berinert* 20 u/kg IV	Plasma-purified C1-INH	32–46 h	Possible viral transmission IV access required	Long half-life Suitable for prophylaxis
Cinryze 1000 u IV	Plasma-purified C1-INH	36–48 h	Possible viral transmission IV access required	Long half-life Suitable for prophylaxis
Rhucin 50–100 u/kg IV	Recombinant C1-INH	3 h	Short half-life IV access required Possible anaphylaxis *(Rabbit allergy is a contraindication)*	No viral risk
Ecallantide* 30 mg SQ	Kallikrein inhibitor	1–2 h	Short half-life Anaphylaxis Local injection site reaction Headache Transient coagulation prolongation Pyrexia	SQ administration
FFP 2 units IV	Plasma product	NA	Possible viral transmission IV access required Anaphylaxis Worsening HAE attack	Cost
Danazol oral tablet	Androgen	Long	Hyperlipidemia Increased LFTs Hepatocellular carcinoma Multiple other adverse effects Delayed action, thus not good for acute treatment	Suitable for prophylaxis Cost Oral administration

Note: *FDA-approved for the treatment of acute attacks of HAE.

reported complication of pain and swelling at the injection site among these 5 case reports.[10] Malbrán et al also reported a series of 19 patients with 163 attacks (including abdominal, cutaneous, and laryngeal) treated with icatibant within 6 hours of attack onset.[14] There was noted symptom improvement within 90 minutes of drug administration, and VAS scores for abdominal symptoms showed significant reduction between 1–57 hours with icatibant compared to observational patients. A second dose of icatibant was given for 1 attack that failed to respond to the first dose and 6 attacks with recurrence of symptoms within 48 hours.[14]

Advantages

These studies and case presentations contribute to the growing evidence supporting the marketing of icatibant in the future in the United States (icatibant has been approved in Europe since 2008). Desirable characteristics of icatibant include its portability, stability at room temperature, accessibility, and ease of administration. Icatibant is supplied as a 3 mL prefilled syringe and can be stored for six months at room temperature (or one year at five degrees Celsius).[15] Therefore, it can be easily carried or kept at home by patients who may unexpectedly suffer from an acute attack of HAE or who may live outside a radius offering them easy access to a healthcare facility equipped to handle recurrent attacks. While other products may require IV training for administration, icatibant's subcutaneous route has been shown to be as efficacious as intravenous dosing,[15] removing the burden of this skill acquisition for both patient or caregiver while still allowing appropriate management of the disease process. Furthermore, although icatibant undergoes

hepatic metabolism and renal excretion, no dose adjusted appears to be required for patients with hepatic or renal impairment, and, in fact, icatibant has been preliminarily studied and proposed as a treatment of refractory ascites.[3,15] According to animal studies, icatibant crosses the placenta and is also excreted in breast milk, but it is unclear what impact this has or will have on the developing fetus or infant; as such, studies including pregnant women with acute attacks of HAE have not utilized icatibant.[15] Overall the data support that icatibant is effective and is welcome addition for the treatment of HAE.[8–15]

Disadvantages

Icatibant's downsides include the possibility of IgE production, although the risk of allergenicity is low because its 10-amino-acid peptide size is below immune surveillance of lymphoctyes. In addition, allergic reactions and IgE production have not been reported to date despite repeat usage of the product. Another disadvantage is the need for cautious use in patients with ischemic cardiac disease or CVA secondary to the inhibition of vasodilatory properties that may be important for perfusion in these conditions.[16] Icatibant is not approved for use in children, and experience is limited with patients >65-years-old.[17] As noted above, it is not approved for use in pregnancy or during lactation. Lastly, the need for re-dosing is considered by some to be a disadvantage. Overall recurrent or persistent symptoms need a second injection in around 10% of cases and a third injection in 1% of cases. Increased toxicity secondary to the need of re-dosing does not appear to be a concern. These extra doses seem to be tolerated well.[8–14]

Use in Ace-Induced, Acquired, and Hae Type III Angioedema

Although icatibant has been studied only for the use of HAE type I and II, there have also been a variety of case reports citing its success in the treatment of acquired angioedema. Schmidt reported a 42-year-old man with laryngeal edema secondary to ACE-inhibitor therapy who avoided emergent tracheotomy after administration of icatibant 30 mg subcutaneously, which was used following failure to respond to IV steroids, IV diphenhydramine, inhaled epinephrine, and C1-INH concentrate infusion. The man was noted to have improvement 10–15 minutes following administration of the dose.[18] Bas also reported on eight patients with acquired angioedema secondary to ACE-inhibitor use whose acute attacks (four laryngeal, four tongue) responded within one hour to icatibant administration.[19] Studies are being conducted to assess the efficacy of icatibant in ACE-Inhibitor induced angioedema.

Bright reported a 49-year-old male with acquired C1-INH deficiency associated with a Monoclonal Gammopathy of Uncertain Significance (MGUS) who experienced facial swelling following intraoral tag removal; his symptoms began to improve 30 minutes after icatibant was given (having failed C1-INH infusion prophylaxis and treatment for this event).[20] Keller reported a 62-year-old woman with CI-INH deficiency secondary to B-non-Hodgkin lymphoma with recurrent facial swelling previously responsive to CI-INH infusion whose symptoms progressed after C1-INH infusion but responded in 1–2 hours following icatibant 30 mg subcutaneously.[21] Zanichelli reported an 83-year-old man with acquired C1-INH deficiency with 7 prior attacks of facial or laryngeal edema treated (4 times unsuccessfully) with Berinert or tranexamic acid who initially responded to Berinert infusion for an attack of facial edema that later recurred and was treated successfully with icatibant 30 mg subcutaneously with symptom relief noted in 2 hours. Another episode of facial edema was treated initially and successfully with icatibant 30 mg subcutaneously with the onset of symptom relief noted in 30 minutes.[22]

Icatibant has also been used for HAE type III. Bouillet reported three attacks (two abdominal, one abdominal/facial) for three patients with type III HAE who reported symptom resolution by two hours, one attack requiring repeat icatibant administration for recurrence six hours after drug administration.[23] Cicardi also reported response to icatibant for one laryngeal and three facial attacks in a patient lacking complete response to C1-INH treatment.[24]

Use as Prophylaxis

One case study suggests that icatibant may also be used for prophylaxis. A 46-year-old female with known acute HAE attack response to icatibant, having been treated on several occasions with 30 mg subcutaneous with good results, was given icatibant one

hour prior to an ultrasound-guided FNA of a thyroid nodule and experienced no swelling following the procedure, despite having experienced edema and dysnea following a FNA one year prior with no prophylaxis provided.[11] However, due to the short half life of icatibant, it is doubtful to be effective for either short (pre-procedural) or long (chronic preventive) term prophylaxis.

Additional Therapies

Although C1-INH infusion has been considered the standard treatment for acute attacks of HAE for many years, there are an additional four products besides icatibant, briefly reviewed here, being used or under study for the treatment of acute attacks of HAE. Three of the products (Berinert, Cinryze and Ecallantide) are currently approved by the FDA for use in the USA (table 1).

Both Berinert (CSL Behring, Marburg, Germany) and Cinryze (Viropharma Pharmaceuticals Inc., Exton, PA, USA) are human-derived concentrates of C1-INH stored as powders that require reconstitution for use; Cinryze undergoes nanofiltration as part of its purification process. Both have reported half-lives ranging from approximately 35–46 hours, and both have been shown to significantly reduce the time to onset of symptom improvement compared to placebo.[25,26] Berinert was approved for use in HAE acute attacks in the US in October 2009 while Cinryze has only been approved for prophylaxis in the USA for three years.[27]

Rhucin (Pharming, Leiden, The Netherlands) is a recombinant C1-INH produced in rabbit's milk with a half-life of three hours.[28] Four studies totaling 105 acute attacks of angioedema have shown significant improvement in both time to onset of symptom relief and time to complete symptom resolution with the use of Rhucin compared to placebo.[25,26,29–33] Potential drawbacks to Rhucin use include hypersensitivity to rabbit proteins and relapse of an acute attack due to its short half-life.[26] There is an ongoing open-label trial for Rhucin,[32] and it appears that Pharming will need to repeat a phase three study in the USA before final approval.

Ecallantide (Kalbitor®, Dyax Corporation, Cambridge, Massachusetts) is a recombinant kallikrein inhibitor that was approved for use in acute HAE attacks in the USA in November 2009.[34] It is stored as a frozen or refrigerated powder that requires reconstitution and is typically given as a 30 mg subcutaneous injection with a half-life of two hours.[34–37] Two phase III trials (EDEMA 3 and 4) showed statistically significant greater improvement in symptoms as well as greater change in symptoms from baseline compared to placebo at 4 and 24 hours.[25,27] The most commonly reported adverse were headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.[37] Of note, up to 3.9% and 2.7% of patients in clinical trials have experienced anaphylaxis with IV and SC ecallantide administration, respectively,[37] and, hence, it must be administered in a monitored setting by someone experienced in treating anaphylaxis. Because some of the symptoms of HAE may be mistaken with symptoms of anaphylaxis leading to an over-estimate of associated anaphylaxis, it is hoped that the true incidence of anaphylaxis will be determined by post-marketing surveillance.

A New Possibility

Although icatibant has shown remarkable use in shortening the time to onset of symptom relief and duration of attack, symptoms may still persist for many hours following administration of icatibant and other medications for HAE. The short half-life of icatibant of 1–2 hours[15] may predispose to rebound symptoms from continued BR2 stimulation, and it is also theorized that the degradation products, des-Arg-bradykinin and lys-des-Arg-bradykinin, and their target, BR1, also play a role in the duration of an attack and rebound even in the setting of BR2 antagonism.[38] BR1, which is only 36% homologous with BR2, has induced expression on vascular endothelial cells (and additional cell types including neurons, macrophages, fibroblasts, and smooth muscle cells) by the action of IL-1beta or TNF-alpha.[38,39] Unlike BR2, BR1 is not internalized following stimulation, and its activity may persist as stimulation continues through a positive feedback loop of continued inflammatory signaling.[39] Recent data has demonstrated the complete blockage of vascular leakage in endothelial cells treated with plasma from patients experiencing an acute HAE attack when both BR2 and BR1 were antagonized (BR2 by icatibant and BR1 by both R715 and R954), suggesting the possibility of future therapies that may further decrease

the time to complete resolution, prevent rebound, and decrease the risk of progression of an attack.[38] At this time, although BR1 antagonists have been developed and patented by several pharmaceutical groups,[39] there is not an anti-BR1 product currently in clinical study for use in HAE attacks.

Conclusion

HAE is a rare hereditary disorder of life-threatening consequence that had limited treatment options in the United States prior to several years ago. The numerable new treatments now gaining favor, including icatibant, provide an exciting opportunity for both patients and providers to take swift control of this disease process. As additional pathophysiology is elicited and therapeutic options explored, we are hopeful that both the morbidity and mortality associated with HAE will be reduced or eliminated, and we are confident that these advancements are sure to change the way we think of HAE.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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