Management of hereditary angioedema in Japan: Focus on icatibant for the treatment of acute attacks

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Abstract

Hereditary angioedema (HAE) is characterized by unpredictable, recurring and painful swelling episodes that can be disabling or even life-threatening. Awareness of HAE has progressively grown worldwide, and options for treatment of acute attacks and prevention of future attacks continue to expand; however, unmet needs in diagnosis and treatment remain. In Japan, recognition of HAE within the medical community remains low, and numerous obstacles complicate diagnosis and access to treatment. Importance of timely treatment of HAE attacks with on-demand therapies is continually demonstrated; recommended agents per the WAO/EAACI treatment guidelines published in 2018 include C1 inhibitor (C1-INH) concentrate, ecallantide, and icatibant. In Japan, multiple factors contribute to delayed HAE treatment (potentially leading to life-threatening consequences), including difficulties in finding facilities at which C1-INH agents are readily available. Recognition of challenges faced in Japan can help promote efforts to address current needs and expand access to effective therapies. Icatibant, a potent, selective bradykinin B2 receptor antagonist, has demonstrated inhibition of various bradykinin-induced biological effects in preclinical studies and has shown efficacy in treating attacks in various clinical settings (e.g. clinical trials, real-world studies), and HAE patient populations (e.g. with C1-INH deficiency, normal C1-INH). Icatibant was approved in Japan for the treatment of HAE attacks in September 2018; its addition to the HAE treatment armamentarium contributes to improved patient care. In Japan, disease awareness and education campaigns are warranted to further advance the management of HAE patients in light of the unmet needs and the emerging availability of modern diagnostic approaches and therapies.

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Introduction

Hereditary angioedema (HAE) is a genetic disease primarily caused by SERPING1 mutations, leading to deficiency or dysfunction of C1-inhibitor (HAE-1/2).1,2 HAE with normal C1-INH levels (HAE nC1-INH), previously known as HAE type III, is a rare form of HAE whose underlying pathophysiology continues to be progressively elucidated.3 Recognition and understanding of HAE have improved worldwide; however, awareness within the general medical community remains low in Japan, underscoring the urgent need for educational efforts focused on this disease.3

Herein we provide a topline overview of HAE-1/2 and HAE nC1-INH, followed by a focus on icatibant, which has recently been added to the treatment armamentarium for acute HAE attacks in Japan.

Epidemiology and genetic features

HAE-1/2 is estimated to affect approximately 1 in 50,000 people globally.4 In Japan, the estimated number of patients with HAE-1/2 is 2000 to 3000, though only ~450 patients have received a formal diagnosis to date.5 Educational activities aimed at improving knowledge of HAE-1/2 within the general medical community in Japan have been effectively contributing to recognition and diagnosis of this condition.6

In patients with HAE-1/2, ~450 different mutations in SERPING1 have been identified to date. HAE type 1 (accounting for ~85% of cases) involves various mutations throughout the gene that lead to reduced C1-INH protein levels and diminished functional activity. In HAE type 2 (~15% of cases), mutations generally involve single amino acid substitutions and lead to normal or slightly increased measurable levels of C1-INH protein but diminished functional activity.8

The underlying genetic abnormality remains unknown in most cases of HAE nC1-INH; however, associated mutations have been found in select genes, including coagulation factor 12 (F12), angiopoietin-1 (ANGPT1), plasminogen (PLG), and kininogen 1 (KNG1).9-13 HAE with F12 mutations (FXII-HAE) accounts for up to 25% of European patients with HAE nC1-INH.13

To date, 23 different genetic C1-INH mutations have been reported in Japanese patients (including those with HAE-1/2 and undetermined type). Thirteen of these mutations were found in a cohort of 13 unrelated Japanese patients with HAE, 7 of which were novel, and 6 had previously been found in patients from European countries. The patterns and molecular basis of the 23 mutations reported are similar to those of non-Japanese patients.15 Per findings from a patient registry in Japan, mutations in PLG (PLG-HAE) have been reported in 4 Japanese patients from 2 of 20 unrelated families with HAE nC1-INH.16

Pathophysiology

HAE-1/2

A detailed review of HAE pathophysiology is described elsewhere.17 Briefly, bradykinin—a potent vasodilator—is a key mediator of swelling in HAE-1/2 attacks.18 Stimulating synthesis of nitric oxide, epoprostenol, and endothelium-derived hyperpolarizing factor.19 Vascular leakage caused by bradykinin release is mediated primarily through the bradykinin B2 receptor.20 Bradykinin is generated from high molecular weight kininogen (HMWK) via the kallikrein–kinin pathway, wherein autoactivation of FXII generates activated FXII (FXIIa), leading to activation of pre-kallikrein to plasma kallikrein, cleavage of HMWK, and release of bradykinin. In a positive feedback loop, plasma kallikrein further activates FXII to generate more FXIIa, eventually leading to increased cleavage of HMWK and further bradykinin release (Fig. 1).1,2,22

C1-INH is the principal inhibitor of plasma kallikrein and FXIIa in the kallikrein–kinin pathway. A functional deficiency of C1-INH leads to unopposed activity of plasma kallikrein and FXIIa, resulting in excessive production of bradykinin, and consequently to the characteristic manifestation of tissue swelling associated with HAE attacks.18,21

HAE nC1-INH

The mediators involved in HAE nC1-INH remain largely unknown;13 as noted above, to date, mutations in F12, ANGPT1, PLG, and KNG1 have been reported. Plasmin, the active enzyme of plasminogen, is believed to play an important role in both PLG-HAE and FXII-HAE.11 The fibrinolytic (coagulation) pathway is a branch of the contact system—both Factor XI in the coagulation pathway and prekallikrein in the contact system form complexes with HMWK and are activated by Factor XIIa (to Factor Xla and to plasma kallikrein, respectively; Fig. 1).22,24,25 Within the fibrinolytic pathway, plasmin can cleave, and subsequently activate Factor XII.24 In patients with PLG-HAE, mutated PLG may lead to structural changes that modify plg function, ultimately resulting in increased fibrinolysis and enhanced activation of FXII, with subsequent overproduction of bradykinin (Fig. 1).1,2,22 In patients with FXII-HAE, new cleavage sites introduced by select F12 mutations enhance sensitivity of FXII for plasmin-induced activation, resulting in accelerated FXII activation that exceeds the inhibitory capacity of C1-INH and leads to angiœdema.14,26 Recently reported findings suggest that the KNG1 mutation may modify the process of bradykinin formation by causing an amino acid change in HMWK that alters its N-terminal cleavage site for bradykinin. This change may potentially lead to cleavage of mutant bradykinin that has prolonged activity.13

Given the role of ANGPT1 in reducing bradykinin-induced plasma leakage, mutations of ANGPT1 may alter permeability of endothelial cells, resulting in angiœdema.21

Clinical manifestations

Symptoms

HAE-1/2 manifests as recurrent episodes of painful, nonpruritic, nonerythematous swelling of subcutaneous or submucosal tissues throughout the body, including the face, neck, extremities, genitals, gastrointestinal tract, or upper airways.27-29 Symptoms recur throughout patients’ lives with unpredictable frequency and severity (sometimes in the absence of identifiable triggers or pruridromes), and when affecting the airways can be life-threatening due to risk of asphyxiation.30

While some observations suggest that differences in HAE symptoms may exist between Asian and non-Asian populations (for example, occurrence of attacks affecting the GI tract may be less common in the latter group),31-34 other analyses show that clinical features reported in Japanese patients are generally similar to those in Western populations, including the occurrence of abdominal and respiratory symptoms.15 In one retrospective questionnaire survey of Japanese physicians evaluating data from 171 HAE patients (108 of whom had HAE-1/2), a mean frequency of 6.2 attacks per patient per-year was reported.4 Airway obstruction, requiring emergency airway management such as intubation and/or tracheotomy, affected ~10% of patients.4
HAE nC1-INH primarily manifests in females and estrogens appear to induce and/or worsen symptoms; age at symptom onset is generally older compared with HAE-1/2. The average attack frequency is lower than with HAE-1/2; however, duration of attacks tends to be prolonged. Facial and tongue swellings are more common, whereas abdominal attacks are less frequent. A family history is present in >50% of patients. Most patients with HAE nC1-INH do not experience prodromal symptoms prior to onset of attacks.

Impact of symptoms on daily life

HAE-1/2 attacks negatively impact ability and/or desire to attend school, work, travel, or participate in social events. Absenteeism from school or work increases with worsening attack frequency and/or severity. In a retrospective study of 94 Japanese physicians caring for patients with HAE (87 of whom were employed), 6.9% of patients reported absences of >10 days due to HAE-related symptoms. Attacks affecting the face or extremities can be disfiguring. Emotional impairment and reduced quality of life have been reported even between attacks, and patients often suffer from depression and anxiety.

Diagnosis-related challenges

Globally, HAE-1/2 is an under-recognized disease because its signs and symptoms are nonspecific and can mimic multiple disorders. Misdiagnosis can lead to unnecessary interventions, including surgery (such as appendectomy) or other invasive procedures. A retrospective study of Japanese patients with HAE-1/2 found that patients experiencing abdominal attacks may have leukocytosis and high hematocrit levels in the presence of low C-reactive protein levels, which can be confused with acute abdominal pain requiring emergency surgery.

Long delays in diagnosis have been reported. In an observational, real-world study in patients with HAE-1/2, the median delay in diagnosis was 8.5 years. In Japan, the diagnostic delay may be even longer due to a low disease awareness. Findings from a retrospective study of 171 Japanese patients with HAE reported a mean (range) delay of 13.8 (0–58) years from onset of initial HAE symptoms to diagnosis.

Overview of HAE diagnosis

HAE-1/2

Diagnosis of HAE-1/2 is generally made based on the presence of clinical symptoms and confirmatory laboratory findings. Various clinical manifestations may be present, including a history of recurrent subcutaneous or submucosal angioedema without wheals or urticaria; recurrent, painful abdominal symptoms; and swelling of the upper airways. Although most patients with HAE-1/2 (>75%) have a positive family history, de novo mutations in the C1-INH gene occur in ~25% of patients. Similarly to findings in Western populations, 2 retrospective evaluations of Japanese patients with HAE revealed that 78%–82.6% of patients had a positive family history. Monitoring for a family history is thus informative when a diagnosis of HAE-1/2 is suspected. Indeed, treatment guidelines emphasize the importance of screening family members of patients diagnosed with HAE, including children, siblings, parents, and grandparents.

Symptoms of HAE-1/2 can occur at any age but usually begin before the age of 20, including in Japanese patients. In a literature analysis of 132 Japanese patients with HAE, onset of symptoms often occurred from 10 to 19 years of age. However, a questionnaire study of Japanese physicians caring for 171 HAE patients (108 of whom had HAE-1/2) reported a mean age at first symptom onset of 24 years, possibly reflecting a low disease awareness and late recognition of symptoms.

Additional manifestations suggestive of HAE-1/2 may include a lack of response to treatment with antihistamines, glucocorticoids, or epinephrine, as well as occurrence of prodromal symptoms. However, HAE attacks can occur in the absence of identifiable prodromes or triggers.

Confirmatory laboratory testing is an integral aspect of HAE-1/2 diagnosis. Patients with HAE-1/2 have low (<50%, type 1) or normal/elevated (type 2) C1-INH protein levels, and low C1-INH functional activity (<50%). Low C4 levels in the presence of low C1-INH functional activity has been shown to have a 98% specificity for HAE-1/2. The current World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines (published in 2018) recommend assessing blood levels of C1-INH protein and function and C4 for all patients in whom HAE-1/2 is suspected. If any of these parameters are low, these tests should be repeated to confirm diagnosis. Japanese HAE treatment guidelines recommended testing C1-INH functional activity and C4 levels; C1-INH protein concentration testing is not covered by public health insurance.

A recap of considerations in the diagnosis of patients with HAE-1/2 is shown in Supplementary Table 1.

HAE nC1-INH

A diagnosis of HAE nC1-INH should be considered in patients with a history of recurrent angioedema without hives whose attacks are unrelated to medication use, in whom levels of C4, C1-INH protein, and C1-INH function are normal or near-normal, and for whom high-dose antihistamines are ineffective at relieving symptoms of attacks. Additional considerations include presence of a positive family history of HAE, as well as exacerbation after exposure to increased levels of estrogens and a tendency for attacks involving the upper airways, face, or tongue. Mutations in F12 are detected in up to 25% of patients in Europe. Mutational analysis is available in some research laboratories for ANGPT1, PLG, and KNG-1. A recap of the currently suggested diagnostic strategy for HAE nC1-INH based on consensus criteria is shown in Supplementary Table 2.

Treatment approach

An overview of the currently recommended guidelines for the treatment of HAE appear below and are summarized in Supplementary Figure 1. Importantly, licensing of HAE therapies varies by country; currently approved therapies for HAE-1/2, based on product labeling in the United States, European Union, Australia, and Japan, are shown in Supplementary Table 3. Additional investigational molecules are being studied for HAE, such as an oral plasma kallikrein inhibitor, BCX7353, for HAE prophylaxis. Sites of action of currently marketed agents are shown in Figure 1.

HAE-1/2

All acute HAE-1/2 attacks should be considered for treatment as early as possible with on-demand therapy, and all patients should be considered for self-administration training or home administration. At all times, patients should carry a sufficient amount of on-demand medication to treat 2 attacks. Recommended treatments include IV-administered plasma-derived or recombinant C1-INH concentrate, ecallantide, or icatibant (based on randomized,
Fig. 1. Complement, contact, and fibrinolytic systems in hereditary angioedema.²² Reprinted with permission from: Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382:1136-48. Copyright ©2020 Massachusetts Medical Society. All rights reserved.
double-blind studies). If these agents are not available, solvent detergent-treated plasma or fresh frozen plasma can be used (based on low-level evidence). Short-term prophylaxis is recommended prior to medical procedures that can trigger an attack; however, high-quality evidence is lacking (recommendations are based on nonrandomized or nonblinded trials, or retrospective observational studies). C1-INH agents are the treatment of choice for short-term prophylaxis; select agents are licensed for this indication in the EU, Australia, and Japan [Supplementary Table 3]. Additional recommendations (based on off-label use) include attenuated androgens, or fresh frozen plasma. Although tranexamic acid is licensed for HAE in Australia and Japan without restriction, its use is generally not recommended for short-term prophylaxis. In Japan, tranexamic acid is licensed for the treatment of urticaria rather than HAE (HAE is considered a subtype of urticaria within the Japanese treatment guidelines for urticaria).

The need to initiate long-term therapy should be considered in all patients whose quality of life is significantly impacted by HAE (based on disease activity, attack frequency, etc.), and the need to treat should be reassessed each physician visit or at least once yearly. Importantly, on-demand medication should always be available for breakthrough attacks, including those occurring during long-term prophylactic treatment. Recommended first-line options include IV or SC pdC1-INH agents (use of SC C1-INH is based on findings from the phase 3, placebo-controlled, double-blind, randomized COMPACT study (NCT01912456)), as well as the monoclonal antibody inhibitor of active plasma kallikrein, lanadelumab (based on findings from the phase 3, randomized, double-blind, placebo-controlled HELP Study (NCT02586805)). Androgens have shown heterogeneous effects in the prevention of HAE attacks in some patients and are not considered first-line therapy. Critical appraisal and diligent patient monitoring is required with androgen use given their anabolic and androgenic effects and contraindications. Anti-fibrinolytics (i.e., tranexamic acid) are not a recommended treatment for long-term prophylaxis; data demonstrating their efficacy are scarce and these agents have been shown to be less effective than newer HAE medications, including in a randomized controlled trial comparing efficacy versus icatibant for treatment of acute attacks (discussed below). They may represent an option when other modern treatments are not available and androgens are contraindicated.

**HAE nC1-INH**

Controlled clinical studies in patients with HAE nC1-INH are lacking. To date, efficacy has been evaluated in observational studies but not in randomized controlled trials. Given that Bradykinin is believed to be a mediator involved in the underlying pathophysiology of HAE nC1-INH, treatments used for HAE-1/2, including bradykinin-targeted therapy and C1-INH agents, are in principle expected to have some effects in this patient population. For instance, findings from case reports have shown beneficial effects of icatibant for the acute treatment of attacks in patients with HAE-FXII or HAE-PLG; and with C1-INH agents in patients with HAE-FXII. The recently published International/Canadian guidelines recommend both icatibant and pdC1-INH for the treatment of acute attacks in patients with HAE nC1-INH, based on available evidence from non-controlled studies. Notably, in Japan, use of icatibant, as well as weight-based intravenous pdC1-INH for the treatment of acute HAE attacks is covered by insurance plans regardless of the HAE type; thus, patients with HAE nC1-INH are eligible for coverage. For long-term prophylaxis, findings from case reports have shown encouraging efficacy with the use of tranexamic acid in some patients with HAE-PLG or HAE-FXII. Given the hypothesized role of the kallikrein–kinin cascade (particularly Factor XII) in the underlying pathophysiology of HAE nC1-INH, lanadelumab may have a place in therapy for the long-term prevention of HAE attacks as an inhibitor of active plasma kallikrein.

**Treatment of HAE in Japan**

**Treatment options**

Per current treatment recommendations published by the Japanese Association of Complement Research, C1-INH therapy is the recommended treatment for acute, nonlaryngeal attacks. It should be noted that these recommendations were developed prior to the approval of icatibant in Japan for on-demand treatment of acute HAE attacks. Tranexamic acid is a second-line choice when C1-INH replacement is not available. For acute laryngeal attacks, C1-INH therapy or endotracheal intubation or tracheostomy are recommended. These guidelines also state that, for short-term prophylaxis (prior to higher-risk procedures), administration of C1-INH is recommended.

Long-term prophylaxis should be considered for patients who experience attacks more often than once a month, symptoms more often than 5 days a month, or laryngeal attacks. Importantly, based on the current WAO/EAACI HAE management guidelines, these recommendations alone are no longer adequate in determining a need for long-term prophylaxis, as this decision may vary among patients based on individual patient-related factors and should not be determined solely by the frequency or location of attacks. Tranexamic acid and danazol are currently the only available treatment options for long-term prophylaxis in Japan and they are recommended for this use per current Japanese guidelines. It should be noted, however, that danazol is not licensed for the treatment of HAE in Japan, and, as mentioned previously, tranexamic acid is licensed for the treatment of urticaria rather than HAE. Furthermore, a systematic review evaluating use of tranexamic acid for on-demand and prophylactic treatment of HAE attacks in patients with HAE-1/2 demonstrated lower efficacy compared with other on-demand and prophylactic treatments. A large unmet need therefore exists for improved access to effective therapies.

HAE treatments are increasingly being studied in Japanese patients. For instance, the safety and efficacy of fixed-dose IV pdC1-INH in the prevention of attacks and treatment of breakthrough attacks in 8 Japanese patients with HAE-1/2 were demonstrated in an open-label, single-arm, phase 3 study (NCT02865720). Additionally, safety of lanadelumab was evaluated in healthy Japanese subjects (NCT03401671), and a phase 3, open-label study evaluating safety and efficacy of lanadelumab in Japanese patients with HAE-1/2 is ongoing (NCT04180163). Also, the efficacy of BCK7353 in preventing HAE attacks in Japanese patients with HAE-1/2 is currently being studied (NCT03873116).

**Challenges and unmet needs**

As mentioned above, prior to the approval of icatibant, C1-INH was the therapy of choice for the acute treatment of HAE attacks in Japan. Due to multiple factors, C1-INH agents appear to be underused by Japanese patients, including the fact that self-administration is not approved, so patients are unable to treat acute attacks at home. Additionally, finding a medical facility at
which these agents are readily available may be challenging, as these treatments are costly to keep in stock.60

The lack of reliable access to acute treatment of HAE attacks with C1-INH agents can be potentially life-threatening.55 For instance, a case report published in 2018 describes the case of a 42-year-old patient with HAE living in a remote area of Japan who was unable to access pdC1-INH at the initial hospital at which he sought care, and experienced a cardiopulmonary arrest after suffocating during an HAE attack. He was eventually treated with pdC1-INH at a different facility and recovered; however, this case underscores the large unmet need that continues to exist in Japan for timely access to HAE treatments.51

Medical associations such as the Japanese Dermatological Association and the Japanese Association for Complement Research are making efforts to improve access to C1-INH medications in Japan.50 Additionally, icatibant is now approved for self-administration in Japan (discussed below), which can further help to address the current challenges with immediate access to acute treatment.

Icatibant for the treatment of acute HAE attacks

The critical role of bradykinin in mediating vascular permeability and tissue swelling in HAE-1/2 provides a strong rationale for its blockade in the treatment of HAE attacks.23 Bradykinin antagonists reduce angioedema by blocking the binding of bradykinin to its receptor (Fig. 1),22 thus preventing vasodilation and increased capillary permeability.24 The first generation B2-selective antagonists, developed in the mid-1980s, had limited potency and metabolic stability,93 leading to the later discovery of the second generation B2 receptor antagonist, icatibant, which addresses these limitations.94,95

Icatibant is a potent, selective, and competitive B2 receptor antagonist that is a synthetic decapeptide with a structure similar to bradykinin, but containing 5 amino acids that are non-proteinogenic.33–36 Icatibant has demonstrated inhibition of various bradykinin-induced biological effects in preclinical studies in vitro and in vivo,58,99 including efficacy in reducing bradykinin-mediated vascular permeability in C1-INH knockout mice.97

Icatibant is not degraded by major enzymes that cleave bradykinin.23,26 Its relative binding affinity for the bradykinin B2 receptor is IC50 1–10 nmol/l, similar to bradykinin.58,99 Pharmacokinetic properties of icatibant are shown in Supplementary Table 4.95,100–103

Icatibant was approved for the treatment of acute HAE attacks in the European Union in 200864 (with label extension for use in children aged >2 years in 2017)104; in the United States in 2011105; and in Japan in 2018.60 It is estimated that as of July 2019, 620,000 HAE attacks have been treated with icatibant in post-marketing clinical practice worldwide (Takeda data on file).

Overview of findings from clinical studies

Efficacy in the treatment of acute HAE-1/2 attacks

The efficacy of icatibant for the treatment of acute attacks in patients with HAE-1/2 has been demonstrated in several pivotal studies (summarized in Table 1).95,97,102,105–108 In Japan, approval was supported by data from a phase 3, single-arm, open-label study in Japanese patients with HAE-1/2.102 Median time to onset of symptom relief (defined as 50% reduction from baseline in the patient composite visual analog scale score) was 1.75 h, and median time to almost complete symptom relief was 5.98 h.102

Findings from another study also suggest that HAE attack duration may be shorter following icatibant treatment than with other on-demand therapies. A prospective, observational, single-center study evaluated on-demand treatment of HAE attacks in 227 patients over an average of 21.4 months.109 Duration of attacks treated with icatibant (median 8 h) or weight-based pdC1-INH (median 11.5 h) was significantly shorter than for those treated with tranexamic acid (38 h) or untreated attacks (45 h). Time from first administration of acute treatment to complete resolution was shorter in patients receiving icatibant (median 5.5 h) than in those treated with pdC1-INH (median 8 h); however, this study was not designed to compare efficacy differences between these 2 agents.109

Efficacy in pediatric patients and adolescents

A phase 3, open-label study evaluated a single 0.4 mg/kg icatibant subcutaneous dose for the treatment of acute HAE attacks in 22 children and adolescents (aged 2 to <18 years) with HAE-1/2.110 TOSR was the primary endpoint, defined as the earliest time after icatibant administration at which >20% improvement was achieved in the composite investigator-assessed symptom score. Icatibant demonstrated rapid relief in this patient population; median TOSR was 1.0 h (95% CI 1.0–1.1).110 These positive findings led to the expansion of the icatibant label in the EU to include use in children aged ≥2 years and adolescents.104 In part 2 of this study, 9 adolescent patients received up to 2 additional icatibant injections for the treatment of acute HAE attacks. Findings were similar to those in part 1 of the study: median TOSR was 1.0 h (95% CI 1.0–2.3) for the second exposure (n = 9), and 1.1 h (95% CI 1.0–3.0) for the third exposure (n = 8).111

Efficacy of self-administration of icatibant/importance of early treatment of attacks

Positive treatment outcomes have been demonstrated with self-administration of icatibant and early treatment of acute attacks; findings from select studies on icatibant self-administration are summarized in Supplementary Table 5.112–117 HAE consensus recommendations encourage self-administration of icatibant, as this helps enable early access to treatment, thus reducing patients’ reliance on hospital services for treatment of acute attacks.6,118 In Europe, icatibant was licensed for self-administration in 2011.119

In Japan, icatibant can be self-administered once a physician confirms that the patient has received appropriate training and education.70 The ability to self-administer acute treatment in a timely manner upon attack onset, as recommended by international guidelines, is particularly relevant for patients in Japan, given the above-mentioned challenges they face in gaining timely access to C1-INH agents in hospitals.

Effectiveness of a single icatibant dose

Per findings from pivotal clinical trials or their open-label extensions, as well as from the Icatibant Outcome Survey (IOS) registry, most HAE attacks are effectively treated with 1 injection of icatibant; the percentage of attacks requiring >1 dose of icatibant is ~10%.103–106,108,115,116,120 In one IOS analysis (based on 632 attacks in 170 patients with HAE type 1/2), a single icatibant dose was used for 87.2% of self-treated attacks and 91.9% of healthcare professional–treated attacks.115 In IOS patients in Germany, 97.1% of icatibant-treated attacks were treated with a single dose of icatibant, compared with 91.6% of attacks treated in other IOS countries.116
Table 1
Key findings from pivotal icatibant clinical studies.

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<th>Study</th>
<th>Efficacy</th>
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<td><strong>Dose-finding study</strong>&lt;br&gt;Open-label, dose-finding pilot study</td>
<td>• Evaluated efficacy of IV icatibant 0.4 mg/kg or 0.8 mg/kg, and SC icatibant 30 mg or 45 mg in 15 adult patients with cutaneous or abdominal HAE attacks (Bork K et al., 2007)</td>
<td>• Symptom severity improved within 4 h of dosing, regardless of route of administration</td>
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<td><strong>Pivotal trials: phase 3, For Angioedema Subcutaneous Treatment (FAST) studies: double-blind, randomized, prospective multi-center trials</strong>&lt;br&gt;FAST-1: Icatibant 30 mg SC (n = 27) vs. placebo (n = 29) [patients with cutaneous or abdominal attacks] (Cicardi M et al., 2010)</td>
<td>• Median time to clinically significant relief of the index symptom (primary endpoint): 2.5 vs. 4.6 h with icatibant and placebo, respectively (P = 0.14)</td>
<td>• No serious AEs were reported</td>
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<td>• Icatibant achieved a significantly shorter median time to first symptom improvement vs. placebo, both when evaluated by the patient (0.8 vs. 16.9 h, respectively; P &lt; 0.001), and the investigator (1.0 vs. 5.7 h, respectively; P &lt; 0.001)</td>
<td>• No icatibant-related serious AEs were reported.</td>
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<td>FAST-2: Icatibant 30 mg SC (n = 36) vs. tranexamic acid 3 g daily for 2 days (n = 38) [patients with cutaneous or abdominal attacks] (Cicardi M et al., 2010)</td>
<td>• Median time to clinically significant relief of the index symptom (primary endpoint): 2.0 vs. 12.0 h with icatibant and tranexamic acid, respectively; P = 0.001</td>
<td>• No reports of serious AEs (including icatibant-related serious AEs), however 2 patients treated with icatibant experienced ≥1 severe AE</td>
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<td>• Icatibant achieved a significantly shorter time to first symptom improvement vs. tranexamic acid, both when evaluated by the patient (0.8 vs. 7.9 h, respectively; P &lt; 0.001) and the investigator (1.5 vs. 6.9 h, respectively; P &lt; 0.001)</td>
<td>• Median time to 50% reduction in symptom severity (primary endpoint): 2.0 vs. 18.3 h; P &lt; 0.001</td>
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<td>FAST-3: Icatibant 30 mg SC (nonlaryngeal population, n = 43; laryngeal, n = 3) vs. placebo (nonlaryngeal population, n = 45; laryngeal, n = 2) (Lumey WR et al., 2011)</td>
<td>• Median time to 50% reduction in symptom severity (primary endpoint) was 2.0 h with icatibant vs. 19.8 h with placebo (P &lt; 0.001)</td>
<td>• Median time to onset of symptom relief (secondary endpoint) was significantly shorter with icatibant vs. placebo (1.5 vs. 18.5 h; P &lt; 0.001) and the investigator (1.5 vs. 6.9 h; P &lt; 0.001)</td>
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<td>• Onset of primary symptom relief (secondary endpoint) was significantly shorter with icatibant vs. placebo (1.5 vs. 18.5 h; P &lt; 0.001) and the investigator (1.5 vs. 6.9 h; P &lt; 0.001)</td>
<td>• Median time to onset of symptom relief: 2.5 vs. 4.6 h with icatibant and tranexamic acid, respectively; P &lt; 0.001</td>
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<td>• 81.9% of patients reported AEs; most were mild-to-moderate</td>
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<td>• 97.2% of patients for the first through fifth treated attack</td>
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<td>• 20 serious AEs and 17 severe AEs were reported; none were considered related to treatment</td>
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<td>• For cutaneous and/or abdominal attacks, median time to onset of primary symptom relief ranged from 1.0 to 2.0 h for attacks 1 through 10</td>
<td>• All patients experienced ISRs</td>
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<td>• For laryngeal attacks, time to initial symptom improvement (as assessed by patients) ranged from 0.1 to 5.3 h</td>
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<td>• For cutaneous and abdominal attacks, TOSR for primary symptom was consistent regardless of number of attacks (median [95% CI]): 2.0 [1.5–2.5] h</td>
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<td>• A single injection was successfully administered to 89.8% of patients</td>
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<td>• 6 icatibant-related severe AEs were reported (headache [n = 3], pain [n = 1], dyspepsia [n = 1], noncardiac chest pain [n = 1]), as well as 2 icatibant-related serious AEs (arrhythmia [n = 1]; noncardiac chest pain [n = 1]).</td>
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<td>• ISRs (mostly mild to moderate) were reported in 94.6–98.2% of patients for the first through fifth treated attack</td>
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<td>Open-label extensions of the FAST studies</td>
<td><strong>FAST-1:</strong> Data from 72 patients receiving icatibant for 340 attacks (Malbran A et al., 2014)</td>
<td>• For cutaneous and/or abdominal attacks, median time to onset of primary symptom relief ranged from 1.0 to 2.0 h for attacks 1 through 10</td>
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<tr>
<td></td>
<td>• For cutaneous and/or abdominal attacks, median time to onset of primary symptom relief ranged from 1.0 to 2.0 h for attacks 1 through 10</td>
<td>• 97.2% of patients reported ISRs; most were mild to moderate and spontaneously resolved</td>
</tr>
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<td></td>
<td>• For cutaneous and/or abdominal attacks, TOSR for primary symptom was consistent regardless of number of attacks (median [95% CI]): 2.0 [1.5–2.5] h</td>
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<td><strong>FAST-2:</strong> Data from 54 patients receiving icatibant for 374 attacks (Bas M et al., 2013)</td>
<td>• Median time to onset of symptom relief: 1.9–2.1 h</td>
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<td>• Most patients (92.7–100%) required a single icatibant injection for the first through fifth treated attack</td>
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<td><strong>FAST-3:</strong> Data from 88 patients with 1–5 icatibant-treated attacks at any location (Lumey WR et al., 2015)</td>
<td>• Median time to onset of symptom relief was 1.75 h and time to almost complete symptom relief was 5.98 h</td>
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<td>• No icatibant-related serious AEs were reported.</td>
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<tr>
<td>Phase 3, open-label study in Japanese patients</td>
<td>• Evaluated efficacy and safety of icatibant 30 mg in 8 Japanese patients who experienced an attack affecting the skin (n = 4) abdomen (n = 3), or larynx (n = 1) (Hide M et al., 2018)</td>
<td>• Median time to onset of symptom relief was 1.75 h and time to almost complete symptom relief was 5.98 h</td>
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<td>• No icatibant-related serious AEs were reported.</td>
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</table>

AE, adverse event; ISR, injection-site reaction; SC, subcutaneous.
Efficacy in patients with HAE nC1-INH

Published findings on efficacy of icatibant in patients with HAE nC1-INH are beginning to emerge but remain scarce. In a case report of 3 women with HAE nC1-INH, 2 of the 3 patients (1 of whom had an identifiable F12 mutation) experienced complete resolution of symptoms within 1–2 h of a single dose of icatibant, and 1 patient required 2 doses to achieve complete symptom relief.24 Recently reported findings from case reports also demonstrate efficacious use of icatibant in treating acute attacks in patients with the PLG mutation.18,87

In a study evaluating French patients enrolled in the IOS, median time to attack resolution was significantly longer in patients with HAE nC1-INH (20.0 h) versus those with HAE type 1 (14.0 h, P = 0.021). The reasons for this difference remain unknown.24 Findings from a retrospective chart review study show encouraging efficacy with use of icatibant in patients with HAE nC1-INH (mutation unknown) in Manitoba, Canada; for 3 of 4 patients for whom time to symptom improvement was captured, symptoms improved within 45 min post icatibant injection.51

Safety/tolerability

Icatibant is generally well tolerated; safety findings from pivotal clinical studies are summarized in Table 1.19,85,102,105 The majority of patients experiencing adverse reactions with icatibant treatment report transient, mild to moderate injection-site reactions (ISRs).36,64,105

Long-term safety of icatibant was evaluated using data from the IOS (based on 3025 icatibant-treated attacks in 557 patients).122 For the majority of treated patients (78.6%), there were no reported AEs. Excluding off-label use and pregnancy-related events, a total of 3.1% patients experienced 43 AEs considered probably or possibly related to icatibant, of which general disorders and administration site conditions were most common (53.5%). Three serious events were possibly or probably treatment-related — gastritis and reflux esophagitis (in one patient with HAE type 1) and drug inefficacy (in one patient with HAE nC1-INH). No icatibant-related serious AEs occurred in patients with cardiovascular disease.122

Dosing and administration

Icatibant is formulated for subcutaneous administration as a single 3-mL (30-mg) prefilled injection, to be preferably administered in the abdominal area. If insufficient relief is achieved or symptoms recur after 1 dose, icatibant injection may be repeated after > 6 h, with a maximum of 3 injections per 24 h. After receipt of proper training by a healthcare professional, patients can self-administer icatibant upon recognition of an HAE attack.56,76

Summary

Significant unmet needs continue to exist in Japan with regard to knowledge about HAE and timely access to effective treatments. Icatibant was shown to be effective and well-tolerated for the treatment of acute HAE attacks and has been additionally studied in the Japanese population, leading to its recent approval in Japan. Clinical development programs focusing on long-term prevention of HAE attacks in Japan are ongoing. Disease education efforts are warranted to further advance patient care in light of the unmet needs and the emerging availability of modern diagnostic approaches and therapies.

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Research and Development employees of Shire, a Takeda company, were involved in reviewing drafts of this manuscript for scientific accuracy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.07.008.

Conflict of interest

MH has received speaker/advisor honoraria from BioCryst, CSL Behring, and Shire,* and has received institutional research funding from CSL Behring. TH has received honoraria as a speaker from CSL Behring and Shire.* IO has received speaker/advisor honoraria from BioCryst, CSL Behring, and Shire.* IA is a full-time employee of Shire* and holds stock/stock options in Takeda. AF has received fees for speaking from Shire* and CSL Behring.

*A Takeda company.

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