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The Icatibant Outcome Survey: treatment of laryngeal angioedema attacks

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Objective **To characterize the management and outcomes of life-threatening laryngeal attacks of hereditary angioedema (HAE) treated with icatibant in the observational Icatibant Outcome Survey (NCT01034969) registry.**

Methods **This retrospective analysis was based on data from patients with HAE type I/II who received healthcare professional-administered or self-administered icatibant to treat laryngeal attacks between September 2008 and May 2013.**

Results **Twenty centers in seven countries contributed data. Overall, 42 patients with HAE experienced 67 icatibant-treated laryngeal attacks. Icatibant was self-administered for 62.3% of attacks (healthcare professional-administered, 37.7%). One icatibant injection was used for 87.9% of attacks, with rescue or concomitant medication used for 9.0%. The median time to treatment was 2.0 h ($n = 31$ attacks) and the median time to resolution was 6.0 h ($n = 35$ attacks).**

Conclusions **This analysis describes successful use of icatibant for the treatment of laryngeal HAE attacks in a real-world setting.** ***European Journal of Emergency Medicine*** **23:224–227**

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Keywords: acquired angioedema, C1-inhibitor deficiency, hereditary angioedema, icatibant, laryngeal edema, observational study, therapy

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Introduction

Hereditary angioedema (HAE) is characterized by recurrent episodes of localized swelling of the skin or mucous membranes [1]. Although rare, laryngeal angioedema attacks are considered medical emergencies because of the potential for airway obstruction [1]. Published guidelines recommend that appropriate pharmacotherapy is administered promptly. Patients may also require intubation or tracheotomy to maintain airway patency [2]. Without timely treatment, minor symptoms may enter a rapidly progressive dyspneic phase, and ultimately fatal asphyxiation may occur within hours of symptom onset [3]. Angioedema of HAE does not respond to conventional treatments such as corticosteroids, antihistamines, or epinephrine and historically, mortality has been as high as 30% [3]. Asphyxiation can affect patients of any age, including children, and may occur during the first occurrence of a laryngeal attack [3]. Because of the seriousness of laryngeal attacks, emergency care specialists should be well informed of appropriate and effective treatment.

Icatibant is licensed in numerous countries as a subcutaneous injection, administered by a healthcare professional (HCP) or the patient, for the treatment of acute HAE attacks in adults with C1-inhibitor (C1-INH) deficiency [4]. The use of icatibant to relieve symptoms of laryngeal angioedema attacks is supported by analyses of subsets of patients in phase III trials [5,6]. However, randomized-controlled trials of treatments for laryngeal attacks have been limited by the low frequency of these attacks and ethical issues associated with manipulating treatment for a potentially fatal condition; thus, data from observational studies are useful.

We analyzed data from the Icatibant Outcome Survey (IOS; NCT01034969) registry to further characterize the clinical profile, management, and outcomes of HAE type I/II patients with icatibant-treated laryngeal attacks. Patients were managed according to routine clinical practice, providing insight into outcomes in a 'real-world' setting.

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Methods

IOS is a prospective, international, multicenter, observational study to monitor safety and clinical outcomes in patients with HAE type I, II or acquired C1-INH deficiency enrolled in the registry and prescribed icatibant. Data were collected for icatibant-treated and untreated attacks. The methodology for IOS has been described previously [7].

IOS is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Approval from local ethics committees and/or local health authorities, and written informed consent, were obtained.

Analyses included data from patients with HAE type I/II who had experienced one or more laryngeal attacks treated with HCP-administered or self-administered icatibant between September 2008 and May 2013. Self-administered icatibant may have been administered by patients or family members/carers after training in the subcutaneous injection technique by an HCP, but this was not a licensed use before 2011.

Patient demographics and characteristics were recorded at enrollment, together with retrospective data for any previous icatibant-treated attacks. Details of attacks treated with icatibant and concomitant medications were obtained at enrollment and routine visits, typically every 6 months thereafter. Attack severity was described by patients and after discussion with an HCP, severity was classified as mild (mild interference with daily activities), moderate (moderate interference with daily activities and no other countermeasures required), severe (severe interference with daily activities and with or without other countermeasures), or very severe (very severe interference with daily activities and countermeasures required).

Laryngeal attacks were defined as such by the patient and/or HCP and may have included swellings in different parts of the tongue, pharynx, and/or upper airway. For each icatibant-treated laryngeal attack with complete time and date information, time to treatment (from the onset of attack to the first icatibant injection), time to resolution (from the first icatibant injection to complete symptom resolution of all angioedema), and duration of attack (from the onset of attack to complete symptom resolution) were calculated. Descriptive statistics were used throughout.

Results

Twenty centers in seven countries (Denmark, France, Germany, Israel, Italy, Spain, UK) contributed data for these analyses. A total of 67 laryngeal angioedema attacks were treated with icatibant in 42 patients with HAE type I/II, most of which were rated as severe/very severe (71.7%; Table 1). Icatibant was self-administered for 62.3% of attacks, and a single icatibant injection was used for 87.9% of attacks. Rescue or concomitant medication was used for 9.0% of attacks [analgesics ($n=1$ attack); antifibrinolytics ($n=2$ attacks); anxiolytics and C1-INH ($n=1$ attack); C1-INH alone ($n=1$ attack); other rescue medications ($n=1$ attack)]. Twenty-one (31.3%) laryngeal attacks occurred in patients receiving long-term prophylaxis (LTP); the most commonly used LTP medications were danazol ($n=9$ attacks) and tranexamic acid ($n=4$ attacks). The treatment was well tolerated: two adverse events (acne and hair loss) in two patients were reported as possibly related to icatibant.

Eight attacks in seven patients were treated with two icatibant injections. Of these, three attacks were initially treated by self-administration and five by an HCP. One of the patients was receiving LTP with danazol, one was receiving LTP with tranexamic acid, and five did not receive any LTP or rescue medications. Two attacks treated with two icatibant injections were evaluable, both

Table 1 Characteristics and management of icatibant-treated laryngeal angioedema attacks in patients with HAE type I/II

Parameters	*n* (%)
Patients [total number (%)]	42 (100.0)
Female sex	27 (64.3)
Experienced attack under LTP	15 (35.7)
Attacks [total number (%)]	67 (100.0)
Affected sites	
Single (larynx)	44 (65.7)
Multiple	23 (34.3)
Skin	16 (23.9)
Abdomen	10 (14.9)
Other	1 (1.5)
Severity[a]	
Mild/moderate	17 (28.3)
Severe/very severe	43 (71.7)
LTP	
No	46 (68.7)
Yes	21 (31.3)
C1-INH	3 (14.3)
Danazol	9 (42.9)
Stanozolol	1 (4.8)
Tranexamic acid	4 (19.0)
Tranexamic acid + oxandrolone	3 (14.3)
Tranexamic acid + oxandrolone + stanozolol	1 (4.8)
Icatibant administration[b]	
HCP-administered	23 (37.7)
Self-administered	38 (62.3)
Number of icatibant injections[c]	
1	58 (87.9)
2	8 (12.1)
Rescue C1-INH administered[c,d]	
No	64 (97.0)
Yes	2 (3.0)
Rescue C1-INH, or any other rescue or concomitant medication, administered[d]	
No	61 (91.0)
Yes	6 (9.0)

C1-INH, C1-inhibitor; HAE, hereditary angioedema; HCP, healthcare professional; LTP, long-term prophylaxis.
[a]Data missing for seven patients.
[b]Data missing for six patients.
[c]Data missing for one patient.
[d]Analgesics were administered for one attack; antifibrinolytics were administered for two attacks; C1-INH was administered for one attack; C1-INH and anxiolytics were administered for one attack; other rescue medications were administered for one attack.

Table 2 Treatment outcomes for icatibant-treated laryngeal angioedema attacks in patients with HAE type I/II

Outcome	Number of patients	Number of attacks (missing)	Median time (h) (IQR)
Time to treatment	26	31 (36)	2.0 (1.0–8.0)
Time to resolution	26	35 (32)	6.0 (2.0–21.0)
Duration of attack	22	25 (42)	8.5 (4.5–19.8)

HAE, hereditary angioedema; IQR, interquartile range.

in patients with HAE type I. Time between the first and the second injection was 3.0 and 8.0 h and time from the second injection to symptom resolution was 4.0 and 2.0 h, respectively. Neither required the use of rescue medication.

Across all HAE type I/II attacks, median time to treatment, time to resolution, and duration of attack were 2.0, 6.0, and 8.5 h, respectively (Table 2).

Twenty-four laryngeal attacks were reported as untreated: 13 in the retrospective phase (pre-IOS entry) and 11 during follow-up. Overall, these lasted a median of 48 (range 2–120) h.

An additional 12 laryngeal attacks were treated with icatibant in four patients with angioedema because of acquired C1-INH deficiency. All of these attacks were treated with a single icatibant injection, and the use of rescue or concomitant medication was infrequent [analgesics, anxiolytics, or C1-INH ($n=0$ attacks); antifibrinolytics ($n=1$ attack); other rescue medications ($n=1$ attack)]. For 10 attacks with available data ($n=3$ patients), the median (interquartile range) time to treatment and time to resolution were 0.2 h (0.1–0.5 h) and 1.1 h (0.2–10.5 h), respectively. Two additional untreated laryngeal attacks, lasting 48 and 72 h, respectively, were reported in the acquired angioedema group retrospectively.

Discussion

These analyses support the use of icatibant for the treatment of laryngeal attacks in patients with HAE type I/II in a 'real-world' setting. Of note, a single icatibant injection was sufficient in the majority of cases, and the use of a second injection or rescue medication was infrequent. This is consistent with the findings of analyses of laryngeal HAE attacks treated in phase III clinical studies of icatibant [5,6].

For evaluable HAE type I/II laryngeal attacks, icatibant was associated with a median duration of attack of 8.5 h. A large retrospective series documented a mean (SD) of 100.8 (26.2) h duration for 324 untreated episodes of laryngeal edema in 24 patients between 1970 and 1999 [8]. Patients treated with icatibant in our series appeared to have a shorter duration of attack, similar to that reported with the alternative treatment C1-INH [mean duration 15.3 (9.3) h] [8].

Icatibant was more commonly self-administered than HCP-administered, facilitating the prompt treatment of laryngeal attacks as patients go about their daily lives. This is pertinent as a previous analysis of the IOS registry indicated that early administration of icatibant reduces attack duration [7]. Published HAE guidelines and consensus statements have recognized the importance of early treatment and, to support this, recommend that patients are trained to self-administer treatment as appropriate [2,9]. However, as per clinical practice recommendations and icatibant prescribing information, even following self-administration of treatment, patients with laryngeal attacks should always seek medical advice and should be managed in an appropriate medical institution after injection [2,4].

Laryngeal attacks occurred in patients with HAE type I/II despite the administration of LTP in almost one-third of cases. This suggests that all patients should be prepared to seek prompt acute treatment for laryngeal attacks, whether or not they use LTP.

Although not a licensed indication for icatibant, patients with angioedema because of acquired C1-INH deficiency, which shares an underlying mechanism and clinical profile with HAE [1], treated laryngeal attacks promptly after onset (median time: 0.2 h) and subsequent resolution occurred relatively rapidly (median time: 1.1 h). The rarity of this condition has limited the feasibility of clinical trials, and therefore, it is important to share observational data within the clinical community. The authors encourage the publication of further observational data on the treatment of angioedema because of acquired C1-INH deficiency in an effort to help address the lack of clinical trial data.

Overall, these analyses are consistent with the efficacy and safety profile of icatibant for laryngeal attacks in phase III studies [5,6], and support recommendations that include icatibant as a first-line treatment option for the management of HAE in emergency departments [10].

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Conflicts of interest

H.L. has received research grant support and/or speaker/consultancy fees from CSL Behring, Dyax, Pharming, Shire, SOBI, and ViroPharma (ViroPharma is part of the Shire Group of Companies); W.A. has acted as a medical advisor and speaker for CSL Behring and Shire, has received funding to attend conferences and other educational events, and has received donations to his departmental fund and participated in clinical trials for Shire; L.B. has received honoraria from CSL Behring, Pharming, Shire and ViroPharma, and her institute has received research funding from CSL Behring and Shire; T.C. has received speaker fees from Shire/Jerini AG and ViroPharma, consultancy fees from CSL Behring, Shire/Jerini AG, SOBI and ViroPharma, and funding for travel and meeting attendance from CSL Behring and Shire, and has participated in clinical trials for CSL Behring, Dyax, Pharming, and Shire/Jerini AG; M.M. has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, Shire/Jerini AG and ViroPharma; V.F. is a full-time employee of Shire, Zug, Switzerland; A.Z. has received speaker fees from CSL Behring, Shire, SOBI and ViroPharma, and consultancy fees from CSL Behring, Shire and ViroPharma.

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