

Treatment of hereditary angioedema with icatibant: Efficacy in clinical trials versus effectiveness in the real-world setting

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ABSTRACT

Icatibant was efficacious and generally well tolerated for type I or II hereditary angioedema (HAE) attacks in adults in the phase III, randomized, placebo-controlled For Angioedema Subcutaneous Treatment (FAST)-3 trial. The Icatibant Outcome Survey (IOS) is an international, observational study assessing icatibant treatment of HAE attacks. We conducted a posthoc analysis to compare for the first time the treatment of HAE type I or II attacks in patients prescribed icatibant in real-world (IOS) versus controlled trial settings (FAST-3). In FAST-3, patients received icatibant administered by health care professionals (HCPs). In IOS, patients self-administered icatibant or were treated by HCPs. Median time to treatment, time to resolution (almost complete resolution [FAST-3] or complete resolution [IOS]), and attack duration in patients who were treated by an HCP were compared between IOS and FAST-3. Descriptive statistical methods compared nonlaryngeal attacks treated less than 12 hours from attack onset. Analysis included 102 patients (376 attacks) from IOS and 43 patients (43 attacks) from FAST-3 (controlled phase). All endpoints were significantly longer for patients in FAST-3 (HCP administration) versus IOS (HCP administration) ($p < .001$; all comparisons). For FAST-3 (HCP administered) versus IOS (HCP administered), median time from attack onset to treatment was 6.5 versus 2.0 hours, median time to symptom resolution was 8.0 versus 3.5 hours, and median attack duration was 16.9 versus 7.3 hours, respectively. For combined HCP and self-administration in IOS, these endpoints were 1.6, 4.4, and 7.8 hours, respectively. This posthoc analysis showed for the first time that type I and II HAE attacks were treated earlier with icatibant in a real-world versus a phase III setting, with a shortened time to symptom resolution and attack duration. ClinicalTrials.gov: NCT00912093 (FAST-3); NCT01034969 (IOS).

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Hereditary angioedema (HAE) is a rare genetic disorder that manifests as recurrent swelling of the skin, abdomen, and larynx,¹ with a profoundly nega-

tive impact on patients' physical, social, and economic well-being.^{2,3} HAE results from the overproduction of bradykinin by the contact system, which becomes continuously activated due to reduced levels (HAE type I) or dysfunctional forms (HAE type II) of C1-inhibitor protein (C1-INH).⁴ International and United States consensus documents recommend that all patients with HAE should be trained in self-administration of medication once a diagnosis of C1-INH deficiency is confirmed and that all patients should have access to on-demand treatment.^{5–8} Icatibant (Firazyr, Shire) is a subcutaneously administered bradykinin B2 receptor antagonist approved for the treatment of acute HAE attacks in adult patients with C1-INH deficiency.^{9,10} Icatibant can be administered by a health care professional (HCP) or patients can self-administer treatment (on completion of training by a HCP).

The efficacy and safety of icatibant in HAE type I and II have been established in three phase III clinical trials: For Angioedema Subcutaneous Treatment (FAST)-1, FAST-2, and FAST-3.^{11,12} In addition to the FAST trials,

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patients eligible for treatment with icatibant have been assessed in an ongoing prospective, international, multicenter, observational, postmarketing study, the Icatibant Outcome Survey (IOS). These two data sources present the opportunity to compare icatibant treatment in the real-world setting with that of the more stringently controlled environment of a clinical trial. In the FAST trials, all icatibant injections were HCP administered and were only given once an attack became moderate/severe, necessitating a lag between symptom onset and treatment due to a requirement for travel to the study center and waiting for sufficient attack severity (treatment was given within 6 hours of attacks of the skin/abdomen becoming at least moderate in severity but no more than 12 hours after attack onset).

Here, we evaluate whether icatibant used in a real-world setting (IOS; NCT01034969) provides similar effectiveness as in a controlled trial setting (FAST-3; NCT00912093) in patients with nonlaryngeal attacks of HAE type I or II.

METHODS

Study Designs

The FAST-3 study design has been described previously.¹² Patients included in FAST-3 were aged more than or equal to 18 years with a documented diagnosis of HAE type I or II experiencing an attack in the skin, abdomen, or larynx. Attacks were moderate to very severe for nonlaryngeal symptoms and mild to moderate for attacks with laryngeal involvement (laryngeal attacks were excluded from the present analysis). Patients were excluded from FAST-3 if they had received previous treatment with icatibant, were receiving treatment with angiotensin-converting enzyme inhibitors, or had a serious concomitant condition, including coronary artery disease. Patients from the United States, Israel, Australia, Romania, Russia, Hungary, South Africa, Canada, and Ukraine were randomized to study treatment in FAST-3.

IOS was initiated in July 2009 to collect safety and effectiveness data for patients with HAE type I or II who were eligible for treatment with icatibant.¹³ Full details of the IOS study design have been described previously.¹³ Briefly, patients were eligible for inclusion in the survey if they had been prescribed icatibant and had a diagnosis of HAE type I or II that was clinically confirmed by laboratory tests (C1-INH concentration and function). Patients attended regular follow-up visits, recommended every 6 months, in accordance with routine clinical practice. Analyses described here included nonlaryngeal attack data from study centers in Austria, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden, and the United Kingdom. In IOS, data were collected via a physician-completed electronic database at routine patient visits.

The FAST-3 study and IOS were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Approval was obtained from local ethics committees and/or local health authorities and written, informed consent was obtained.

Treatment

In FAST-3 (Table 1), patients received icatibant 30 mg subcutaneously administered by an HCP within 6 hours of an abdominal and/or cutaneous attack becoming moderate and 12 hours of attack onset. Severe laryngeal attacks were treated with open-label icatibant in FAST-3, thus laryngeal attacks were excluded from the present analysis, which was designed to compare a controlled clinical trial with a real-world setting. In IOS (Table 1), patients could self-administer icatibant or be treated by an HCP. To be consistent and aid comparison with controlled phase FAST-3 study results, HAE attacks in IOS were excluded from this analysis if they were not treated within 12 hours of attack onset or were laryngeal attacks.

Analyses

IOS data on nonlaryngeal attacks between July 2009 and March 2013, and nonlaryngeal attack data collected during the controlled phase of the FAST-3 clinical trial, were analyzed. Attack data from IOS were included in the analyses if date and time of the start of the attack and date and time to injection and symptom resolution were available. Only attacks treated less than 12 hours from attack onset were analyzed.

Median time to treatment from attack onset, time to symptom resolution, and duration of attack for HAE type I and II nonlaryngeal attacks were compared in a posthoc analysis of HCP administration data from IOS versus FAST-3.

The time to symptom resolution and attack duration were defined slightly differently in the two studies. In IOS, time to complete resolution was defined as the duration from icatibant subcutaneous injection to complete symptom resolution. In FAST-3, time to almost complete symptom resolution was defined as the time between treatment and the earliest of three consecutive nonmissing measurements for which all visual analog scale (VAS) scores were less than 10 millimeters (VAS anchors were 0 millimeters = no symptoms and 100 millimeters = the worst possible symptom). VAS measurements in patients with abdominal or cutaneous attacks included skin swelling, skin pain, and abdominal pain. Patients that did not achieve almost complete symptom resolution (*i.e.*, did not have three consecutive measurements with all VAS score <10 millimeters) were censored at the time of last available assessment. In IOS, attack duration was defined as the time from

Table 1. Comparison of IOS and FAST-3 study designs

	IOS	FAST-3
Outcome	1. Time to complete symptom resolution (time from injection to complete resolution of all symptoms)	1. Almost complete symptom relief (score <10 mm on the VAS for at least three consecutive measurements of all symptoms)
Design	2. Total duration of attack (attack onset to complete symptom resolution) Prospective, international, multicentre, observational patient study	2. Duration of attack (attack onset to almost complete symptom relief) Phase III, international, multicentre, randomized, placebo-controlled trial
Centers	31 sites* 10 countries*	67 sites 11 countries
Time to treatment	No limitation/requirement for inclusion in IOS	Attack had to be at least moderate in severity, <6 hr of the attack becoming at least moderate, and <12 hr of attack onset
Administration type	HCP and self-administration	HCP administration
HAE attacks	Several HAE attacks: For each patient with several HAE attacks, the median time to event was calculated	One HAE attack in the controlled phase, after which patients could enroll in the open-label extension phase, during which multiple attacks could be treated; #median time to event was calculated

*Included in the analyses described here.

#Attacks during the open-label extension were excluded from this analysis of controlled clinical trial data.

FAST = For Angioedema Subcutaneous Treatment; HAE = hereditary angioedema; HCP = healthcare professional; IOS = Icatibant Outcome Survey; VAS = visual analog scale.

attack onset to complete symptom resolution, whereas in FAST-3, attack duration was defined as the time from attack onset to almost complete symptom resolution.

Statistical Methods

Time to treatment was analyzed using the Wilcoxon-Mann-Whitney test. Time to symptom resolution and duration of attack were analyzed using the log-rank test. Kaplan-Meier curves were generated and used to display the estimated survival functions and median times for each end point.

RESULTS

Overall, this analysis included 102 patients (376 attacks) who self-administered or were treated by an HCP in IOS (combined HCP and self-administration) and 43 patients (43 attacks) who were treated by an HCP in the controlled phase of FAST-3 (HCP administration). Data from 49 patients (72 attacks) from IOS and 43 patients (43 attacks) from the controlled phase of FAST-3 were included in the analysis of HCP administration data from IOS compared with FAST-3.

The median time to treatment after attack onset was 2.0 hours for patients in IOS (HCP administration) compared with 6.5 hours for patients in the randomized controlled FAST-3 study (HCP administration) ($p < .001$) (Table 2). For combined HCP and self-administration in IOS, the median time to treatment after attack was 1.6 hours.

Time to symptom resolution and duration of attack were significantly shorter ($p < .0001$) for patients in IOS (HCP administration) compared with FAST-3 (HCP administration) (Fig. 1). The median time to symptom resolution and duration of attack was 3.5 and 7.3 hours, respectively, for patients treated in IOS (HCP administration) compared with 8.0 and 16.9 hours, respectively, for patients in FAST-3 (HCP administration) ($p < .001$) (Table 2). For combined HCP and self-administration in IOS, the median time to symptom resolution and duration of attack was 4.4 and 7.8 hours, respectively.

DISCUSSION

The results of this posthoc analysis indicate that for patients treated within 12 hours of attack onset,

Table 2. Outcomes in patients treated with icatibant within 12 hours of attack onset

Endpoint	IOS			FAST-3		
	HCP Administered			HCP Administered		
	n*	Mean $\pm$ SD	Median (25%, 75% quartiles)	n*	Mean $\pm$ SD	Median (25%, 75% quartiles)
Time from attack onset to treatment, hr	49	2.7 $\pm$ 2.8***	2.0 (0.5, 3.8)	43	7.1 $\pm$ 3.2	6.5 (4.3, 9.8)
Time to symptom resolution, hr§	44	7.9 $\pm$ 10.7***	3.5 (1.0, 8.6)	43	28.3 $\pm$ 30.2	8.0 (2.5, 50.1)
Duration of attack, hr#	44	10.8 $\pm$ 11.5***	7.3 (2.8, 12.7)	43	35.4 $\pm$ 30.5	16.9 (10.6, 58.8)

*In order to calculate time to symptom resolution, date and time to injection and symptom resolution were required for patients to be included. Similarly, to calculate duration of attack, date and time of the start of the attack and of symptom resolution were required; for some attacks, not all of these data were available.

#Almost complete symptom resolution in FAST-3.

§In FAST-3, patients that did not achieve almost complete symptom resolution (i.e., did not have three consecutive measurements with all visual analog scale score <10 mm) were censored at the time of last available assessment.

*** $p < .001$ versus FAST-3.

FAST = For Angioedema Subcutaneous Treatment; HCP = healthcare professional; IOS = Icatibant Outcome Survey; n = number of attacks; SD = standard deviation.

Time to treatment: Wilcoxon-Mann-Whitney test; time to complete resolution and duration of attacks: log-rank test.

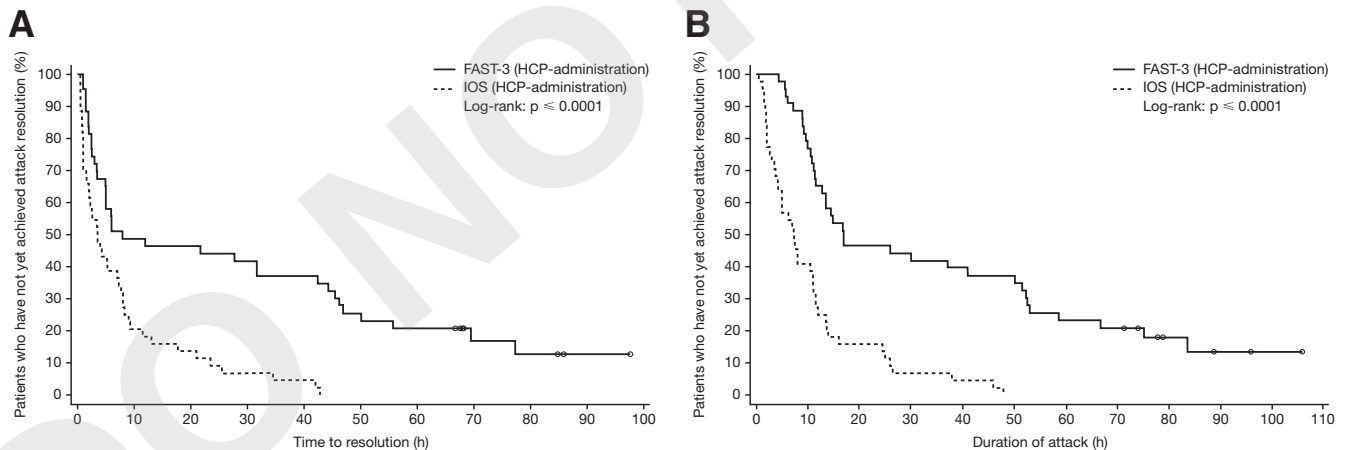


Figure 1. Kaplan-Meier graphs of (A) time to resolution and (B) duration of attack in IOS (HCP administration) compared with FAST-3 (HCP administration). In FAST-3, patients that did not achieve almost complete symptom resolution (i.e., did not have three consecutive measurements with all visual analog scale scores < 10 mm) were censored at the time of last available assessment; these patients are represented by dots on the Kaplan-Meier curve. FAST = For Angioedema Subcutaneous Treatment; HCP = healthcare professional; IOS Icatibant Outcomes Survey.

time to treatment, time to symptom resolution, and attack duration were shorter in the observational IOS study compared with the FAST-3 clinical trial ($p < .001$ for all comparisons). Thus, the efficacy of icatibant treatment for HAE attacks observed in clinical trials appears to be translated into clinical efficacy in a real-world setting. Other recent results from IOS support these findings, indicating that early icatibant treatment reduced attack duration and time to symptom resolution in patients with HAE type I and II.¹³ Outcomes with C1-INH prophylaxis (i.e., proportion

of patients with improvement of attack symptoms within 4 hours) during an open-label extension study that mimicked the real-world setting were reportedly better than those reported in two randomized clinical trials.^{14,15} Taken in the context of our findings, these results suggest that for conditions such as HAE, where patients tend to be well educated regarding their disease, pharmacological treatments can be used among the broader patient population without concerns regarding loss of efficacy outside controlled clinical trials.

Limitations of this analysis include the comparison of data from studies with different designs and different endpoints, and the inclusion of outliers, which may have contributed to the greater levels of variance seen in the results. In addition, IOS was initiated before publication of the Hereditary Angioedema International Working Group consensus paper⁶ and before icatibant was approved for self-administration by the European Medicines Agency in 2011.⁹ As a result, patients who self-administered may not have followed recommended practice, and the response to icatibant may have varied according to patient practice and according to its use. Nevertheless, our findings were statistically robust and support current international and United States guideline recommendations^{5–8} that HAE attacks should be treated early using a self-administered on-demand therapy, where labeling allows.

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