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EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study

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Abstract

Background: The *For Angioedema Subcutaneous Treatment* (FAST)-2, a phase III, double-blind, randomized, multicenter, placebo-controlled study (ClinicalTrials.gov identifier: NCT00500656), established the efficacy and safety of single injections of icatibant, a bradykinin B₂ receptor antagonist, in the treatment of hereditary angioedema (HAE) attacks. Here, we evaluate the efficacy and safety of repeated treatment with icatibant in adult patients experiencing HAE attacks during the FAST-2 open-label extension (OLE) phase.

Methods: Patients completing the controlled phase were eligible to participate in the OLE phase and receive open-label icatibant (30 mg subcutaneously) for the treatment of cutaneous, abdominal, and/or laryngeal HAE attack(s) severe enough to warrant treatment. Time to onset of symptom relief was calculated for each attack. Descriptive analyses (median, 95% CIs) were performed for all attacks; *post hoc* analyses were conducted in patients with at least five icatibant-treated attacks throughout the FAST-2 OLE phase. Safety was also monitored.

Results: Fifty-four patients received icatibant for 374 attacks (176 cutaneous, 168 abdominal, and 30 laryngeal). For cutaneous and/or abdominal attacks (attacks 2–5), the median times to onset of symptom relief ranged between 2.0 and 2.5 h. For all laryngeal attacks, the median times to regression (start of improvement) of symptoms ranged between 0.3 and 4.0 h. *Post hoc* analyses showed that the overall median time to onset of symptom relief was 2.0 h. Overall, 89.8% of attacks resolved with a single icatibant injection. No drug-related serious adverse events were reported.

Conclusions: These findings have demonstrated the efficacy and safety of repeated icatibant treatment for HAE attacks.

Hereditary angioedema (HAE) is a rare and debilitating disorder characterized by recurrent, unpredictable episodes of tissue swelling and pain, involving the skin, gastrointestinal

tract, upper respiratory tract, and other organs (1). Attacks can be severe and prolonged and, in the case of laryngeal and hypolaryngeal attacks, are potentially life-threatening

when left untreated (2, 3). Given the unpredictable nature, severity, and duration of attacks, patients should seek immediate access to treatment (4).

In HAE, deficiency of C1-esterase inhibitor (C1-INH), a key regulator of the kallikrein–kinin plasma cascade system and classical complement pathway (5), activates kallikrein and leads to an overproduction of bradykinin (5–8). Bradykinin interacts with B₂ receptors causing vasodilatation, increased vascular permeability, extravasation, and rapid accumulation of fluid in interstitial tissues (9, 10). In patients with HAE, C1-INH deficiency leads to uninhibited bradykinin production that culminates in the development of disease symptoms (11–16). Blockade of the bradykinin B₂ receptor therefore represents a valid therapeutic rationale for HAE treatment.

Icatibant, a selective bradykinin B₂ receptor antagonist, was initially investigated in an open-label phase II study, with results demonstrating that single subcutaneous injections (30 mg) were clinically effective (17). Single-dose efficacy was also demonstrated in three phase III, randomized, controlled, multicenter studies: *For Angioedema Subcutaneous Treatment* (FAST)-1, 2 and 3 (18, 19).

However, as HAE is a chronic disease, characterized by recurrent attacks over a patient's lifetime, the demonstration of the effect of repeated treatment on efficacy and safety is of high therapeutic value. Here, we report data from the open-label extension (OLE) phase of FAST-2, which investigated the efficacy and safety of repeated icatibant treatment in an HAE patient population.

Methods

Study design

For Angioedema Subcutaneous Treatment-2 was a phase III, randomized, double-blind, multicenter, tranexamic acid-controlled study of subcutaneous icatibant (30 mg) for the treatment of patients experiencing cutaneous, abdominal, or laryngeal HAE attacks. The 36-month study, conducted at 35 centers in 12 countries, comprised two phases: a controlled phase reported previously (18) and an OLE phase. The OLE phase included patients from the controlled phase who received treatment for an attack or were eligible to participate but did not experience an attack or did not experience an attack severe enough to warrant treatment. These latter two cohorts entered the OLE phase following the controlled phase closure.

The study was approved by the Independent Ethics Committees of each participating center and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and current regulatory requirements. All patients gave written informed consent.

Patients

Inclusion criteria for participation in the OLE phase were the same as for the controlled phase (18). A brief summary of these inclusion criteria is as follows: patients were aged

≥18 years with a documented diagnosis of HAE type I or II who presented with cutaneous, abdominal, or laryngeal attacks severe enough to warrant treatment. However, unlike in the controlled phase, a visual analog scale (VAS) score of ≥30 mm was not a prerequisite for treatment in the OLE phase. The VAS score, based on a 100 mm scale (0 mm = no symptom and 100 mm = worst possible symptom), was used to measure the intensity of cutaneous swelling, cutaneous pain, abdominal pain, and nausea at prespecified timepoints. Visual analog scale scores were not used for the assessment of laryngeal symptoms.

Exclusion criteria included diagnoses of other angioedema, serious concomitant illness, and pregnancy or lactation. Patients were also excluded if they received pain medication prior to the treatment of the current attack, C1-INH products within 3 days of attack onset, or treatment with angiotensin-converting enzyme inhibitors. The first patient was treated in the OLE phase in March 2005, and the last patient visit was March 2008.

Treatment

Patients were treated by a healthcare professional with a single subcutaneous icatibant injection (30 mg) in the abdominal region. If symptoms worsened within 48 h, further injections of icatibant (30 mg) were permitted up to a maximum of three (at least 6 h apart). The attack was considered new if symptoms worsened 48 h or more after initial treatment. Rescue medication, including C1-INH and symptomatic therapy (e.g., for nausea or vomiting), was permitted.

Not all attacks were treated with icatibant. Some subjects had untreated attacks and/or attacks treated with other medication. The subset of attacks treated with icatibant is reported here.

Patient assessments

Pretreatment assessments included a urine pregnancy test and vital signs, symptom assessment (patient-assessed VAS and symptom score), and global assessment (investigator-assessed). Rescue medication and concomitant medications were documented.

Following treatment, patients were monitored for 4–5 h and their symptoms assessed by VAS every 30 min from 1 to 4 h and at 5, 6, 8, 10, and 12 h. A symptom score assessment, based on a five-point scale (0 = absence of symptoms; 1–4 = mild, moderate, severe, or very severe symptoms, respectively), was performed at 2, 4, 6, and 10 h post-treatment. Follow-up visits were scheduled 24–48 h post-treatment. The final assessment was carried out on Day 14 (±2). Investigators recorded rescue medication use, adverse events (AEs), and injection site reactions (ISRs).

Efficacy measures

Cutaneous and abdominal attacks

Irrespective of cutaneous symptom severity, patients experiencing both cutaneous and abdominal symptoms were classi-

fied as 'abdominal' if at least one abdominal symptom was moderate-to-very severe. Efficacy measures included times to onset of symptom relief, almost complete symptom relief, and regression (start of improvement) of symptoms (patient-assessed).

Primary symptom relief was defined as a reduction from pretreatment in a single primary symptom VAS score. Symptom relief was classified as any reduction below (6/7)* pretreatment value-16 for pretreatment VAS ≥ 30 mm, corresponding to a 31 mm reduction for pretreatment VAS of 100 mm and 21 mm for pretreatment VAS of 30 mm. For abdominal attacks, primary VAS was defined as abdominal pain; for cutaneous attacks, it was the more severe of either skin swelling or skin pain. Time to almost complete symptom relief was defined as a VAS score between 0 and 10 mm for at least three consecutive measurements. Time to regression of symptoms was recorded as the time the patient started to feel improvement. For cutaneous and abdominal attacks, patients recorded symptom scores for severity of cutaneous swelling and pain, skin irritation, erythema, abdominal pain, nausea, vomiting, and diarrhea.

Laryngeal attacks

Irrespective of cutaneous and/or abdominal symptom severity, patients with laryngeal symptoms at pretreatment were always defined as such and treated with open-label icatibant. Efficacy measures included patient-assessed time to regression of symptoms, change in symptom score severity, and investigator's global assessment of attack severity.

Patients also recorded symptom scores for difficulty swallowing and voice change (in addition to those recorded for cutaneous and abdominal attacks). The investigator's global assessment of attack severity classified symptoms as cutaneous, abdominal, and laryngeal, using the same five-point scale as described previously.

Safety measures

Safety was evaluated up to 24 weeks post-treatment and included all patients. Assessments included the incidence and severity of AEs and ISRs.

Statistical analysis

Efficacy and safety analyses included all patients treated in the OLE phase stratified by on-study attack number (first attack, second attack, etc.). Times to onset of symptom relief, almost complete symptom relief, and regression of symptoms were analyzed using Kaplan–Meier methods. Descriptive statistics, medians, and 95% CIs were recorded by attack number for attacks where data for ≥ 10 patients were available.

The majority of patients experienced their first-treated attack (attack 1) during the controlled phase; data from their first-treated attack in the OLE phase were therefore categorized as attack 2. Eight patients experienced their first attack during the OLE phase, and for completeness, these data are also presented.

Post hoc analyses

For the cohort of patients with at least five icatibant-treated attacks (including attacks treated in the controlled phase), descriptive statistics, medians, and 95% CIs are presented and stratified by icatibant-treated attack number. The purpose of this analysis was to assess the efficacy of repeated treatment with icatibant. Observation period AEs are also reported. These are defined as treatment-emergent AEs occurring prior to or on the date of the Day 14 visit or study discontinuation (whichever occurs first) for each study drug-treated attack.

Table 1 Efficacy measures evaluated in patients treated during the open-label extension phase†

Icatibant-treated attack (number)	Time to onset of symptom relief‡, h			Time to almost complete symptom relief¶, h			Time to regression of symptoms††, h		
	N§	Censored	Median (95% CI), h	N	Censored	Median (95% CI), h	N	Censored	Median (95% CI), h
Attack 2	39	0	2.0 (1.5, 2.8)	45	6	6.0 (5.0, 14.0)	49	4	0.7 (0.5, 1.5)
Attack 3	24	0	2.5 (1.5, 3.0)	26	5	10.0 (5.0, 29.7)	29	6	0.8 (0.5, 1.5)
Attack 4	14	1	2.3 (1.0, 17.8)	17	2	6.1 (3.5, 42.3)	20	2	1.2 (0.5, 3.2)
Attack 5	10	0	2.5 (1.3, 10.0)	11	1	22.0 (3.0, 31.6)	11	3	2.6 (0.8, –)

†Where data for ≥ 10 patients were available.

‡Onset of symptom relief was defined as any reduction below (6/7)*pretreatment value-16 for pretreatment VAS ≥ 30 mm for a single primary symptom VAS score. For abdominal attacks, the primary VAS score was defined as abdominal pain and for cutaneous attacks was the more severe of either skin swelling or skin pain was determined retrospectively after symptom relief had been documented at three consecutive measurements. The median time to onset is calculated using Kaplan–Meier methodology.

§Number of patients with pretreatment VAS ≥ 30 mm.

¶Almost complete symptom relief (defined as a score between 0 and 10 mm on the VAS scale) was determined retrospectively after symptom relief had been documented at least three consecutive measurements. The median time to almost complete symptom relief is calculated using Kaplan–Meier methodology.

††Time to regression of symptoms was defined as the start of improvement in symptoms according to the patient. The median time to onset is calculated using Kaplan–Meier methodology.

Results

Patient population

Overall, 54 patients received icatibant for 374 attacks (44 patients from the controlled phase and ten patients entered directly into the OLE phase [eight patients who did not receive treatment during the controlled phase and two patients with laryngeal symptoms]). A total of 24 patients were treated for a single attack, and 30 patients were treated for multiple attacks. Moreover, our analyses included five patients treated for 17, 20, 28, 51, and 142 attacks. During the study period, the majority (83.8%) of patients had fewer than five icatibant-treated attacks. All patients received icatibant administered by a healthcare professional, even those patients with multiple attacks. The mean age and weight of patients treated in the FAST-2 OLE phase (42.3 years, 77.61 kg) were similar to those of icatibant-treated patients in the controlled phase (40.4 years, 80.06 kg). The majority of patients were female in both the controlled (66.7%) and OLE (64.8%) phases. Of the 54 patients, 40 experienced 176 cutaneous attacks, 25 experienced 168 abdominal attacks, and 10 experienced 30 laryngeal attacks.

Post hoc analyses of patients with at least five icatibant-treated attacks included 11 patients treated for at least five attacks, seven patients treated for at least ten attacks and five patients treated for at least 15 attacks.

Clinical efficacy

Cutaneous and abdominal attacks

OLE phase. For the cutaneous and/or abdominal attacks where data for ≥ 10 patients were available, the median times to onset of symptom relief were comparable with increasing attack number (Table 1). When the location for these attacks was individualized, this median value ranged from 2.5 to 2.9 h for cutaneous attacks and 1.0 to 2.7 h for abdominal attacks (95% CIs).

Although the median time to almost complete symptom relief involved several confirmatory measurements at nonuniform timepoints, where data for ≥ 10 patients were available, no noticeable variation in the range of median values (95% CIs) was observed between attacks (Table 1).

Patient-assessed median times to regression of symptoms (where data for ≥ 10 patients were available) were also generally similar with increasing attack number (Table 1). For cutaneous attacks, this value ranged between 1.5 and 2.4 h, and for abdominal attacks, the range was 0.5–1.1 h.

Post hoc analyses. *Post hoc* analyses of the cohort of 11 patients treated for at least five attacks in the controlled and OLE phases of FAST-2 demonstrated that the time to onset of primary symptom relief was consistent (Fig. 1A). No noticeable variation with increasing attack number was observed (Table 2).

Time to almost complete symptom relief was generally similar with increasing attack number (Fig. 1B). Median times to almost complete symptom relief ranged between

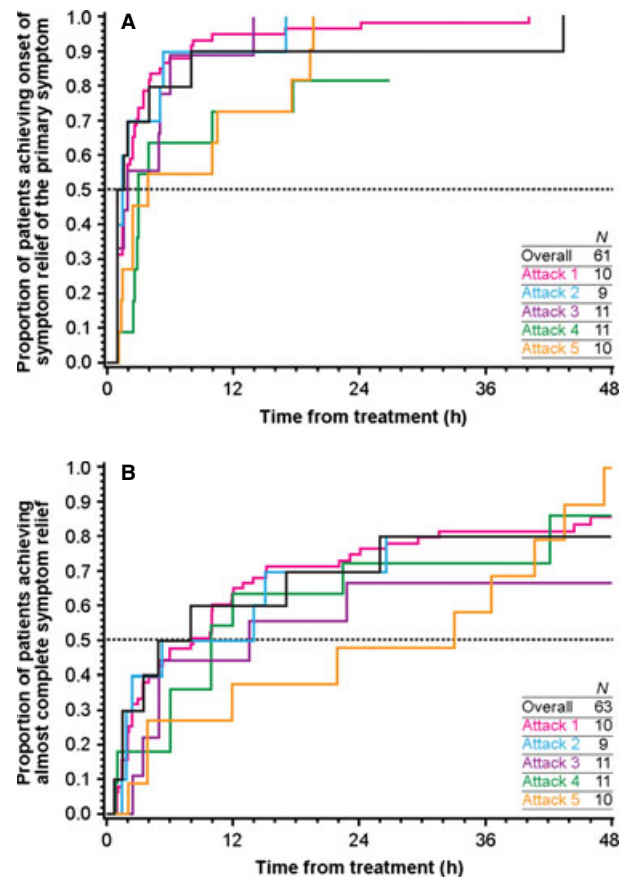


Figure 1 Proportion of patients achieving (A) onset of symptom relief of the primary symptom† and (B) almost complete symptom relief‡. The cohort of patients demonstrated here are from the post hoc analyses of those treated for at least five attacks with icatibant during the controlled and open-label extension phases of FAST-2. †Defined as a reduction from pretreatment in the score for a single primary visual analog scale (VAS) symptom. Symptom relief was defined as any reduction below (6/7)*pretreatment value-16 for patients with a pretreatment VAS ≥ 30 mm. Symptom relief was defined as a 68% reduction from pretreatment in patients with pretreatment VAS < 30 mm. Patients who did not achieve symptom relief within the observation period were censored at the last observation time. The median time to onset of symptom relief of the primary symptom was calculated using Kaplan-Meier methodology. ‡Almost complete symptom relief (defined as a score between 0 and 10 mm on the VAS scale) was determined retrospectively after symptom relief had been documented at least three consecutive measurements. The median time to almost complete symptom relief was calculated using Kaplan-Meier methodology. Please refer to Table 2 for the absolute values.

6.5 and 33.1 h over the first five icatibant-treated attacks (Table 2).

Laryngeal attacks

For laryngeal attacks ($N = 30$), patient-assessed median times to regression of symptoms ranged between 0.3 and 4.0 h for

Table 2 Efficacy measures evaluated in patients treated for at least five attacks with icatibant during the controlled and open-label extension phases of FAST-2†

Icatibant-treated attack (number)	Time to almost complete symptom relief‡, h			Time to onset of symptom relief of the primary symptom§, h		
	N	Censored	Median (95% CI), h	N	Censored	Median (95% CI), h
Attack 1	10	1	9.7 (2.0, 26.7)	10	0	1.5 (1.0, 5.0)
Attack 2	9	2	13.6 (5.0, 66.9)	9	0	2.0 (1.0, 5.0)
Attack 3	11	2	10.0 (6.0, 42.3)	11	1	3.0 (2.6, 17.8)
Attack 4	11	1	33.1 (3.9, 40.8)	11	0	3.9 (1.5, 17.6)
Attack 5	10	2	6.5 (1.5, 26.0)	10	0	1.3 (1.0, 4.0)
Overall	63	–	8.3 (3.5, 12.0)	61	–	2.0 (1.5, 2.5)

†Post hoc analyses.

‡Almost complete symptom relief was determined retrospectively as the earliest of three consecutive measurements in which all VAS scores were between 0 and 10 mm. The median time to almost complete symptom relief is calculated using Kaplan–Meier methodology.

§Onset of symptom relief of the primary symptom was determined retrospectively as the earliest of three consecutive measurements in which there was a reduction below (6/7)*pretreatment value–16 for patients with a pretreatment VAS ≥ 30 mm or a 68% reduction from pretreatment in patients with pretreatment VAS < 30 mm. The median time to onset of symptom relief of the primary symptom was calculated using Kaplan–Meier methodology.

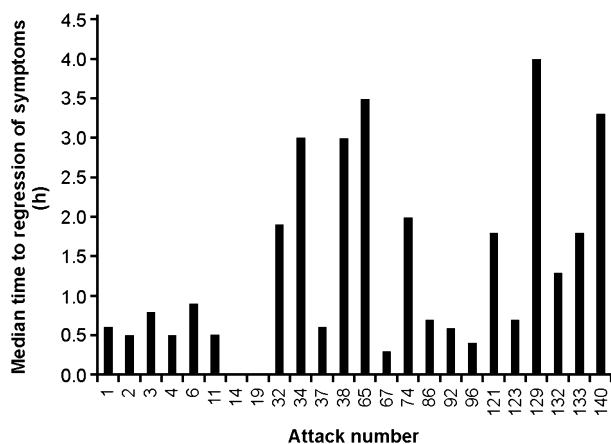


Figure 2 Efficacy† of repeated treatment with icatibant in the treatment of laryngeal attacks across FAST-2. All evaluable patients were included. Irrespective of cutaneous and/or abdominal symptom severity, patients with laryngeal symptoms at pretreatment were always defined as such and treated with open-label icatibant. †Efficacy was measured using the time to regression of symptoms (defined as the start of improvement in symptoms according to the patient). The median time to onset is calculated using Kaplan–Meier methodology).

all attacks (Fig. 2). At pretreatment, three attacks were classified as mild, 11 attacks were moderate, 13 attacks were severe, and six attacks were very severe (three laryngeal attacks were treated during the controlled phase). Irrespective of attack severity, rapid improvement was observed in the severity of laryngeal symptoms within 4 h post-treatment, at which point the majority of laryngeal symptoms were assessed as mild or absent. The pretreatment investigator's global assessment demonstrated that three patients experienced severe ($N = 1$) or very severe ($N = 2$) laryngeal symptoms. At 4 h post-treatment, laryngeal symptoms were absent in two patients and mild in one patient.

Pretreatment patient-assessed symptom scores classified voice change and difficulty swallowing as severe-to-very severe in four and 12 patients, respectively. By 4 h post-treatment, voice change was not sustained and only one patient still had difficulty swallowing.

Safety

OLE phase

Overall, 36 (66.7%) patients experienced 172 AEs. The most commonly occurring AE, reported in 12 (22.2%) patients, was HAE attacks (either a worsening of the current attack or a new attack). Eight (14.8%) patients experienced 17 (9.9%) drug-related AEs; of these, 16 were 'possibly related' and one was 'definitely related' (moderate ISR). All drug-related AEs were either mild (88.2%) or moderate (11.8%). Ten (18.5%) patients reported 20 serious AEs (SAEs); none were considered drug-related. Additionally, 17 (9.9%) of the 172 AEs were reported as severe by ten patients (18.5%); none were considered drug-related. All 54 (100%) patients reported ISRs (mostly erythema and swelling).

No clinically relevant changes in laboratory safety measures, vital signs, or antibody response toward icatibant were observed in patients.

Post hoc analyses

Post hoc analyses demonstrated no trend toward an increasing number of observation period AEs or drug-related AEs with increasing attack number. No observation period SAEs were reported by patients after attack five (Table 3).

Rescue medication and icatibant retreatment

OLE phase

Rescue medication was required by five patients for 11 (2.9%) attacks (seven abdominal and four cutaneous) and was typically due to the worsening of an attack or the

Table 3 *Post hoc* analyses of the safety of repeated treatment with icatibant†

Icatibant-treated attack (number)	Number and % of patients with any event and total number of events					
	Any AE		Any related AE		Any SAE‡	
	N (%)	Events	N (%)	Events	N (%)	Events
Attack 1 (N = 11)	6 (54.5)	7	1 (9.1)	1	0	0
Attack 2 (N = 11)	4 (36.4)	9	1 (9.1)	2	0	0
Attack 3 (N = 11)	3 (27.3)	4	0	0	1 (9.1)	1
Attack 4 (N = 11)	2 (18.2)	3	0	0	1 (9.1)	1
Attack 5 (N = 11)	3 (27.3)	5	1 (9.1)	1	1 (9.1)	2

AE, adverse event; SAE, serious AE.

†*Post hoc* analyses of safety included patients treated for at least five attacks with icatibant across the controlled and open-label extension phases of FAST-2.

‡No SAEs were reported after the fifth icatibant-treated attack.

Table 4 *Post hoc* analyses of the overall number of attacks requiring more than one icatibant injection†

Icatibant-treated attack (number)	N	N (%)
Attack 1	11	1 (9.1)
Attack 2	11	1 (9.1)
Attack 3	11	3 (27.3)
Attack 4	11	0
Attack 5	11	1 (9.1)

†*Post hoc* analyses of safety included patients treated for at least five attacks with icatibant across the controlled and open-label extension phases of FAST-2.

occurrence of a new attack. No patients experiencing laryngeal attacks required rescue medication.

The majority of attacks (89.8%) were successfully treated with a single icatibant injection, with one patient being successfully treated for 141 attacks with 154 icatibant injections. Overall, 38 (10.2%) attacks (21 abdominal, 15 cutaneous, and two laryngeal) in 11 patients required retreatment with icatibant; 37 attacks required a second injection, and one required a third injection. Of these, 12.5% were abdominal attacks, 8.5% were cutaneous attacks, and 6.7% were laryngeal attacks.

Post hoc analyses

Post hoc analyses demonstrated that for those patients who were treated for at least five attacks, the proportion requiring additional injections ranged between 0 and 27.3% (Table 4) and did not increase with repeated icatibant treatment.

Discussion

The results of the FAST-2 OLE phase and *post hoc* analyses demonstrate, for the first time, that the efficacy and safety of repeated treatment with icatibant in HAE attacks are comparable between attacks. The continued response to repeated icatibant treatment in the OLE phase was similar to the

initial response observed in the controlled phase (18). Icatibant was generally well tolerated: no observation period SAEs were reported after the fifth attack, and ISRs were mild to moderate and resolved without medical intervention.

Although this analysis may be limited by the number of patients included, the descriptive nature of these data, particularly for patients experiencing laryngeal attacks, is clinically meaningful. Laryngeal attacks are potentially life-threatening, and early symptom control may help to prevent complications (8, 20). In the 30 laryngeal attacks analyzed in our study, icatibant evoked a median time to regression of symptoms of less than 4 h.

Generally, the efficacy of repeated HAE treatment, for example with antifibrinolytics and anabolic androgens, has been demonstrated with experience, rather than controlled clinical studies (21). Although similar open-label studies have been performed using nanofiltered C1-INH (22) and plasma-derived C1-INH (23), this is one of the first structured, open-label trials to assess icatibant's application in repeated HAE attacks. The results of this study demonstrate that the efficacy and safety of repeated treatment with icatibant have no apparent trend toward a delay in time to onset of symptom relief or a need for additional injections/rescue medication. The durability of effect reported here is particularly important given that a recent international HAE consensus report has reiterated that any angioedema attack can be disabling and/or life-threatening and that all attacks should be effectively treated (ideally self-treated at home by the patients themselves) before these visible or disabling symptoms develop (24).

Conclusion

The findings from this study corroborate the consistent efficacy and safety of subcutaneous icatibant (30 mg) in adults with HAE types I and II across repeated attacks.

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Author contributions

Murat Baş, Jens Greve, Thomas K. Hoffmann, Avner Reshef, Werner Aberer, Marcus Maurer, Shmuel Kivity, Henriette Farkas, Bernard Floccard, Francesco Arcoleo, Ludovic Martin, Brigita Sitkauskiene, Laurence Bouillet, Peter Schmid-Grendelmeier, and Andrea Zanichelli were involved in the conception and design of the study as well as in its conduct and the generation of data. Hongbin Li was the study statistician and was involved in the analysis and interpretation of the study data. All authors critically reviewed the manuscript and approved the final version for submission.

Conflicts of interest

Dr Baş has acted in a consultant/advisor capacity, has received a research grant for participating in a company-sponsored scientific study, has received a travel grant, and has lectured/spoken at a company-sponsored meeting for Shire, has been an investigator in a company-sponsored scientific study for Shire, Jerini AG, ViroPharma GmbH, and Pharming Group NV, and has received honoraria from HAL Allergy Group and Shire.

Dr Greve has been an investigator in a company-sponsored scientific study for Jerini AG, ViroPharma GmbH, and BioAlliance Pharma SA, and has received a travel grant for presenting at a scientific congress from Shire. He has lectured/spoken at a company-sponsored meeting for Shire.

Professor Hoffmann has acted in a consultant/advisor capacity, has received a travel grant, and has lectured/spoken at a company-sponsored meeting for Shire, and has been an investigator in a company-sponsored scientific study for Jerini AG, ViroPharma GmbH, and BioAlliance Pharma SA.

Dr Reshef has acted in a consultant/advisor capacity for Shire and has received a research grant for participating in a company-sponsored scientific study from Jerini AG, Shire,

Pharming, CSL Behring, Dyax, Teva, and Cephalon. He has been an investigator in a company-sponsored scientific study for Jerini AG, Shire, Pharming, CSL Behring, Dyax, Teva, and Cephalon. He has received a travel grant for presenting at a scientific congress from Shire, Pharming, and CSL Behring. He has lectured/spoken at a company-sponsored meeting for Jerini AG, Shire, and Pharming and has received other honoraria payments from Jerini AG and Shire for presentations and consultations.

Professor Aberer has acted as a medical advisor and speaker for Shire and CSL Behring, received funding to attend conferences and other educational events, received donations to his departmental fund, and participated in clinical trials for Shire.

Professor Maurer has acted in a consultant/advisor capacity for Jerini AG, Shire, ViroPharma, and Biocryst. He has received a research grant for participating in a company-sponsored scientific study from Shire and ViroPharma and has been an investigator in a company-sponsored scientific study for CSL Behring, Shire, ViroPharma, and Pharming. He has received a travel grant for presenting at a scientific congress from Shire and ViroPharma and has lectured/spoken at a company-sponsored meeting for Shire and ViroPharma.

Professor Kivity has been an investigator for Shire, Pharming, Dyax, Cephalon, and Actelion.

Professor Farkas has acted in a consultant/advisor capacity for Shire, CSL Behring, ViroPharma, Pharming, and SOBI and has received a research grant for participating in a company-sponsored scientific study from CSL Behring, ViroPharma, and Pharming. She has been an investigator in a company-sponsored scientific study for Shire, CSL Behring, and Pharming and has lectured/spoken at a company-sponsored meeting for Shire.

Dr Floccard has received payment for lectures from Shire and CSL Behring and has been an investigator in a company-sponsored scientific study for Jerini/Shire. He has received a travel grant for presenting at a scientific congress from Shire, Pharming, and CSL Behring.

Dr Arcoleo has been a coinvestigator in a company-sponsored scientific study for Shire/Jerini and Pharming.

Professor Martin has received honoraria from Shire and CSL Behring.

Professor Sitkauskiene has been an investigator in a company-sponsored scientific study for Jerini AG and Shire.

Professor Bouillet has received honoraria from Shire, CSL Behring, Pharming, and ViroPharma.

Professor Schmid-Grendelmeier has acted in a consultant/advisor capacity for Jerini AG, Shire, and CSL Behring. He has been an investigator in a company-sponsored scientific study for Shire and has lectured/spoken at a company-sponsored meeting for Shire.

Dr Li is an employee of Shire.

Dr Zanichelli has acted as an advisor for Shire and has been an invited speaker for CSL Behring and Shire.

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