Original Article

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

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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.

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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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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;■:■-■)**

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.