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Original Article

Efficacy, pharmacokinetics, and safety of icatibant for the treatment of Japanese patients with an acute attack of hereditary angioedema: A phase 3 open-label study^{*}



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ABSTRACT

Background: Hereditary angioedema (HAE) is a genetic disease characterized by recurrent swelling episodes affecting the skin, gastrointestinal mucosa, and upper respiratory tract.

Methods: A phase 3, single-arm, open-label study was performed to evaluate a selective bradykinin B_2 receptor antagonist, icatibant, for the treatment of acute attacks in Japanese patients with HAE Type I or II. After the onset of an acute attack, icatibant 30 mg was administered by the patient or a healthcare professional via subcutaneous injection in the abdomen.

Results: Eight patients who had an attack affecting the skin (n = 4), abdomen (n = 3), or larynx (n = 1) were treated with icatibant (3 of the injections were self-administered). The median time to onset of symptom relief was 1.75 h (95% confidence interval, 1.00–2.50), and all patients had symptom relief within 5 h after administration. The time to maximum plasma concentration of icatibant was 1.79 h, and the maximum plasma concentration was 405 ng/ml. Seven patients experienced an injection site reaction, and 3 patients had adverse events (2 patients had a worsening or repeat HAE attack 29.0 and 18.3 h after icatibant administration, respectively, and 1 had headache).

Conclusions: Although the number of patients is small, the efficacy and tolerability of icatibant for acute attacks were demonstrated in Japanese patients with HAE, regardless of self-administration or administration by healthcare professional.

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Introduction

* This article is a secondary publication of Hide M, Fukunaga A, Maehara J, Eto K, Hao J, Vardi M, et al. [Efficacy, pharmacokinetics, and safety of icatibant for the treatment of Japanese patients with an acute attack of hereditary angioedema: A phase 3 open-label study]. *Arerugi* 2018;**67**:139–47 (in Japanese). Additionally, partial findings from this study were presented at the 116th General Meeting of The Japanese Dermatological Association 2017 and European Academy of Allergy and Clinical Immunology Congress 2017.

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¹ Moshe Vardi was an employee of Shire, a Takeda company, at the time this study was conducted.

Hereditary angioedema (HAE) is an autosomal-dominant genetic disease characterized by recurrent swelling episodes affecting the skin, gastrointestinal mucosa, and upper respiratory tract.¹ HAE attacks are unpredictable in their onset, duration, severity, frequency, and anatomical location,^{2,3} and attacks affecting the larynx may be life-threatening.⁴ Most often, HAE is caused by genetic mutation of C1 inhibitor (C1-INH)⁵ and classified into HAE Type I, which is caused by deficient C1-INH synthesis, and HAE Type II, which is caused by point mutations resulting in lowered activity of C1-INH.¹ Both types of mutations lead to activation of the kallikrein-kinin (or "contact") system and a subsequent increase in

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circulating bradykinin levels that mediates the clinical symptoms of HAE. $^{\rm 16,7}$

The World Allergy Organization guidelines for the management of HAE^{8,9} recommend that acute HAE attacks be treated with C1-INH therapy, ecallantide, or icatibant acetate (hereon referred to as icatibant). Icatibant is a selective bradykinin B2 receptor antagonist¹⁰ that has, in phase 3 randomized controlled trials and open-label extensions of a single subcutaneous injection, consistently provided rapid improvement in clinical symptoms of HAE.^{11–14} However, because neither ecallantide nor icatibant was approved for use in Japan until recently,[#] Japanese guidelines for the treatment of HAE, created by the Japanese Association for Complement Research in 2010, propose treatment of acute HAE attacks with tranexamic acid or C1-INH therapy.¹⁵ Further, a survey of Japanese physicians found that HAE diagnosis was delayed due to mis- or underdiagnosis and that HAEspecific treatment options were not always used.¹⁶ This suggests that in Japan, optimal treatment for HAE has not always been provided to patients.

The objective of this study was to evaluate the efficacy, pharmacokinetics, and safety of icatibant for the treatment of acute attacks in Japanese patients with Type I or Type II HAE.

Methods

Study design

This study was conducted as a phase 3, single-arm, open-label study at 8 medical institutions in Japan from 18 March 2015 to 12 February 2016. The study plan was approved by the institutional review board of each medical institution, and the study was performed according to the Declaration of Helsinki, International Conference on Harmonisation guidelines for good clinical practice, and the associated laws and regulations. Written consent was obtained from all patients as a requirement of study participation.

Study population

This study included patients who were living in Japan and were Japanese (defined as having been born in Japan with Japanese parents and grandparents). The main inclusion criteria were age 18 years or older; a definitive diagnosis of HAE Type I or II based on family history, genetic analysis of angioedema, or other reliable information; presentation with an HAE attack of specified severity; or a finding of C1-INH deficiency or dysfunction. Physicians evaluated the severity of HAE attacks before icatibant administration; the severity was rated as moderate or severe in the case of an attack affecting the skin or abdomen, and as mild or moderate in the case of an attack affecting the larynx.

The main exclusion criteria included the requirement for airway maintenance as an intervention for the attack, or having a severe laryngeal attack. Other exclusion criteria included prior treatment with icatibant; receiving C1-INH products or fresh frozen plasma replacement therapy within 5 days before onset of the current attack; or receiving an angiotensin-converting enzyme inhibitor.

Test methods

A single icatibant dose of 30 mg was subcutaneously administered in the abdomen within 6 h of the symptoms of the acute attack becoming moderate/severe for abdominal and/or cutaneous attacks, or mild/moderate for laryngeal attacks. However, icatibant was to be administered within 12 h after the attack. The injection was administered by a healthcare professional (HCP), such as a physician or nurse, or self-administered by the patient at the hospital/clinic under HCP supervision. The entire volume of the syringe was administered over 30 s or more. A single dose was planned, but if the symptom was not relieved sufficiently or worsened within 48 h after administration, up to 2 more doses with an interval of 6 h or more from the initial administration was allowed. If the symptoms worsened after 48 h from the initial administration of icatibant, or if angioedema recurred at the same site or developed at another site, it was regarded as a new attack and was managed according to the current HAE standard of care in Japan.¹¹

After icatibant administration, patients stayed at the hospital for at least 8 h, or until their physician judged them clinically stable. Physicians and patients evaluated HAE symptoms and safety during this period. Patients self-evaluated HAE symptoms for 5 days after icatibant administration and recorded adverse events and concomitant medications over 7 days. Following icatibant administration, patients had a final follow-up visit on Day 7. Blood was drawn 0.75 and 2 h after icatibant administration for the pharmacokinetic analysis.

Efficacy and endpoints

Efficacy of icatibant was evaluated based on the following measures:

Comprehensive assessment by physician: The severity of symptoms affecting the skin, abdomen, and larynx were assessed at baseline using a 5-point scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Extremely severe).

Evaluation of each symptom by physician: Evaluations were made at baseline, every 30 min from 1 to 4 h after icatibant administration, 5 and 6 h after the administration, and then every 2 h until discharge. Eight symptoms (abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, and skin swelling) for the skin and abdominal attacks, and 13 symptoms for laryngeal attacks (in addition to the 8 symptoms above: voice change, difficulty in swallowing, dyspnea, stridor, and asphyxia) were evaluated using a 5-point scale (0 = None, 1 = Mild,

[#] Icatibant was approved in Japan on 21 September 2018.²¹

2 = Moderate, 3 = Severe, 4 = Extremely severe). The mean of each evaluation was regarded as the composite symptom score by the physician.

Evaluation by patient's visual analog scale (VAS) score: Evaluations were made at baseline, every 30 min from 1 to 4 h after icatibant administration, 5 and 6 h after the administration, and then every 2 h until discharge. Furthermore, evaluations were made 3 times a day (morning, afternoon, evening) for 5 days after discharge. Skin swelling, skin pain, and abdominal pain for cutaneous and abdominal attacks, in addition to difficulty in swallowing and change of voice for laryngeal attacks, were evaluated by VAS (1–100 mm; 0 = No symptom, 100 = Worst imaginable symptom). The mean of each score was regarded as the composite VAS score.

Evaluation of each symptom by patient: Evaluations were made at baseline, every 30 min from 1 to 4 h after icatibant administration, 5 and 6 h after the administration, and then every 2 h until discharge. Furthermore, evaluations were made 3 times a day (morning, afternoon, evening) for 5 days after discharge. Eight symptoms (abdominal pain, nausea, vomiting, diarrhea, skin pain, skin redness, skin irritation, and skin swelling) for the skin and abdominal attacks and 10 symptoms (in addition to the 8 symptoms above: voice change and dysphagia) were evaluated using a 5point scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Extremely severe). The mean of each evaluation was regarded as the composite symptom score by patient. Change of type or tone of voice (e.g., hoarseness or deepening of the voice) were assumed for the voice change, but it was stipulated as "voice change" on the protocol in conformity with the previous overseas studies.

Time to initial symptom improvement (TISI): The time when the symptom started to improve was recorded by both physician and patient.

Evaluation on self-administration: For patients who selfadministered icatibant, convenience and satisfaction of selfadministration were investigated using a questionnaire.

Pharmacokinetics

Plasma concentrations of icatibant and its main metabolites (M1, M2) were measured using a validated, high-performance liquid chromatography-tandem mass spectrometry method. Pharmacokinetic parameters were estimated using a population pharmacokinetic modeling analysis.

Safety

The safety of icatibant was evaluated by adverse events, vital signs, physical examination, electrocardiogram, and laboratory tests. Adverse events were classified using Medical Dictionary for Regulatory Activities version 16.1. Injection site reactions of ery-thema, swelling, cutaneous pain, burning sensation, itching, and feeling of warmth were assessed by the study physician with grading (absent, mild, moderate, or severe).

Statistical analysis

The analysis included all patients who received icatibant. The primary endpoint was time to onset of symptom relief (TOSR) based on the patient composite VAS score, defined as a 50% reduction from baseline in patient composite VAS score.

The key secondary efficacy endpoint was time to onset of primary symptom relief (TOSR-P), defined by a reduction from baseline patient VAS score (less than 6/7 times baseline score minus 16 if VAS was greater than or equal to 30 mm, or 0.32 times baseline score if VAS was less than 30 mm) for the primary symptom. The primary symptom was determined according to the site of attack (abdominal pain for abdominal attacks, the more severer one of skin swelling or skin pain for cutaneous attacks, the more severer one of swallowing difficulty or voice change for laryngeal attacks). Time to almost complete symptom relief (TACSR), defined as the earliest time when 3 consecutive patient VAS scores were all less than 10 mm, was also assessed as a secondary endpoint.

TOSR, TOSR-P, TACSR, and TISI were summarized using the Kaplan—Meier method, and other endpoints were summarized using descriptive statistics. Missing values were calculated using the last observation carried forward method. Statistical analysis was performed using SAS® version 9.3 (SAS Institute, Cary, NC, USA). A nonlinear mixed effects model was used for the population pharmacokinetic analysis.

Results

Patient disposition

Of 16 patients who underwent screening, 8 patients received icatibant. Every patient received icatibant once, and all 8 patients completed the study. Three patients (37.5%) self-administered icatibant, and 5 patients (62.5%) received administration by an HCP.

Of 8 patients who received icatibant, 5 patients (62.5%) were female and 3 patients (37.5%) were male. The mean age was 45.5 years, and the average body mass index was 27.4 kg/m² (Table 1). The time from HAE diagnosis (mean \pm standard deviation [SD]) was 10.2 \pm 9.2 years, and the time (mean \pm SD) from the last HAE attack (skin or abdominal attack in many cases) was 4.0 \pm 2.6 months (Table 1). The sites of attack were skin (4 patients, 50.0%), abdomen (3 patients, 37.5%), and larynx (1 patient, 12.5%), and the severity was moderate in most cases. The mean duration from attack to

Table 1

Baseline characteristics: Demographics, history of HAE attacks, and on-study HAE attacks.

Characteristic	$\begin{array}{l} \text{Self-administration} \\ (n=3) \end{array}$	$\begin{array}{l} HCP\\ administration\\ (n=5) \end{array}$	Overall (N = 8)
Demographics			
Female, n (%)	2 (66.7)	3 (60.0)	5 (62.5)
Male, n (%)	1 (33.3)	2 (40.0)	3 (37.5)
Age, years	42.5 (10.3)	47.3 (20.9)	45.5 (16.9)
BMI, kg/m ²	26.0 (9.0)	28.3 (7.0)	27.4 (7.3)
History of HAE attacks			
Family history of HAE, n (%)	1 (33.3)	3 (60.0)	4 (50.0)
Years since diagnosis	4.8 (3.2)	13.4 (10.4)	10.2 (9.2)
Months since last attack	3.8 (3.5)	4.2 (2.3)	4.0 (2.6)
Number of attacks in			
previous 6 months			
Cutaneous	5.7	15.0	8.0
Abdominal	11.0	8.8	9.5
Cutaneous + abdominal	1.0	1.0	1.0
Laryngeal	1.0	1.0	1.0
On-study HAE attacks			
Type of attack, n (%)			
Cutaneous	2 (66.7)	2 (40.0)	4 (50.0)
Abdominal	1 (33.3)	2 (40.0)	3 (37.5)
Laryngeal	0	1 (20.0)	1 (12.5)
Severity of attack, n (%)			
Mild	0	1 (20.0)	1 (12.5)
Moderate	3 (100)	3 (60.0)	6 (75.0)
Severe	0	1 (20.0)	1 (12.5)
Hours from onset to administration of icatibant	7.2 (2.9)	6.1 (2.3)	6.5 (2.4)

Data are presented as mean (standard deviation) unless stated otherwise. BMI, body mass index; HAE, hereditary angioedema; HCP, healthcare professional. icatibant administration was slightly longer for patients who selfadministered icatibant—7.2 h with self-administration and 6.1 h with administration by an HCP (Table 1).

Time to symptom relief

Symptom relief and improvement were observed in all patients after icatibant administration.

The median TOSR was 1.75 h (95% confidence interval [CI] 1.00-2.50); TOSRs were similar between self-administration (1.53 h; 95% CI 1.52-2.50) and administration by an HCP (1.97 h; 95% CI 1.00-5.00) (Fig. 1). After icatibant administration, some patients had symptom relief by as early as 1 h, and the symptoms were relieved within 5 h in all patients (Fig. 1A,C).

The median TOSR-P was 1.07 h (95% CI 1.00–2.00), which is shorter than TOSR (Fig. 1B), indicating that primary symptom relief



Fig. 1. Time to symptom relief after icatibant injection. (**A**) Proportion of patients achieving symptom relief during the first 8 h after icatibant injection. (**B**) Proportion of patients achieving symptom relief for the primary symptom during the first 8 h after icatibant injection. (**C**) Median time to symptom relief. Error bars are 95% CI; upper CI is shown. CI, confidence interval; HCP, healthcare professional; TACSR, time to almost complete symptom relief; TISI, time to initial symptom relief; TOSR, time to onset of symptom relief.

is earlier compared to TOSR. Moreover, primary symptom relief was observed in all self-administered patients approximately 1 h after administration (Fig. 1B,C).

The median TACSR was 5.98 h (95% CI 1.50–8.00) (Fig. 1C). The median TISI was 0.98 h (95% CI 0.30–2.00) when evaluated by the physician and 1.04 h (95% CI 0.30–2.05) when evaluated by the patient, showing equivalence regardless of the evaluator (Fig. 1C).

VAS score and evaluation of each symptom

The composite VAS score (mean \pm SD) decreased to 1.38 \pm 1.79 mm 8 h after icatibant administration, compared with baseline (30.78 \pm 13.47 mm). The greatest decrease in this VAS score was largely seen relatively early after administration (Fig. 2A). The VAS scores from Day 2 to Day 5 after icatibant administration remained low, less than 4 mm at all measurement points.

The mean of the composite symptom score was evaluated as mild (<1) by either the physician or the patient at all measurement points. The mean \pm SD score was highest at baseline (evaluated by the physician: 0.59 ± 0.28 ; evaluated by the patient: 0.68 ± 0.41), and it decreased linearly over 8 h after icatibant administration (Fig. 2B) and remained low (less than 0.15) for the next 5 days.

Evaluation on self-administration

In the questionnaire completed by 3 patients who selfadministered icatibant, the following responses were obtained: training was sufficient; there was no stress associated with selfadministration; both preparation of the injection site and assembly of the syringe were easy; and self-administration was not particularly difficult.

(A) Composite VAS score







Fig. 2. Mean composite (**A**) VAS scores and (**B**) symptom scores assessed by the investigator and patient for the first 8 h after icatibant injection. Error bars are standard deviation. VAS, visual analog scale.

Table 2			
Estimated	pharmacokinetic	parameters	of icatibant.

C _{max} , ng/m	T _{max} , h	$T_1/_{2\alpha}$, h	$T_{1/2\beta}$, h	$\text{AUC}_{0-2}\text{, }ng \times h/ml$	$\text{AUC}_{0-4}\text{, }ng \times h/ml$	AUC_{0-6}, ng \times h/ml	CL/F, L/h	V/F, L	CL/F, L/h/kg	V/F, L/kg
Mean (SD) 405 (194)	1.79 (0.51)	1.14 (0.23)	2.86 (0.17)	611 (338)	1198 (495)	1506 (509)	17.5 (4.4)	31.4 (12.1)	0.25 (0.07)	0.44 (0.10)

AUC, area under the concentration-time curve (e.g., 0–2, from 0 to 2 h after icatibant injection); CL/F, apparent systemic clearance; C_{max}, maximum plasma concentration; SD, standard deviation; T_{1/2g}, distribution half-life; T_{1/2g}, terminal half-life; T_{max}, time of maximum observed plasma concentration; V/F, apparent central volume of distribution.

Pharmacokinetics

Mean \pm SD plasma concentrations 0.75 and 2 h after a single subcutaneous dose of icatibant were 352 \pm 265 ng/ml and 366 \pm 131 ng/ml, respectively; those of M1 were 166 \pm 62 ng/ml and 286 \pm 49 ng/ml, respectively; and those of M2 were 729 \pm 563 ng/ml and 386 \pm 122 ng/ml, respectively.

The mean time to maximum plasma concentration of icatibant was 1.79 h and the mean maximum plasma concentration was 405 ng/ml. Table 2 shows the pharmacokinetic parameters.

Safety

Three adverse events developed in 3 of 8 patients (37.5%): 2 cases of worsening or repeat angioedema, and 1 case of headache. One case of worsening or repeat angioedema occurred 29.0 h after a patient self-administered icatibant, and 1 case occurred 18.3 h after icatibant was administered by an HCP. Headache occurred in 1 patient 2.2 h after icatibant was administered by an HCP. All these events were mild and evaluated as not related to icatibant. No deaths, serious adverse events, or adverse events requiring discontinuation of icatibant were reported.

An injection site reaction was reported in 7 of 8 patients (87.5%); and erythema, swelling, and feeling of warmth were frequently reported (Table 3). One case of erythema in a patient for whom icatibant was administered by an HCP was considered a severe injection site reaction, but it resolved by 2 h after the administration. Furthermore, a burning or warm sensation and skin pain were found only in patients for whom icatibant was administered by an HCP.

No clinically important changes were found in vital signs, physical examination, electrocardiogram, or laboratory tests.

Discussion

This is the first clinical study showing that icatibant is effective for acute attacks in Japanese patients with HAE Type I or II. Our study included patients who self-administered icatibant, as this has been shown to be as effective as HCP administration^{17,18} and preferred by most patients.¹⁷ We found that a single subcutaneous injection of icatibant was well tolerated and was able to quickly

Table 3

Injection site reactions after icatibant injection.

	$\begin{array}{l} \text{Self-administration} \\ (n=3) \end{array}$	$\begin{array}{l} \text{HCP administration} \\ (n=5) \end{array}$	$\begin{array}{l} \text{Overall} \\ (\text{N}=8) \end{array}$
Any injection site reaction	2 (66.7)	5 (100)	7 (87.5)
Erythema	2 (66.7)	5 (100)	7 (87.5)
Swelling	2 (66.7)	5 (100)	7 (87.5)
Burning sensation	0	2 (40.0)	2 (25.0)
Itching	1 (33.3)	2 (40.0)	3 (37.5)
Warm sensation	0	4 (80.0)	4 (50.0)
Skin pain	0	1 (20.0)	1 (12.5)
Severe injection site reaction	0	1 (20.0)	1 (12.5)
Erythema	0	1 (20.0)	1 (12.5)

Data are presented as n (%).

HCP, healthcare professional.

(within about 2 h) relieve the clinical symptoms of the HAE attack, regardless of the administration technique.

The primary endpoint of this study, TOSR, and the efficacy endpoints such as TOSR-P, TACSR, and TISI for HAE acute attacks affecting the skin, abdomen, and larynx, were consistent with the results of global trials in non-Japanese patients.^{11–14,17} In addition, there was no noticeable difference in each efficacy endpoint between patients who self-administered icatibant and those for whom icatibant was administered by an HCP, as with previous findings in the global studies.^{17,18}

Notably, median TOSR-P (1.07 h) was slightly shorter (primary symptom relief occurred slightly earlier) than the TOSR (1.75 h). This may have occurred based on the differences in these 2 assessments. TOSR-P reflects the primary (most severe) symptom a patient experienced during an HAE attack, and therefore this symptom is likely to resolve first upon treatment. On the other hand, TOSR reflects an average of VAS scores across all domains measured. As such, greater improvement in the affected domains needs to occur before the average VAS is reduced by 50% (i.e. TOSR is reached).

All adverse events that developed during the study period were mild, including aggravation or relapse of angioedema in 2 of 8 patients (25%), headache in 1 patient (12.5%), and temporary injection site reaction at the time of injection in 7 patients (87.5%). The safety findings in this study were comparable to the results of the previous global studies,^{11–14,17} confirming that there were no new safety signals in Japanese patients.

Per pharmacokinetic analysis of blood samples from Japanese patients treated with icatibant, mean time to maximum plasma concentration was 1.79 h and mean maximum plasma concentration was 405 ng/ml. The plasma concentration 0.75 h after icatibant administration was 352 ng/ml, which was lower than the plasma concentration (approximately 1000 ng/ml)¹⁹ when the same dose of icatibant was administered in healthy Caucasian volunteers in a previous pharmacokinetic study, but symptom relief and improvement were observed in Japanese patients in this study. This was thought to have occurred because the plasma concentrations 0.75 h and 2 h after icatibant administration were higher than 50% effective concentration (9.5 ng/ml) and 85% effective concentration (54 ng/ml)²⁰ in all patients. The correlation of icatibant plasma concentration and efficacy was not analyzed in this study.

Although the number of patients in this study was small, both icatibant self-administration and administration by an HCP were effective and well tolerated in Japanese patients who developed HAE acute attacks affecting the skin, abdomen, or larynx. Our findings confirm that subcutaneous icatibant administration may quickly relieve the symptoms of acute HAE attacks in Japanese patients.

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Conflict of interest

JH is an employee of Shire, a Takeda company, and owns company stocks. MV was an employee of Shire, a Takeda company, at the time of this analysis and owns company stocks. MH, AF, JM, KE, and YN have no conflict of interest to declare.

Authors' contributions

MH was involved in the planning of the manuscript; MH, AF, JM, KE, JH, and YN were involved in data collection; and all authors were involved in the interpretation of results, writing of the manuscript or critical evaluation of revisions, and approval of the final submission draft.

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