Original Article

Treatment Effect and Safety of Icatibant in Pediatric Patients with Hereditary Angioedema

Henriette Farkas, MD, PhD, DSc[a], Avner Reshef, MD[b], Werner Aberer, MD[c], Teresa Caballero, MD[d], Laura McCarthy, BSc[e], James Hao, PhD[e], Wolfram Nothaft, MD[e], Jennifer Schranz, MD[e], Jonathan A. Bernstein, MD[f], and H. Henry Li, MD[g] *Budapest, Hungary; Tel-Hashomer, Israel; Graz, Austria; Madrid, Spain; Lexington, Mass; Cincinnati, Ohio; and Chevy Chase, Md*

What is already known about this topic? Initial symptoms of hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) often begin in childhood or early adolescence and can be severe. There is a paucity of evidence-based treatment options for HAE attacks in pediatric patients.

What does this article add to our knowledge? Our phase 3, open-label study is the first to report efficacy, safety/tolerability, and pharmacokinetics of the subcutaneously administered bradykinin B2 receptor antagonist, icatibant, as treatment for pediatric patients with C1-INH-HAE.

How does this study impact current management guidelines? Icatibant provided rapid relief and was well tolerated in pediatric patients with C1-INH-HAE, suggesting that this agent is a feasible option for children and adolescents experiencing HAE attacks.

BACKGROUND: Clinical manifestations of hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) usually begin in childhood, often intensifying during puberty. Currently there are insufficient efficacy/safety data for HAE therapies in children and adolescents due to the small number of pediatric patients enrolled in studies.

[a]Hungarian Angioedema Center, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[b]Chaim Sheba Medical Center, Allergy, Immunology and Angiodema Center, Tel-Hashomer, Israel
[c]Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria
[d]Allergy Department, Hospital La Paz Institute for Health Research (IdiPaz), Biomedical Research Network on Rare Diseases (CIBERER, U754), Madrid, Spain
[e]Shire, Lexington, Mass
[f]University of Cincinnati Physicians Immunology Research Center, Cincinnati, Ohio
[g]Institute for Asthma and Allergy, Chevy Chase, Md

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Conflicts of interest: H. Farkas has received research support from Shire; is on the advisory boards for CSL Behring, Shire, BioCryst, and Swedish Orphan Biovitrum; has received consultancy fees from CSL, Shire, BioCryst, and Swedish Orphan Biovitrum; and has received lecture fees from CSL and Swedish Orphan Biovitrum. A. Reshef has received research funding, travel grants, and speaker honoraria from Dyax,* CSL Behring, Shire, Pharming, Cephalon, and Teva, and served as an advisor and speaker for Shire Human Genetic Therapies and CSL Behring. W. Aberer is on the boards for Shire (HAE-Register), Novartis (Urticaria Guideline), and BioCryst (HAE-Clinical Studies); has acted as a medical advisor and speaker for BioCryst, CSL Behring, Pharming, and Shire; has received funding to attend conferences/educational events and donations to his departmental fund from, and participated in clinical trials for, Shire; has received consultancy fees from CSL Behring; and has received lecture fees from Shire and Novartis. T. Caballero has received speaker fees from GlaxoSmithKline, MSD, Novartis, and Shire; consulting fees from BioCryst, CSL Behring, Novartis, Shire, and Sobi; funding for travel and meeting attendance from CSL Behring, Novartis, and Shire; and has participated in clinical trials/registries for BioCryst, CSL Behring, Dyax, Novartis, Pharming, and Shire. She is a researcher from the IdiPaz Program for promoting research activities. L. McCarthy, J. Hao, W. Nothaft, and J. Schranz are employed by and have stock/stock options in Shire. J. A. Bernstein has been a clinical investigator for CSL Behring, Dyax, Pharming, Santarus, Shire, BioCryst, and ViroPharma; a speaker for CSL Behring, Dyax, Shire, and ViroPharma*; and a consultant for CSL Behring, Dyax, Pharming, Santarus, Shire, and ViroPharma. H. H. Li has received personal fees from Shire; has received personal fees and research support from Shire/ViroPharma/Dyax, CSL Behring, and Pharming/Salix; has received research support from BioCryst; and serves as a member of the Medical Advisory Board of the Hereditary Angioedema Association.

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Corresponding author: Henriette Farkas, MD, PhD, DSc, Semmelweis University, Kutvolgyiut 4, H-1125 Budapest, Hungary. E-mail: farkas.henriette@med.semmelweis-univ.hu.

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Abbreviations used
AE- adverse event
C1-INH- C1 inhibitor
C1-INH-HAE- hereditary angioedema with C1-inhibitor deficiency
C_{max}- *maximum plasma concentration*
FLACC- Faces, Legs, Activity, Cry, and Consolability
FPS-R- Faces Pain Scale-Revised
HAE- hereditary angioedema
PK- pharmacokinetic
SC- subcutaneous
TEAEs- treatment-emergent adverse event
T_{max}- *time to peak concentration*
TOSR- time to onset of symptom relief
TTMS- Time to minimum symptoms

OBJECTIVE: The objective of this phase 3 study was to evaluate the efficacy/safety of a single subcutaneous dose of icatibant (0.4 mg/kg; maximum 30 mg) in pediatric patients with C1-INH-HAE.

METHODS: Patients aged 2 years to younger than 18 years were categorized as prepubertal (children) and pubertal/postpubertal (adolescents). The primary end point was time to onset of symptom relief—earliest time posttreatment to 20% or more improvement in composite symptom score.

RESULTS: Thirty-two patients received icatibant (safety population: 11 children with attack, 10 adolescents without attack, and 11 adolescents with attack). The efficacy population consisted of 11 children and 11 adolescents with edematous attacks. Most attacks in the efficacy population (16 [72.7%]) were cutaneous, 5 (22.7%) were abdominal, and 1 (4.5%) was both cutaneous and abdominal; none was laryngeal. Overall, the median time to onset of symptom relief was 1.0 hour, the same for children and adolescents. Thirty-two treatment-emergent adverse events (all mild or moderate) occurred in 9 (28.1%) patients. Gastrointestinal symptoms were most common (9 events in 3 [9.4%] patients). Injection-site reactions affected most (90.6%) patients (particularly erythema and swelling), but almost all resolved by 6 hours postdose. Icatibant demonstrated a monophasic plasma concentration-time profile. Time to peak concentration was approximately 0.5 hours postdose.

CONCLUSIONS: Symptom relief was rapid, and a single icatibant injection in pediatric patients with C1-INH-HAE was well tolerated (ClinicalTrials.gov identifier, NCT01386658). **(J Allergy Clin Immunol Pract 2017;5:1671-8)**

Key words: *Hereditary angioedema; Bradykinin; C1 inhibitor deficiency; Bradykinin B2 receptor antagonist; Icatibant; Children; Adolescents; Pediatrics; Treatment*

Hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency (C1-INH-HAE) is a rare disease caused by *SERPING1* gene mutations.[1,2] C1-INH-HAE type I mutations occur throughout the whole gene and lead to low C1-INH plasma concentrations,[3,4] whereas C1-INH-HAE type II mutations involve single amino acid substitutions and lead to normal or elevated C1-INH plasma levels but less than normal activity.[5] HAE is characterized by recurrent edematous episodes in subcutaneous (SC) or submucosal tissues.[6] Swelling episodes are often painful and can occur with unpredictable frequency and severity.[7-9] Edematous attacks affecting the upper airway can lead to asphyxia,[6] which may occur more rapidly in children than in adults because of smaller airway caliber.[8]

Most patients with CI-INH-HAE experience their initial attack before puberty[10]; symptoms may begin as early as 1 year[10] or during adolescence.[7-9,11] Laryngeal attacks have been reported in children as young as 3 years.[6] Symptom severity and attack frequency often intensify during peak times of physiologic and hormonal changes, such as between 3 and 6 years, and during puberty.[8,12,13] C1-INH-HAE is associated with a heavy burden of illness[14]; the earlier symptoms begin, the more severe the subsequent disease course (ie, increased attack frequency) and negative impact on daily life.[15]

Over the last decade, multiple C1-INH-HAE treatment guidelines and consensus recommendations have been developed.[13,16-21] Despite this progress, there is a paucity of evidence-based treatments in pediatric patients; few studies have evaluated acute management exclusively in children and adolescents. As such, some agents are approved for adults but not yet for pediatric patients, and approval status for acute treatment differs among countries.

Efficacy and safety of the bradykinin B2 receptor antagonist icatibant (Firazyr; Shire, Lexington, Mass)—a subcutaneously administered on-demand treatment for HAE attacks—have been demonstrated in adults[22,23]; however, clinical studies in patients younger than 18 years have not been reported to date. Herein, we present efficacy, safety/tolerability, and pharmacokinetic (PK) findings from a phase 3 study of icatibant in pediatric patients with C1-INH-HAE.

METHODS

Study overview

This multicenter, open-label, nonrandomized, single-arm study was conducted according to local ethical/legal requirements, including the International Conference on Harmonisation of Good Clinical Practice and the principles of the Declaration of Helsinki. All participants (or their parents/legal guardians) provided written informed consent and assent. All study sites were required to operate under an ethics committee and/or institutional review board that approved the protocol and related amendments, informed consent documents, recruitment information, and relevant supporting materials before initiation. This study was sponsored by Shire, Lexington, Mass.

Patients

Eligible children and adolescents aged 2 years to less than 18 years had a documented diagnosis of C1-INH-HAE type I/II, with no restriction on location of attacks. Diagnosis was confirmed by a complement test measuring C1-INH levels (C1-INH antigenic level less than the lower limit of normal, or normal/elevated and functional level <50% of normal), as performed by a central laboratory. Blood samples were analyzed at the National Jewish Health research facility (Denver, Colo). Key exclusion criteria were diagnosis of angioedema other than C1-INH-HAE type I/II, presence of congenital or acquired cardiac anomalies, use of angiotensin-converting enzyme inhibitors within 7 days or hormonal contraceptives or androgens within 90 days before icatibant, and pregnancy or breast-feeding.

Patients were categorized on the basis of clinical assessment of developmental age: prepubertal (children, Tanner stage I) and pubertal/postpubertal (adolescents, Tanner stages II-V). Icatibant was administered to all recruited children, and to a portion of adolescents during an HAE attack. For the purposes of evaluating safety and PK data, the remaining recruited adolescents received icatibant in the absence of an HAE attack.

Evaluation of repeated icatibant exposure among adolescents during HAE attacks (3 attacks maximum) is pending. The findings presented herein are limited to the initial study phase evaluating a single icatibant administration, with a minimum follow-up of 8 days for all patients.

Study interventions and assessments

Patients received a single SC icatibant dose in the abdominal region (0.4 mg/kg, up to a maximum of 30 mg [the currently approved adult dose]).[24] Based on PK/pharmacodynamic modeling in healthy volunteers, 0.4 and 0.8 mg/kg intravenous icatibant doses were predicted to provide therapeutic effect for 9 and 13 hours, respectively; 0.4 mg/kg was deemed the minimum effective dose for HAE attacks, corresponding to a 30-mg dose in a 75-kg subject. In a subsequent phase 2 dose-ranging proof-of-concept study in patients with C1-INH-HAE, 0.4 and 0.8 mg/kg intravenous and 30 and 45 mg SC doses were evaluated; icatibant 45 mg SC was not better than 30 mg SC. Based on consistent efficacy of a single 30-mg SC dose in phase 3 studies in adults with C1-INH-HAE, icatibant 0.4 mg/kg SC was deemed an appropriate dose to study tolerability/safety, efficacy, and PK in pediatric patients. Icatibant was supplied as a 10 mg/mL solution in 3-mL glass syringes. A single dose was withdrawn from the prefilled syringe using the adaptor and administered via SC injection (by the investigator or the patient).

This study was conducted in open-label fashion within 12 hours of symptom onset, and patients were closely monitored for at least 6 to 8 hours after treatment. Telephone follow-up occurred 24 and 48 hours after treatment. Scheduled onsite assessments occurred on days 8 and 90.

Other than the protocol-defined single icatibant injection, any additional agent (eg, pain medications, plasma-derived C1-INH) was allowed as rescue, at physicians' discretion. In addition, prophylactic therapies were allowed, other than attenuated androgens. However, with the exception of fibrinolysis inhibitors, therapies known to attenuate an HAE attack (eg, plasma-derived C1-INH and fresh-frozen plasma) were not allowed during an icatibant-treated attack unless required as rescue.

Symptom severity (before and after treatment) was measured by investigators using a 5-point (nonvisual) scale based on the degree to which symptoms interfered with patients' daily activities: 0 = none (absence of symptoms); 1 = mild (no to mild interference); 2 = moderate interference; 3 = severe interference; and 4 = very severe interference. For attacks classified as *cutaneous* and/or *abdominal*, the following signs and symptoms were rated: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, and skin swelling. A composite investigator-assessed symptom score was then calculated by taking an average of these individual symptom scores. Patients 4 years or older also self-assessed their pain via the validated Faces Pain Scale-Revised (FPS-R) tool.[25,26]

Safety/tolerability was evaluated via assessments of adverse events (AEs), including injection site—related symptoms (by the investigator or medical personnel); clinical laboratory measurements (ie, serum chemistry, hematology); vital signs; and reproductive hormone levels (ie, follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, and testosterone). AEs and treatment-emergent adverse events (TEAEs; occurring or worsening on or after first icatibant administration) were categorized using the Medical Dictionary for Regulatory Activities, Version 16.0. Injection-site reactions were evaluated by the investigator while patients were still at the hospital/study center.

Plasma samples were assayed for concentrations of icatibant and its 2 major (pharmacologically inactive) metabolites (M1 and M2) using a validated HPLC-MS/MS method with a lower limit of quantification of 1 ng/mL (range, 1-1000 ng/mL).[27] PK variables were determined by full sampling and noncompartmental methods where possible, and elsewhere by sparse sampling (at least 4-7 time points). For adolescents (with or without attacks), PK samples on day 1 were taken before and during the following times posttreatment: 15 (±5) minutes, 30 (±5) minutes, 45 (±5) minutes, 1 hour (±10 minutes), 2 hours (±10 minutes), 4 (±0.5) hours, and 6 (±0.5) hours after treatment. For children, PK samples on day 1 were taken before and during the following times posttreatment:15 (±5) minutes, 30 (±5) minutes, 2 hours (±10) minutes, 4 (±0.5) hours, and 6 (±0.5) hours after treatment. A population PK approach used nonlinear mixed-effects modeling software (eg, Phoenix NLME module, Pharsight Corp, Mountain View, CA). The following PK parameters were evaluated: time to peak concentration (T_{max}), maximum plasma concentration (C_{max}), total plasma clearance (CL/F), volume of distribution, elimination half-life, and area under the plasma concentration-time curve for the following 3 time points: 0 to 4 hours postdose, 0 to 6 hours postdose, and 0 to infinity.

Analysis populations and study end points

Efficacy was assessed in patients treated with icatibant during an HAE attack, whereas safety was assessed in patients receiving icatibant at least once during the study. PK parameters were analyzed for patients from the safety population who received icatibant and provided evaluable plasma drug concentrations.

The primary efficacy end point was time to onset of symptom relief (TOSR) based on the investigator-assessed composite posttreatment symptom score, defined as earliest time posttreatment when 20% or more improvement in the composite symptom score was achieved, without worsening of any single component score. An additional efficacy end point was time to minimum symptoms (TTMS), defined as earliest time posttreatment when all symptoms were mild or absent (clinical remission).

Other end points included observed values and changes from pretreatment in mean composite investigator-reported symptom score; time to initial symptom relief (when overall patient improvement was first noted); scores associated with individual symptoms; and TOSR, TTMS, and change from pretreatment in FPS-R (for patients ≥4 years old) and Faces, Legs, Activity, Cry, and Consolability (FLACC) scores[28] (for patients <4 years old). TOSR was defined as the earliest time when the posttreatment score improved by at least 1 level (FPS-R scale) or when 20% or more improvement was seen in the total posttreatment pain score (FLACC scale). For both scales, TTMS was defined as the earliest time when the posttreatment score improved to 0 (or no pain). An additional end point was the time to first use of rescue medication.

Statistical analyses

All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC), except for the population PK modeling (described previously). Summary statistics for continuous variables included the number of subjects, the mean, median, SD, and range. For categorical data, summaries included counts and

TABLE I. Patients' demographic characteristics and history of HAE (safety population)

Characteristic	Children (n = 11)	Adolescents (n = 21)	Overall (N = 32)
Age at treatment (y), mean ± SD	8.6 ± 3.0	14.3 ± 1.2	12.3 ± 3.5
Sex: male, n (%)	6 (54.5)	13 (61.9)	19 (59.4)
White, n (%)	11 (100.0)	20 (95.2)	31 (96.9)
BMI (kg/m^2), mean ± SD	19.5 ± 4.33	22.4 ± 3.97	21.4 ± 4.26
BMI percentile, mean ± SD	65.5 ± 38.8	70.4 ± 27.0	68.7 ± 31.0
Age at treatment (y), mean ± SD	8.6 ± 3.0	14.3 ± 1.7	12.3 ± 3.5
Age at diagnosis (y), median (min, max)	2.9 (0.6, 6.4)	8.4 (0.2, 14.2)	6.3 (0.2, 14.2)
Time since last attack (mo), median (min, max)	4.0 (1.1, 17.5)	9.8 (0.6, 72.6)	9.4 (0.6, 72.6)
Type of last attack, n (%)			
Cutaneous	3 (27.3)	10 (47.6)	13 (40.6)
Abdominal	3 (27.3)	7 (33.3)	10 (31.3)
Cutaneous and abdominal	3 (27.3)	1 (4.8)	4 (12.5)
Laryngeal	1 (9.1)	1 (4.8)	2 (6.3)

BMI, Body mass index.

percentages. Time-to-event data (eg, median time and 95% CI for TOSR and TTMS) were calculated using Kaplan-Meier methodology.

The planned sample size for this single-arm study was empirically derived to include at least 30 evaluable patients: 10 children and 20 adolescents. Of note, this study was not powered to meet a predetermined treatment effect. The sample size of 30 patients was selected after deliberation with experts in the field and regulatory agencies. Given the rarity of the disease, and in particular its presentation in the pediatric population, 30 patients was deemed an acceptable sample size.

RESULTS

A total of 32 patients received icatibant at least once during the study (11 children with an attack, 11 adolescents with an attack, and 10 adolescents without an attack); all completed assessments through day 8. Baseline demographic characteristics and history of HAE are summarized in Table I. Most children and adolescents were male (54.5% and 61.9%, respectively) and white (100% and 95.2%, respectively). The mean age at time of icatibant administration was 8.6 ± 3.0 years for children and 14.3 ± 1.7 years for adolescents. Most patients (90.6%) had a positive family history of HAE. The median time since patients' last attack was 9.4 months. Type of last attack was mostly cutaneous (40.6%) or abdominal (31.3%).

Efficacy

Investigator-assessed composite symptom score. During the study, 16 patients (72.7%) in the efficacy population experienced a cutaneous attack, 5 patients (22.7%) had an abdominal attack, and 1 patient (4.5%) had a combined cutaneous and abdominal attack; none presented with a laryngeal attack. Overall, median TOSR was 1.0 hour (95% CI, 1.0-1.1), with no differences between children and adolescents (median, 1.0; 95% CI, 1.0-2.0; Figure 1). More than 70% of patients experienced symptom relief at 1.1 hours, and more than 90% by 2 hours posttreatment. Overall, the median TTMS was 1.1 hours (95% CI, 1.0-2.0). Findings for children (1.9 hours; 95% CI, 1.0 -2.0) were similar to those for adolescents (1.0 hour; 95% CI, 1.0-2.0). Approximately 50% of patients reached minimum symptoms at 1 hour, and 80% at 2 hours posttreatment.

The mean composite investigator-reported symptom score showed improvement over time in both patient groups (Figure 2); observed values and changes from pretreatment levels are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

Individual symptom scores were similar for children and adolescents. For symptoms that were moderate or worse at pretreatment, aside from skin swelling, median time for symptoms to become mild or absent was approximately 1 hour for children and adolescents. For skin swelling, median time for symptom relief was 2.0 hours for children and 1.0 hour for adolescents.

Time to initial symptom relief was rapid. Approximately 70% and 95% of patients first noted overall symptom improvement by 1 hour and 2 hours posttreatment, respectively.

Patient self-assessment of pain. Twenty patients 4 years or older were eligible for analysis by the FPS-R; however, TOSR was analyzed for 15 patients (5 patients for whom pretreatment levels were 0 or missing were excluded from analysis). The overall median TOSR was 1.0 hour (95% CI, 0.8-1.0), with similar findings for children and adolescents (median, 0.9 hour [95% CI, 0.8-1.0] and 1.0 hour [95% CI, 0.6-1.0], respectively). TTMS was analyzed via the FPS-R score for 16 patients (3 patients with pretreatment values of 0 were excluded from analysis, and 1 patient who did not achieve minimum symptoms for FPS-R until 19 hours posttreatment was censored). The overall median TTMS was 3.4 hours (95% CI, 1.8-5.3). Findings for children and adolescents were similar (median TTMS, 2.4 hours [95% CI, 1.9-5.3] and 3.8 hours [95% CI, 1.0-6.8], respectively).

Pain was evaluated via FPS-R scores for all 20 patients (9 children and 11 adolescents). Scores reflected improvement from pretreatment at all time points; the observed values and changes over time are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

Investigator assessment of pain in children younger than 4 years. Two patients in the efficacy population were younger than 4 years and thus eligible for pain assessment via the FLACC scale. One patient had a pretreatment value of 0 and was excluded from the time-to-event analyses. For the 1 eligible patient, TOSR and TTMS were both 1.0 hour.

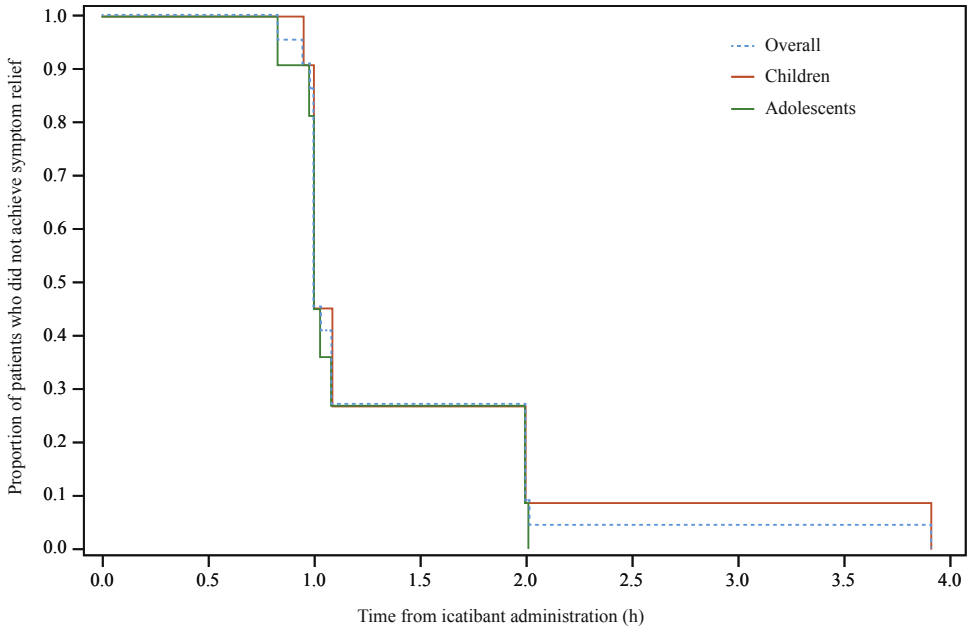

FIGURE 1. Kaplan-Meier curves for TOSR.

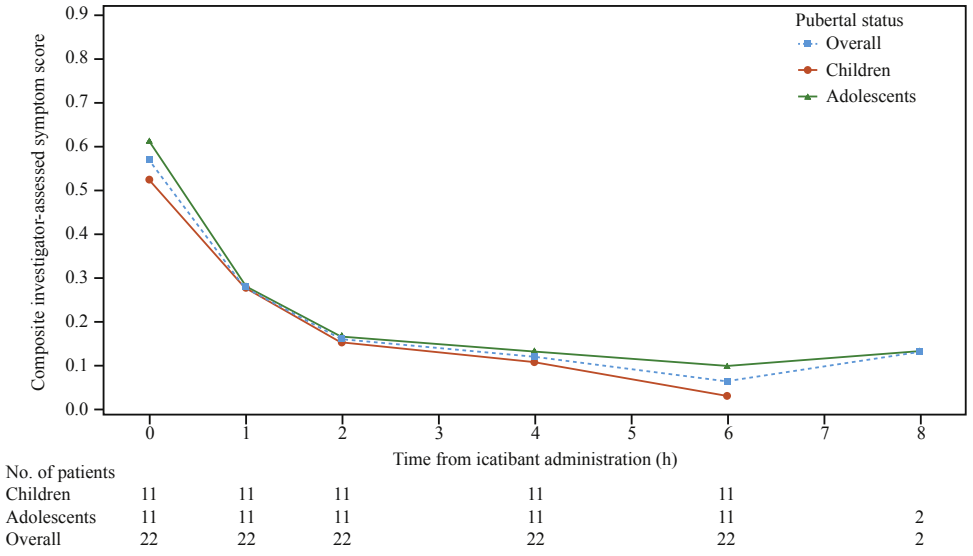

FIGURE 2. Mean composite investigator-assessed symptom score (efficacy population). The symptom score is calculated by taking an average of 8 cutaneous or abdominal attack components.

Use of rescue medication. No patients in the efficacy population required rescue medications within 48 hours of icatibant use. One adolescent in the safety (but not efficacy) population (for whom icatibant was administered without an attack) experienced an HAE attack 6 hours after icatibant use and received C1-INH as rescue. This attack was recorded as an AE, moderate in severity; the type of attack could not be determined.

Safety and tolerability

All 32 (100.0%) patients received 1 injection of icatibant and were included in the safety analysis. A total of 32 TEAEs occurred in 9 (28.1%) patients, most often in adolescents (Table II). All TEAEs were mild or moderate, including gastrointestinal disorders, which occurred most frequently (in 3 patients [9.4%]). No TEAEs were severe and no treatment-emergent serious AEs occurred. No TEAEs led to study discontinuation or death. Two TEAEs in 1 adolescent were considered "possibly related" to icatibant (dry mouth and fatigue, both mild). Most patients (90.6%) experienced injection-site reactions (Table III), most commonly erythema (84.4%) and swelling (68.8%). Most injection-site reactions were mild or moderate, and most (90%-100%) resolved by 6 hours postdose.

TABLE II. Summary of TEAEs occurring in ≥2 patients, by System Organ Class (safety population)*

	Children (n = 11)		Adolescents (n = 21)		Overall (N = 32)	
TEAE	Patients	Events	Patients	Events	Patients	Events
Any adverse event	2 (18.2)	9	7 (33.3)	23	9 (28.1)	32
Gastrointestinal	0	0	3 (14.3)	9	3 (9.4)	9
Nervous system	1 (9.1)	2	2 (9.5)	2	3 (9.4)	4
General disorders/administration site conditions	0	0	2 (9.5)	2	2 (6.3)	2
Infections/infestations	1 (9.1)	1	1 (4.8)	1	2 (6.3)	2
Musculoskeletal/connective tissue disorders	1 (9.1)	1	1 (4.8)	1	2 (6.3)	2
Respiratory, thoracic, and mediastinal	1 (9.1)	2	1 (4.8)	1	2 (6.3)	3

Values are n (%).
*Two TEAEs occurring in 1 adolescent were considered possibly related to icatibant: dry mouth and fatigue.

TABLE III. Injection-site reactions (safety population)

Injection-site reaction	Children (n = 11)	Adolescents (n = 21)	Overall (N = 32)
Any reaction	9 (81.8)	20 (95.2)	29 (90.6)
Erythema	9 (81.8)	18 (85.7)	27 (84.4)
Swelling	7 (63.6)	15 (71.4)	22 (68.8)
Burning sensation	4 (36.4)	9 (42.9)	10 (31.3)
Warm sensation	3 (27.3)	6 (28.6)	10 (31.3)
Skin pain	1 (9.1)	4 (19.0)	7 (21.9)
Itching/pruritus	1 (9.1)	3 (14.3)	4 (12.5)
Any severe reaction	0	2 (9.5)	2 (6.3)
Erythema	0	2 (9.5)	2 (6.3)
Swelling	0	1 (4.8)	1 (3.1)
Burning sensation	0	1 (4.8)	1 (3.1)
Warm sensation	0	1 (4.8)	1 (3.1)

Values are n (%).

Two patients (6.3%) experienced severe injection-site reactions; both resolved by 6 hours postdose.

No clinically significant changes were observed in laboratory values, vital signs, electrocardiograms, or reproductive hormones. Most patients (both genders) maintained normal hormone levels at all time points, regardless of pubertal status. Three female children (60.0%) had low progesterone levels at pretreatment that were unchanged 6 hours posttreatment, and at day 8 posttreatment; 2 of these continued to have low levels at day 90.

Pharmacokinetics

PK analysis was performed on 31 patients from the safety population who received icatibant and had evaluable plasma drug concentrations. Of these, 1 patient was excluded from PK evaluation because his or her predose concentration was more than 5% of C_{max} (for unknown reasons); descriptive statistics were thus summarized for 30 patients (57% males; mean age, 7.9 ± 2.72 years for children and 14.3 ± 1.62 years for adolescents). Based on a dosage of 0.4 mg/kg SC, the mean total SC icatibant dose was 14.0 ± 5.97 mg for children and 23.8 ± 5.1 mg for adolescents. The minimum dose was 4.9 mg (for a 3-year-old patient); the maximum dose was 30 mg (in 4 patients weighing ≥75kg).

Icatibant (and its major metabolites) demonstrated a monophasic plasma concentration-time profile across the pediatric C1-INH-HAE population (Figure 3).

The estimated PK parameters of icatibant are presented in Table IV. Icatibant was rapidly absorbed in both age groups; the mean T_{max} was approximately 0.5 hour after the SC dose for children with an attack, adolescents with an attack, and adolescents without an attack. The mean area under the plasma concentration-time curve from time 0 to t hours was 1289, 1573, and 1398 (h • ng)/mL, and mean C_{max} was 659, 805, and 761 ng/mL for children with an attack, adolescents with an attack, and adolescents without an attack, respectively.

The estimated PK parameters for M1 and M2 are presented in Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org. Compared with icatibant, M1 and M2 were slowly formed (T_{max} was ~2.0 hours after the SC dose) and showed a lower exposure, based on lower area under the plasma concentration-time curve from time 0 to 4 hours postdose, area under the plasma concentration-time curve from time 0 to t hours postdose, and C_{max}. These findings are consistent with the data seen in adults receiving icatibant 30 mg.[29]

DISCUSSION

Symptoms of C1-INH-HAE typically begin before adulthood and can be severe.[7] Data supporting HAE treatments in children and adolescents remain sparse, although pediatric subpopulations are increasingly being evaluated in key clinical studies and patient registries,[12,30-37] We report efficacy, safety/tolerability, and PK profile of a single SC icatibant dose in pediatric patients with C1-INH-HAE, representing one of the few trials enrolling children younger than 6 years with C1-INH-HAE with HAE attacks.

Icatibant provided rapid symptom relief, regardless of age, pubertal status, or HAE attack location or severity. Median TOSR and TTMS were notably similar, perhaps because most

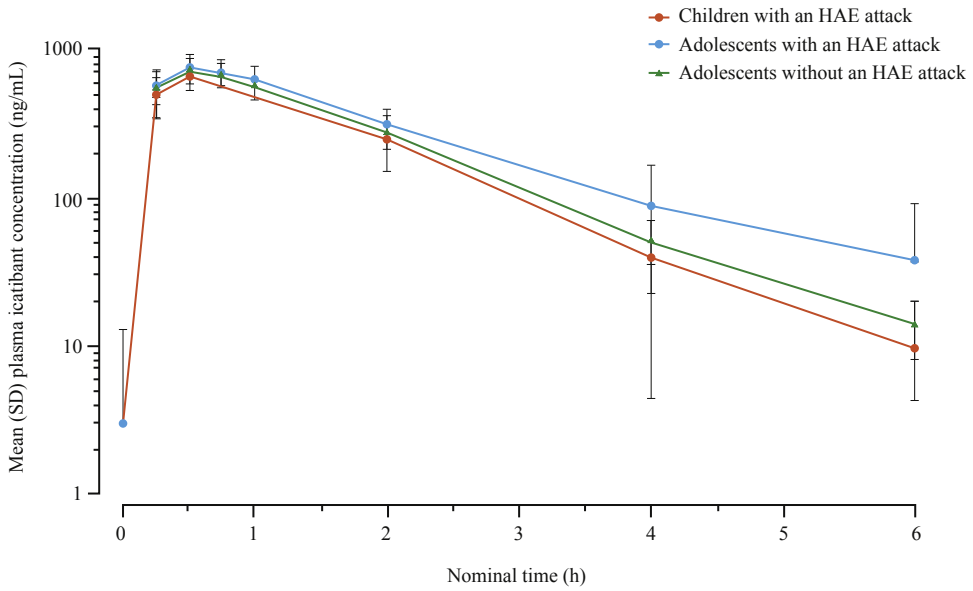

FIGURE 3. Mean plasma concentration-time profile of icatibant (semi-log scale).

TABLE IV. Estimated PK parameters for icatibant

Parameter	Children with HAE attack (n = 9)	Adolescents with HAE attack (n = 11)	Adolescents without HAE attack (n = 10)
$AUC_{0\text{-}4}$ (h • ng)/mL	1241 ± 319	1448 ± 304	1335 ± 211
$AUC_{0\text{-}t}$ (h • ng)/mL	1289 ± 325	1573 ± 372	1398 ± 225
$AUC_{0\text{-}\infty}$ (h • ng)/mL	1243 ± 244	1710 ± 569	1416 ± 229
C_{max} (ng/mL)	659 ± 158	805 ± 125	761 ± 133
T_{max} (h)	0.42 ± 0.13	0.55 ± 0.19	0.57 ± 0.17
$t_{1/2}$ (h)*	0.80 ± 0.04	1.34 ± 0.96	0.90 ± 0.10
CL/F (mL/min)*	10.8 ± 4.63	13.1 ± 3.42	19.3 ± 4.84
CL/F/weight (L/h/kg)*	0.33 ± 0.08	0.26 ± 0.08	0.29 ± 0.05
V_z/F (L)*	12.5 ± 5.28	23.5 ± 13.9	25.4 ± 8.87
V_z/F/weight (L/kg)*	0.39 ± 0.11	0.44 ± 0.18	0.37 ± 0.09

$AUC_{0\text{-}4}$, Area under the plasma concentration-time curve from time 0 to 4 h postdose; *$AUC_{0\text{-}t}$*, area under the plasma concentration-time curve from time 0 to *t* h postdose; *$AUC_{0\text{-}\infty}$*, area under the plasma concentration-time curve from time 0 to infinity; *CL/F*, total plasma clearance; $t_{1/2}$, elimination half-life; *Vz/F*, volume of distribution.
Values are mean ± SD.
*n = 6 for children.

symptoms at onset were mild to moderate. As such, when symptom improvement began (TOSR), the symptom severity had already reached mild or absent (TTMS) level. Also, because the allowable treatment window was wide (12 hours, vs 6 hours for abdominal or cutaneous attacks in the phase 3 For Angioedema Subcutaneous Treatment study in adults),[23] spontaneous improvement may have begun at time of assessment. In addition, TTMS in adolescents was faster than in children.

Although direct efficacy comparisons between pediatric and adult patients cannot be made (given the differences in patient populations and study designs), our findings demonstrated rapid resolution of symptoms in pediatric patients experiencing HAE attacks, consistent with the treatment response shown in adults. The mean composite symptom scores improved over time, in keeping with findings in the phase 3 For Angioedema Subcutaneous Treatment study.[23]

Icatibant was generally well tolerated. Most patients experienced injection-site reactions; however, most were mild or moderate severity and resolved by 6 hours postdose. With regard to impact on hormone levels, bradykinin has been shown to play a role in regulating follicular development and ovulation in mice.[38] Preclinical studies of icatibant in rats and dogs demonstrated delayed maturation of reproductive organs.[39] In our study, no clinically significant impact on reproductive hormones was observed after a single icatibant injection, regardless of pubertal status.

The PK analysis of icatibant demonstrated a monophasic plasma concentration-time profile, with similar findings regardless of patient pubertal status and absence or presence of an HAE attack. Icatibant demonstrated rapid absorption, and systemic exposure (ie, C_{max} and area under the curve) was sufficiently high to achieve a clinically meaningful response.

Our study had several limitations, including an open-label, nonrandomized design, small patient cohort (few children <6 years), efficacy analysis based on a single icatibant administration, and a long pretreatment window. In addition, dose ranges were not evaluated, and all HAE attacks were mild to moderate. However, this study was prospectively designed and assessed efficacy and safety via a robust 5-point scale. A randomized

double-blind design would be deemed unethical in this patient population.

Despite the limitations, this study helps fulfill an important unmet need for phase 3 trials in pediatric patients with rare diseases, as emphasized in international consensus guidelines.[21] Taken together, our findings suggest an important place in therapy for icatibant in treating HAE attacks in children and adolescents.

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TABLE E1. Composite investigator-assessed symptom score (efficacy population): Observed values and change from pretreatment

	Children (n = 11)		Adolescents (n = 11)		Overall (N = 22)	
Time	Actual value	Change from predose	Actual value	Change from predose	Actual value	Change from predose
Pretreatment (0 h)	0.523 ± 0.374	—	0.614 ± 0.318	—	0.568 ± 0.342	—
1 h posttreatment	0.273 ± 0.109	−0.250 ± 0.301	0.273 ± 0.295	−0.341 ± 0.384	0.273 ± 0.217	−0.295 ± 0.340
2 h posttreatment	0.148 ± 0.146	−0.375 ± 0.280	0.159 ± 0.178	−0.455 ± 0.341	0.153 ± 0.159	−0.415 ± 0.307
4 h posttreatment	0.102 ± 0.094	−0.420 ± 0.350	0.125 ± 0.177	−0.489 ± 0.342	0.114 ± 0.139	−0.455 ± 0.340
6 h posttreatment	0.023 ± 0.051	−0.500 ± 0.391	0.091 ± 0.149	−0.523 ± 0.335	0.057 ± 0.114	−0.511 ± 0.355
8 h posttreatment	NA	NA	0.125* ± 0.000	−0.188* ± 0.088	0.125* ± 0.000	−0.188* ± 0.088

NA, Not applicable.
Values are mean ± SD.
*n = 2.

TABLE E2. FPS-R score: Observed value and change from pretreatment (efficacy population)

	Children (n = 9)		Adolescents (n = 11)		Overall (N = 20)	
Time	Actual value	Change from predose	Actual value	Change from predose	Actual value	Change from predose
Pretreatment (0 h)	4.7 ± 3.74 [n = 9]	—	6.2 ± 2.33 [n = 9]	—	5.4 ± 3.13 [n = 18]	—
1 h posttreatment	2.2 ± 2.11 [n = 9]	−2.4 ± 2.60 [n = 9]	2.7 ± 2.65 [n = 9]	−3.6 ± 2.79 [n = 9]	2.4 ± 2.33 [n = 18]	−3.0 ± 2.68 [n = 18]
2 h posttreatment	1.3 ± 2.24 [n = 9]	−3.3 ± 3.61 [n = 9]	2.0 ± 2.31 [n = 7]	−3.7 ± 3.15 [n = 7]	1.6 ± 2.22 [n = 16]	−3.5 ± 3.31 [n = 16]
4 h posttreatment	0.9 ± 2.03 [n = 9]	−3.8 ± 3.80 [n = 9]	0.7 ± 1.35 [n = 11]	−5.3 ± 2.24 [n = 9]	0.8 ± 1.64 [n = 20]	−4.6 ± 3.13 [n = 18]
6 h posttreatment	0 ± 0 [n = 9]	−4.7 ± 3.74 [n = 9]	1.6 ± 3.07 [n = 11]	−4.2 ± 3.07 [n = 9]	0.9 ± 2.38 [n = 20]	−4.4 ± 33.3 [n = 18]
8 h posttreatment	0 ± 0 [n = 4]	−5.0 ± 3.46 [n = 4]	2.0 ± 3.32 [n = 9]	−4.0 ± 3.06 [n = 9]	1.4 ± 2.87 [n = 13]	−4.4 ± 3.07 [n = 11]
24 h posttreatment	1.1 ± 2.27 [n = 7]	−2.3 ± 2.93 [n = 7]	1.1 ± 2.07 [n = 11]	−4.9 ± 3.33 [n = 9]	1.1 ± 2.08 [n = 18]	−3.8 ± 3.34 [n = 16]
48 h posttreatment	0 ± 0 [n = 7]	−4.0 ± 4.00 [n = 7]	1.8 ± 2.71 [n = 8]	−3.7 ± 3.90 [n = 7]	0.9 ± 2.12 [n = 15]	−3.9 ± 3.80 [n = 14]

Values are mean ± SD.

TABLE E3. Estimated PK parameters for M1

Parameter	Children with HAE attack (n = 9)	Adolescents with HAE attack (n = 11)	Adolescents without HAE attack (n = 10)
$AUC_{0\text{-}4}$ (h • ng)/mL	446 ± 175	665 ± 94	708 ± 80
$AUC_{0\text{-}t}$ (h • ng)/mL	605 ± 249	896 ± 180	922 ± 91
$AUC_{0\text{-}\infty}$ (h • ng)/mL	NC*	1052 ± 493†	1323 ± NC‡
C_{max} (ng/mL)	158 ± 62.4	218 ± 28.2	237 ± 26.9
T_{max} (h)	2.05 ± 0.86	1.70 ± 0.51	1.80 ± 0.42
$t_{1/2}$ (h)	NC*	2.18 (0.79)†	2.91 ± NC‡
Icatibant to M1 $AUC_{0\text{-}t}$ ratio	1.09 ± 0.46	0.81 ± 0.13	0.70 ± 0.12

$AUC_{0\text{-}4}$, Area under the plasma concentration-time curve from time 0 to 4 h postdose; *$AUC_{0\text{-}t}$*, area under the plasma concentration-time curve from time 0 to *t* h postdose; *$AUC_{0\text{-}\infty}$*, area under the plasma concentration-time curve from time 0 to infinity; *NC*, not calculated; $t_{1/2}$, elimination half-life.
Values are mean ± SD.
*n = 0.
†n = 3.
‡n = 2.

TABLE E4. Estimated PK parameters for M2

Parameter	Children with HAE attack (n = 9)	Adolescents with HAE attack (n = 11)	Adolescents without HAE attack (n = 10)
$AUC_{0\text{-}4}$ (h • ng)/mL	592 ± 204	828 ± 186	828 ± 105
$AUC_{0\text{-}t}$ (h • ng)/mL	816 ± 274	1128 ± 283	1089 ± 135
$AUC_{0\text{-}\infty}$ (h • ng)/mL	NC*	883 ± NC†	1417 ± NC†
C_{max} (ng/mL)	213 ± 76.9	281 ± 64.1	276 ± 33.5
T_{max} (h)	2.27 ± 1.08	2.18 ± 1.33	1.80 ± 0.42
$t_{1/2}$ (h)	NC*	1.89 ± NC†	2.84 ± NC†
Icatibant to M2 $AUC_{0\text{-}t}$ ratio	0.74 ± 0.27	0.62 ± 0.07	0.56 ± 0.05

$AUC_{0\text{-}4}$, Area under the plasma concentration-time curve from time 0 to 4 h postdose; *$AUC_{0\text{-}t}$*, area under the plasma concentration-time curve from time 0 to *t* h postdose; *$AUC_{0\text{-}\infty}$*, area under the plasma concentration-time curve from time 0 to infinity; *NC*, not calculated; $t_{1/2}$, elimination half-life.
Values are mean ± SD.
*n = 0.
†n = 2.