

Analysis of characteristics associated with reinjection of icatibant: Results from the icatibant outcome survey

Hilary J. Longhurst, M.B.B.S., Ph.D.,¹ Werner Aberer, M.D.,² Laurence Bouillet, M.D., Ph.D.,³ Teresa Caballero, M.D., Ph.D.,⁴ Vincent Fabien, Ph.D.,⁵ Andrea Zanichelli, M.D.,⁶ and Marcus Maurer, M.D.,⁷ for the IOS investigators

ABSTRACT

Purpose: Phase 3 icatibant trials showed that most hereditary angioedema (HAE) (C1 inhibitor deficiency) acute attacks were treated successfully with one injection of icatibant, a selective bradykinin B2 receptor antagonist. We conducted a post hoc analysis of icatibant reinjection for HAE type I and II attacks in a real-world setting by using data from the Icatibant Outcome Survey, an ongoing observational study that monitors the safety and effectiveness of icatibant treatment.

Methods: Descriptive retrospective analyses of icatibant reinjection were performed on Icatibant Outcome Survey data (February 2008 to December 2012). New attacks were defined as the onset of new symptoms after full resolution of the previous attack. Potential associations between the patient and attack characteristics and reinjection were explored by using logistic regression analysis.

Results: Icatibant was administered for 652 attacks in 170 patients with HAE type I or II. Most attacks (89.1%) were treated with a single icatibant injection. For attacks that required two or three injections, the second injection was given a median of 11.0 hours after the first injection, with 90.4% of second injections administered ≥ 6 hours after the first injection. Time to resolution and attack duration were significantly longer for two or three injections versus one icatibant injection ($p < 0.0001$ and $p < 0.05$, respectively). Multivariate logistic regression analysis identified sex, attack severity, and laryngeal attacks as significantly correlated with reinjection (all $p \leq 0.05$). These factors did not remain predictors for reinjection when two outlier patients with distinct patterns of icatibant use were excluded.

Conclusions: In this real-world setting, most HAE attacks resolved with one icatibant injection. There was no distinct profile for patients or attacks that required reinjection when outliers with substantially different patterns of use were excluded. Because new attacks were not distinguished from the recurrence of symptoms, reinjection rates may be slightly higher than shown here. Clinical trial identifier: NCT01034969

(Allergy Asthma Proc 36:399–406, 2015; doi: 10.2500/aap.2015.36.3892)

Hereditary angioedema (HAE) is a rare condition characterized by recurrent and unpredictable attacks of cutaneous or submucosal edema.^{1–3} The

edema is mediated by C1-inhibitor (C1-INH) deficiency (HAE type I) or dysfunction (HAE type II), which leads to the overproduction of bradykinin and the activation of bradykinin B2 receptors.^{1,4–6}

Untreated HAE attacks can be associated with debilitating symptoms,^{1,2,7} and serious attacks may necessitate hospitalization,⁸ with laryngeal attacks that potentially cause fatal asphyxiation.⁹ However, effective

From the ¹Department of Immunology, Barts Health NHS Trust, London, United Kingdom, ²Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria, ³National Reference Centre for Angioedema, Internal Medicine Department, Grenoble University Hospital, Grenoble, France, ⁴Hospital La Paz Institute for Health Research (IdiPaz), Biomedical Research Network on Rare Diseases (CIBERER, U754), Madrid, Spain, ⁵Shire, Zug, Switzerland, ⁶Dipartimento di Scienze Cliniche, Università degli Studi di Milano, Milano, Italy, and ⁷Department of Dermatology and Allergy, Allergie-Centrum-Charité, Universitätsmedizin, Berlin, Germany

The Icatibant Outcome Survey is funded and supported by Shire, Zug, Switzerland. Medical writing support was provided by David Finch, PhD, Complete Medical Communications, and was funded by Shire

Collaborators: The IOS Study Group: The following investigators are included in the IOS Study Group: W. Aberer (Austria); A. Bygum (Denmark); C. Blanchard Delaunay, I. Boccon-Gibod, L. Bouillet, O. Fain, A. Gompel, S. Guez, P.Y. Jeandot, G. Kanny, D. Launay, H. Maillard, L. Martin, A. Masseau, Y. Ollivier (France); M. Baş, K. Bork, M. Maurer (Germany); F. Psarros (Greece); Y. Graif, E. Toubi (Israel); M. Bova, F. Arcoleo, G. Marone, V. Montinaro, A. Zanichelli (Italy); M.L. Baeza, T. Caballero, M. Guilarte, D. Hernández Fernández de Rojas, C. Hernando de Larramendi, R. Leonart, L. Marqués (Spain); J. Bjoerkander (Sweden); and M. Helbert, H. Longhurst (U.K.)

H. Longhurst has received research grant support and/or speaker/consultancy fees from CSL Behring, Dyax, Pharming, Shire, SOBI, and ViroPharma. W. Aberer 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. Bouillet has received honoraria from CSL Behring, Pharming, Shire, and ViroPharma; and her institute has received research funding from CSL Behring and Shire. T. Caballero 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. V. Fabien is a full-time employee of Shire, Zug, Switzerland. A. Zanichelli has received speaker fees from CSL Behring, Shire, SOBI, and ViroPharma, and consultancy fees from CSL Behring, Shire, and ViroPharma. M. Maurer has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, Shire/Jerini AG, and ViroPharma. Presented at the EAACI-WAO World Allergy and Asthma Congress Meeting, Milan, Italy, June 22–26, 2013 and at the American Academy of Allergy, Asthma & Immunology Annual Scientific Meeting, San Diego, California, February 28 to March 4, 2014

Supplemental data available at www.lingentaconnect.com
Address correspondence to Hilary Longhurst, Department of Immunology, Barts Health NHS Trust, 80 Newark Street, London E1 2ES, U.K.

E-mail address: hilary.longhurst@bartshealth.nhs.uk

Copyright © 2015, OceanSide Publications, Inc., U.S.A.

treatment administered early in the course of an attack may reduce attack duration and pain severity.^{1,10}

Icatibant is a bradykinin B2 receptor antagonist that has been approved for the treatment of acute attacks of HAE in adults (age > 18 years) with C1-INH deficiency. Efficacy and a good safety profile have been demonstrated in the three phase III For Angioedema Subcutaneous Treatment studies and in “real world” experience.^{11–13} Icatibant is administered as a subcutaneous injection by a health care professional (HCP) or by the patient (after training by HCP).^{14,15} The recommended dose is a single subcutaneous injection of icatibant 30 mg.¹⁶ In case of insufficient relief or recurrence of symptoms, a second icatibant injection can be administered after 6 hours, and a third injection may be given after a further 6 hours (maximum of three injections allowed in 24 hours). Although a single injection was sufficient for the successful treatment of the majority of HAE attacks in the For Angioedema Subcutaneous Treatment studies, reinjection was required in a minority of cases.^{11,12,17} Improved understanding of why reinjection is sometimes required may be useful to help minimize the associated costs and disruption and to reduce the burden for the patient.

The aim of this analysis was to determine icatibant reinjection rates in a real-world setting by using data from the Icatibant Outcome Survey (IOS) (NCT01034969), an ongoing, international, observational postmarketing study that monitors the safety and effectiveness of icatibant during long-term treatment. Potential associations between patient and/or attack characteristics and the need for reinjection were also explored.

METHODS

Study Design and Patients

Details of the IOS study design and setting have been described previously.¹⁰ The IOS is 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.

Eligible patients were required to have a diagnosis of HAE type I or II 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. Attack frequencies and characteristics were reported by the patients, in most cases with assistance from diaries, and recorded by the investigator. Severity was classified as mild (no more than 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).

Descriptive, retrospective analyses of attack characteristics for patients who received icatibant were performed by using data obtained between July 2009 and December 2012, including data for icatibant-treated attacks in the year before enrollment in IOS (data available from February 2008 through December 2012). During this period, a total of 36 centers in 10 countries contributed data for this analysis: Austria ($n = 1$), Denmark ($n = 1$), France ($n = 13$), Germany ($n = 4$), Greece ($n = 1$), Israel ($n = 2$), Italy ($n = 4$), Spain ($n = 7$), Sweden ($n = 1$), and the United Kingdom ($n = 2$). Adverse events were recorded throughout the study and were classified as not related, possibly related, or probably related to icatibant treatment as judged by the study investigators.

Statistical Analyses

For each HAE attack, data were collected for the time to first injection (time between the start of the attack and time to first icatibant injection), time to resolution (time between the first injection of icatibant and complete resolution of symptoms), and duration of attack (time between the start of the onset of the attack and complete resolution of symptoms). The start of the attack was defined as the time of first onset of symptoms of acute HAE and did not include prodromal symptoms. Recurrence of symptoms after full resolution was defined as a new attack. When descriptive characteristics are reported for a particular outcome, attacks with missing data for that outcome were excluded from the analysis.

This *post hoc* analysis of IOS data included logistic regression to identify the predictive value of factors, including patient sex, weight category, type of administration (HCP versus self-administration), attack severity, attack frequency, attack location, family history, long-term prophylaxis (LTP), and time to first injection. A multivariate model was built by using a backward selection process, which incorporated variables from the univariate model with p values of <0.20 and removed factors with the highest p values until only significant factors remained ($p \leq 0.05$).

The χ^2 test was used to evaluate the relationship between C1-INH use and the need for reinjection and the reinjection rate for patients who received or did not receive LTP. A mixed-model analysis of repeated measures (Proc Mixed; SAS Institute, Cary, NC) was used to compare the time to resolution and attack duration data for one icatibant injection versus two or three injections.

The analyses reported herein included attack data from all patient treated with icatibant and with HAE

Table 1. Patient characteristics

Characteristic	All Patients (N = 170)	Patients Reinjecting <6 hr (n = 3)*	Patients Reinjecting ≥6 hr (n = 12)*
Sex, no. (%)			
Men	66 (38.8)	3 (100)	6 (50.0)
Women	104 (61.2)	—	6 (50.0)
Age, median (IQR), y	39.6 (27.2, 49.4)	30.3 (24.8, 45.3)	34.3 (20.4, 44.4)
HAE, no. (%)			
Type I	157 (92.4)	3 (100)	12 (100)
Type II	13 (7.7)	—	—
Concomitant and/or rescue medications, no. (%)	48 (28.2)	2 (66.7)	3 (25.0)
Long-term prophylaxis, no. (%)#			
Yes	62 (36.5)	2 (66.7)	4 (33.3)
No	108 (63.5)	1 (33.3)	8 (66.7)
Attack frequency, no. (%)§			
≥1/wk	13 (7.7)	—	1 (8.3)
12–51/y	50 (29.4)	1 (33.3)	6 (50.0)
7–11/y	22 (12.9)	—	1 (8.3)
3–6/y	40 (23.5)	2 (66.7)	3 (25.0)
1–2/y	14 (8.2)	—	1 (8.3)
<1/y	13 (7.7)	—	—

*Although 24 patients used two or more icatibant injections, the time to injection data were available for only 15 patients.

#At any time during the analysis period.

§Data were missing for 18 patients.

type I or II enrolled in IOS to represent the real-world situation. However, during the analysis of HAE attack characteristics and treatment, two patients were identified whose treatment profiles were substantially different from those of other patients in the data set, and they, therefore, were considered as outliers. A description of these outlier patients is presented in the supplementary material (Supplemental Table of Contents). We compared data for icatibant reinjection and C1-INH rescue medication usage for the data sets with and without outliers. We repeated the logistic regression analysis, excluding the two outliers, to ascertain whether the icatibant treatment pattern in these patients was the basis for any of the results. Other analyses, excluding data for the outlier patients, are presented in the supplementary material (566 attacks, 168 patients) (Supplemental Resource 1).

RESULTS

Patient Characteristics

A total of 170 patients were enrolled, and one patient withdrew during the study period (at the request of the investigator; only one attack was treated with icatibant). Overall, data for 652 HAE type I or type II attacks were analyzed from 170 patients treated with icatibant (Table 1). The majority of patients were women (61.2% [104/170]), and most had a diagnosis of HAE type I (92.4%

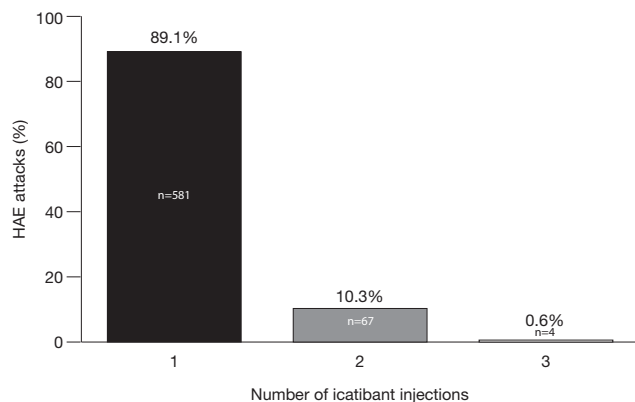
[157/170]). Patients had a median age of 39.6 years (interquartile range [IQR], 27.2–49.4 years). The analysis included three patients who enrolled as adolescents ages <18 years (16.5, 17.1, and 17.6 years, respectively). However, only one of these patients used icatibant before the age of 18 years and received two injections at the ages of 17.6 and 17.8 years.

Attack Severity

Patients reported a median of 2 (range, 1–54) icatibant-treated attacks during a follow-up period of 2.27 years (range, 0.04–5 years). Overall, the majority of HAE attacks were severe/very severe (71.6% [439/613]), 21.7% were moderate (133/613), and 6.7% were mild (41/613). Most attacks affected the abdomen only (44.9% [292/650]) or skin only (34.2% [222/650]), and 5.1% of attacks affected the larynx only (33/650). Attacks that affected the larynx only were mostly severe/very severe (80.6% [25/31]) or moderate (19.4% [6/31]); no mild laryngeal attacks were reported. Of the 48 attacks with laryngeal involvement, 68.8% affected the larynx only (33/48), and 31.2% affected multiple locations (15/48).

Use of Long-Term Prophylaxis and Concomitant Medication

Of the 170 patients included in this analysis, approximately one-third were using LTP (n = 62 [36.5%])



Number of attacks treated with C1-INH rescue medication		
1 injection	>1 injection	p-value
53/581 (9.1%)	23/71 (32.4%)	<0.001

C1-INH, C1-inhibitor

Figure 1. Overall proportion of attacks treated with one, two, or three icatibant injections ($N = 652$), showing the number of attacks treated with C1-inhibitor rescue medication.

(Table 1). Danazol was the most commonly used LTP treatment (100 attacks, 24 patients). Other prophylactic drugs used (number of attacks [number of patients]) were stanazolol (45 [18]), tranexamic acid (49 [15]), C1-INH (3 [2]), and combinations of danazol-tranexamic acid (11 [3]), oxandrolone-tranexamic acid (6 [1]), C1-INH-danazol (2 [1]), and stanazolol-tranexamic acid (1 [1]). Concomitant and rescue medication was used by 28.2% of patients (48/170) (Table 1). Of these, 11.2% of patients (19/170) were recorded as having used C1-INH concentrate as rescue medication.

Icatibant Reinjection

Overall. For most attacks (89.1% [581/652]), a single icatibant injection was used; for 10.3% of attacks (67/652), two injections were used; and, for 0.6% of attacks (4/652), three injections were used (Fig. 1). When the two outliers were excluded from the analysis, a single injection was used for 94.3% of attacks (534/566), 5.5% (32/566) of attacks required two injections, and 0.2% (1/566) required three injections (Supplemental Fig. 1).

Rescue Medication. C1-INH rescue medication was used for 9.1% of attacks (53/581) treated with one injection and 32.4% of attacks (23/71) treated with more than one injection ($p < 0.001$ for C1-INH use after one injection versus more than one injection) (Fig. 1). When excluding the two outliers from the analysis, C1-INH rescue medication was used for 5.4% of attacks (29/534) treated with one injection and 3.1% of attacks (1/32) treated with more than one injection ($p = 0.572$

for C1-INH use after one injection versus more than one injection) (Supplemental Fig. 1).

In total, 81.0% (528/652) of attacks resolved with only a single injection of icatibant compared with 19.0% (124/652) of attacks that required one or more injections of icatibant and/or C1-INH rescue medication. When data for the two outlier patients were excluded, 89.2% (505/566) of attacks resolved with only a single icatibant injection versus 10.8% (61/566) of attacks that required one or more injections of icatibant and/or C1-INH rescue medication.

Long-term prophylaxis. Patients who were taking LTP had 217 attacks during the analysis period. The majority of these attacks (92.2% [200/217]) were treated with a single icatibant injection, which was similar to the rate in patients who did not receive LTP (87.6% [381/435]; $p = 0.077$). Data obtained for the data set, which excluded the two outliers, were consistent with this (Supplemental Table 7).

Patient and Attack Characteristics. The proportion of attacks treated with one and more than one icatibant injection according to patient weight, attack severity, attack frequency, and attack location are shown in Fig. 2. The majority of attacks were treated with a single icatibant injection, regardless of patient weight (Fig. 2 A), attack severity (Fig. 2 B), attack frequency (Fig. 2 C), or attack location (Fig. 2 D). One injection was used in 87.0% (382/439) of severe/very severe attacks, 78.8% (26/33) of attacks that involved only the larynx, and 90.7% (351/387) and 84.6% (186/220) of attacks in patients with <20 and ≥ 20 attacks/y, respectively. Most attacks were treated with a single injection regardless of whether the attack affected a single location (89.1% of attacks [506/568]) or multiple locations on the body (89.0% of attacks [73/82]), or whether the first injection of icatibant was administered by the patient (87.2% of self-administered attacks [376/431]) or by their HCP (91.9% of HCP-administered attacks [182/198]).

Treatment End Points. The median time to first icatibant injection was 1.8 hours (IQR, 0.5–5.8 hours; 353 attacks in 114 patients). Just over one-fourth of attacks (28.6% [101/353]) were treated >5 hours after attack onset. The median time to the first injection was slower for patients who used a single injection (2.0 hours [IQR, 0.5–6.5 hours]) than for those who used more than one injection (1.0 hour [IQR, 0.5–2.3 hours]; $p = 0.0337$). The median time between the first and second injections was 11.0 hours (IQR, 6.5–13.0 hours). The majority of attacks treated with a second injection had the second injection administered ≥ 6 hours after the first (90.4% [47/52]). Five attacks in three patients were

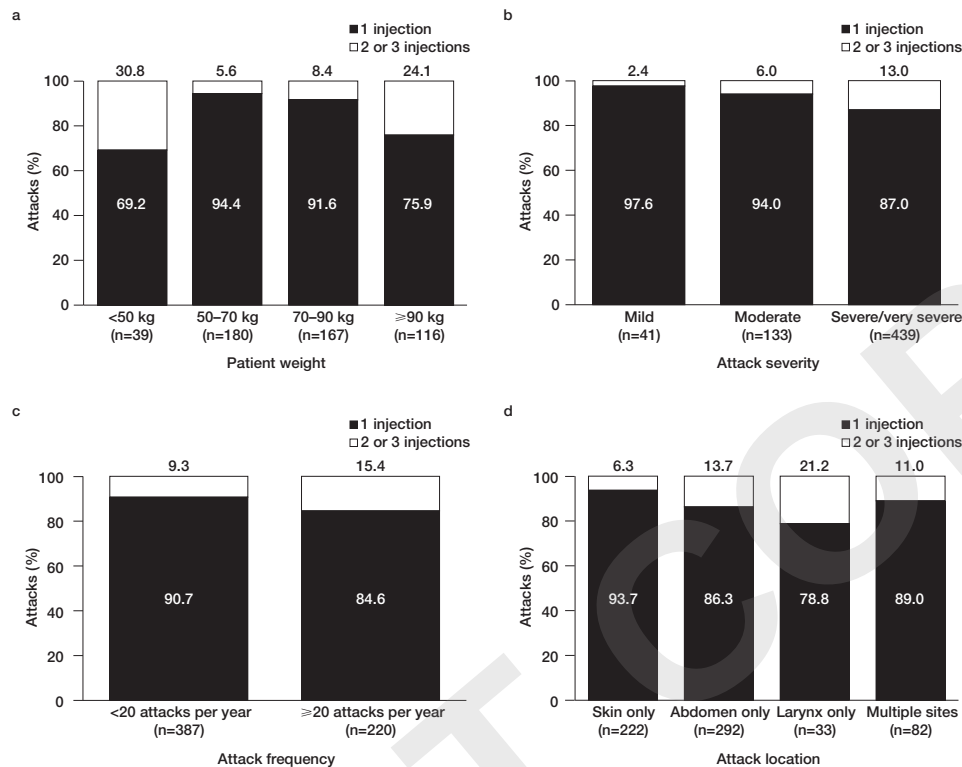


Figure 2. Proportion of attacks treated with one versus two or three injections according to (A) patient weight, (B) attack severity, (C) attack frequency, and (D) attack location.

Table 2. Time to complete symptom resolution and attack duration, overall and for one, two, and three injections

	Overall	1 Injection	2 Injections	3 Injections
Time to complete symptom resolution#				
No. attacks	361	317	42	2
Median (IQR), hr	3.5 (1.0–10.0)	2.5 (1.0–7.3)**	10.6 (7.3–17.5)	26.0 (24.0–28.0)
Time from second injection to complete symptom resolution				
No. attacks	44	—	—	—
Median (IQR), hr	0.5 (0.5–3.8)	—	—	—
Attack duration				
No. attacks	326	284	40	2
Median (IQR), hr	8.0 (3.0–17.5)	7.0 (2.5–17.0) *	12.0 (8.6–19.0)	46.5 (26.0–67.0)

* $p = 0.039$ for 1 vs 2 or 3 injections; ** $p < 0.0001$ for 1 vs 2 or 3 injections.

#Reported on a continuous scale, starting from the time of the first injection.

treated with a second injection <6 hours after the first injection.

Overall, the median time to complete symptom resolution, regardless of the injection number, was 3.5 hours (IQR, 1.0–10.0 hours) (Table 2). The median attack duration, regardless of the injection number, was 8.0 hours (IQR, 3.0–17.5 hours) (Table 2). Both the time to resolution and attack duration were significantly longer for two or three injections versus one icatibant injection (Table 2).

Patient and/or Attack Characteristics and Reinjection Rate

All the factors included in the logistic regression model are presented in Table 3. Based on the univariate model, factors identified as potentially predictive of icatibant reinjection (*i.e.*, $p < 0.20$) were laryngeal attacks, severe/very severe attacks, HCP administration of icatibant, and male sex. Multivariate analysis revealed that the following factors were statistically cor-

Table 3. Univariate and multivariate logistic regression analysis of factors predictive for reinjection

Factor	Univariate Analysis*	Multivariate Analysis#		
	Odds Ratio	<i>p</i> Value§	Odds Ratio	<i>p</i> Value§
Larynx affected (yes vs no)	5.56	0.063	4.34	0.002
Severity (severe/very severe vs mild/moderate)	2.56	0.034	2.43	0.021
Family history (no vs yes)	2.97	0.237	—	—
Type of administration (HCP vs self-administration)	2.10	0.177	—	NS
Frequency of attacks <20/y vs ≥20/y)	1.64	0.375	—	—
Sex (men vs women)	2.37	0.084	3.01	0.037
Weight (women < 80 kg or men < 90 kg vs women > 80 kg or men > 90 kg)	1.40	0.590	—	—
Abdomen affected (no vs yes)	0.75	0.612	—	—
Skin affected (no vs yes)	1.55	0.281	—	—
Time to first injection (0–2 vs ≥2 hr)	1.35	0.787	—	—
Time to first injection (0–5 vs ≥5 hr)	1.28	0.744	—	—
Location of attack (single vs multiple)	0.62	0.267	—	—
Long-term prophylaxis treatment (no vs yes)	—	ND	—	—

ND = Not defined; NS = not statistically significant ($p > 0.05$).

*Includes all factors included in the univariate analysis.

#Multivariate model was built by using a backward selection process, which incorporated variables from the univariate model with p values of <0.20.

§The p value from 2-sided logistic regression analysis (repeated measures).

related with an increased rate of icatibant reinjection: laryngeal attacks (odds ratio 4.34; $p = 0.002$, for the presence versus absence of laryngeal attacks), severe/very severe attacks (odds ratio 2.43, $p = 0.021$, for severe/very severe versus mild/moderate), and male sex (odds ratio 3.01, $p = 0.037$, for male versus female sex). However, when the two outliers were excluded from the logistic regression analysis, none of the factors examined were statistically correlated with an increased rate of icatibant reinjection in the multivariate analysis (all $p > 0.05$) (Supplemental Table 8).

Safety

Overall, 14 adverse events reported by four patients were considered possibly or probably related to icatibant treatment (injection site erythema, chest discomfort, drug ineffective, feeling hot, gastritis, decreased blood pressure, headache, and depression). There was one treatment-related serious adverse event (gastritis). No deaths were reported.

DISCUSSION

The natural history of an HAE attack is variable, and some patients may experience symptom worsening or recurrence, or emergence of new symptoms after initial symptom improvement.¹⁸ Treatment of acute HAE at-

tacks aims to resolve angioedema symptoms as quickly as possible.¹⁹ If symptoms persist or worsen, patients can use additional treatments, such as subsequent injections of icatibant (≥6 hours after the first injection) or other rescue medications, *e.g.*, C1-INH. In this analysis of IOS reinjection data, which characterizes icatibant reinjection use for the first time in a real-world setting, 89.1% of all HAE attacks were treated with only one injection of icatibant (94.3%, excluding the two outliers) (Supplemental Table 2), and only a small proportion of attacks required more than one injection. C1-INH rescue medication was used for almost 10% of attacks treated with one injection and almost one-third of attacks treated with more than one injection. However, excluding the two outliers from the analysis resulted in a similar proportion of attacks that required C1-INH rescue medication whether they were treated with one icatibant injection or more than one injection (5.4% versus 3.1%, respectively; $p = 0.572$). Evaluating attacks that did not require the use of C1-INH as rescue medication revealed that a single injection of icatibant alone was sufficient to successfully treat the majority of all HAE attacks recorded in IOS (81.0% of all attacks, 89.2% if outliers are excluded) (Supplemental Table 2).

If a patient experiences insufficient relief or recurrence of symptoms, up to three icatibant injections can

be administered within a 24-hour period.¹⁶ Therefore, icatibant reinjection may indicate incomplete resolution, worsening of symptoms after initial improvement, or, in rare cases, a lack of response to icatibant. Analysis of our data shows that the time between the first and second icatibant injections was ≥ 6 hours in 90.4% of attacks, which indicates that icatibant was administered appropriately in the majority of cases.¹⁶ The duration of action of icatibant is between 6 and 8 hours, and this pattern of use is supportive of this pharmacokinetic profile.²⁰

IOS is an observational study, which documents the use of icatibant in clinical practice. During these analyses, we identified two patients with HAE and with substantially different patterns of icatibant use when compared with other patients with HAE in the survey (Supplemental Resource 1; Outlier Patients). Parallel analyses of IOS data for all patients and for data that excluded the two outlier patients were performed to further understand how variations in treatment patterns may influence icatibant reinjection and outcomes. As might be expected from the pattern of drug usage by the two outlier patients (one administered icatibant at the prodromal stage and the other had very high reinjection and C1-INH rescue medication use), exclusion of these outliers resulted in a lower reinjection rate (5.7%) compared with the analysis that included attacks for all the patients (10.9%) and reduced the usage of C1-INH rescue medication. Multivariate analysis that included the outlier patients identified attack severity, sex, and laryngeal attacks as being associated with icatibant reinjection (all $p \leq 0.05$). When the two outliers were excluded from the multivariate analysis, none of the parameters examined were significantly correlated with reinjection (all $p > 0.05$). These results indicate that the three predictors for reinjection (attack severity, sex, and laryngeal attacks) were due to the inclusion of data from the two outliers.

This analysis is the first time that real-world icatibant reinjection patterns have been characterized, which enables indirect comparison with data available from the controlled clinical studies of icatibant. In this data extract from IOS, most self-administered attacks (87.2%) were treated with a single icatibant injection, which is consistent with the rate reported during the open-label extension phase of the phase III For Angioedema Subcutaneous Treatment-3 study (95.4%), in which icatibant was administered by an HCP,²¹ and with the rate of reinjection reported with icatibant self-administration in the open-label Evaluation of the Safety of Self-administration with Icatibant study (91.8% treated with a single injection).¹⁵

Patients in IOS were managed according to routine clinical practice, and this data set provides a comprehensive real-world description of patients with HAE types I and II treated with icatibant. Potential limita-

tions of the analysis include the fact that, although IOS is a prospective observational study, the analysis was *post hoc*, with missing data for some end points, and that attacks were self-reported, including for a retrospective period of 1 year before study entry. It was not possible to evaluate whether patients with frequent attacks (≥ 1 attack/wk) were more likely to reinject than patients with < 1 attack/wk because the sample size for the high-frequency group was too small. The specific reasons for reinjection were not recorded, and further information on what triggers the patient to reinject would be useful to guide optimal use of icatibant. Another limitation of IOS data is that attack severity was assessed by patients and verified by their HCP. Furthermore, as demonstrated by the treatment patterns for the two outlier patients, self-administration of icatibant may not follow recommended practice. However, the experience of the two outlier patients highlights that physicians should be vigilant, carefully monitoring patients' use of treatment, modifying treatment that leads to suboptimal outcomes as early as possible, and recognizing the possibility of different treatment practices that develop according to patient preferences. Finally, symptoms that occurred after the full resolution of the previous attack were considered to be a new attack; the recurrence of symptoms was not recorded in this study. In patients who had at least one injection and > 1 attack, 153 attacks in 33 patients had available data between consecutive attacks; 7 (4.6%) and 6 (3.9%) succeeding attacks occurred < 24 hours and 24 to 48 hours after the previous attack, respectively. Because symptom relapse may occur due to the transient nature of the inhibition of the bradykinin receptor by icatibant, some of the subsequent attacks that were considered to be new could have in fact been a recurrence of the original attack. Thus, the reinjection rate may be slightly higher than presented here; at most, if all attacks that occurred < 48 hours after the previous attack were considered to be the same attack, then the reinjection rate would be 13.8% when including the outliers and 7.5% when excluding the outliers. It should be noted, though, that attacks tend to cluster, and the presence of two or more attacks within a short period of time may not necessarily signify a recurrence.

In conclusion, analyses of data collected from IOS, a real-world survey of icatibant treatment use, has shown that most HAE acute attacks are treated effectively with a single injection of icatibant, without the need for further injection, and minimal use of other HAE drugs to achieve complete symptom relief.

ACKNOWLEDGMENTS

We thank the following IOS investigators and study staff for their contributions to the IOS: M. Wiednig M (Austria); B. Coppere B

(France); J. Arnolds (Germany), M. Cicardi, E. Cillari, A. Zito (Italy); M. Caminoa, E. Ibáñez, T. Lobera, M.C. López Serrano, A. Sala (Spain); L. Lorenzo L (U.K.).

The IOS Executive Committee: W. Aberer, L. Bouillet, T. Caballero, H. Longhurst, M. Maurer, A. Zanichelli

REFERENCES

- Longhurst H, and Cicardi M. Hereditary angio-oedema. *Lancet* 379:474–481, 2012.
- Ghazi A, and Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. *Biologics* 7:103–113, 2013.
- Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 114:S51–S131, 2004.
- Cicardi M, and Johnston DT. Hereditary and acquired complement component 1 esterase inhibitor deficiency: A review for the hematologist. *Acta Haematol* 127:208–220, 2012.
- Cugno M, Zanichelli A, Foiени F, et al. C1-inhibitor deficiency and angioedema: Molecular mechanisms and clinical progress. *Trends Mol Med* 15:69–78, 2009.
- Kaplan AP, and Ghebrehwet B. The plasma bradykinin-forming pathways and its interrelationships with complement. *Mol Immunol* 47:2161–2169, 2010.
- Caballero T, Aygoren-Pursun E, Bygum A, et al. The humanistic burden of hereditary angioedema: Results from the Burden of Illness Study in Europe. *Allergy Asthma Proc* 35:47–53, 2014.
- Zilberberg MD, Nathanson BH, Jacobsen T, and Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in the United States, 2004–2007. *Allergy Asthma Proc* 32:248–254, 2011.
- Bork K, Hardt J, and Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 130:692–697, 2012.
- Maurer M, Aberer W, Bouillet L, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS One* 8:e53773, 2013.
- Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 363:532–541, 2010.
- Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B(2) receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 107:529–537, 2011.
- Maurer M, Longhurst HJ, Fabien V, et al. Treatment of hereditary angioedema with icatibant: Efficacy in clinical trials versus effectiveness in the real-world setting. *Allergy Asthma Proc* 35:377–381, 2014.
- Aberer W. Hereditary angioedema treatment options: The availability of new therapies. *Ann Med* 44:523–529, 2012.
- Aberer W, Maurer M, Reshef A, et al. Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema. *Allergy* 69:305–314, 2014.
- Shire. Firazyr 30 mg solution for injection in pre-filled syringe: Summary of product characteristics. Available online at <http://www.medicines.org.uk/emc/medicine/21761/SPC/Firazyr+30+mg+solution+for+injection+in+pre-filled+syringe/>; accessed July 14, 2015.
- Longhurst HJ. Management of acute attacks of hereditary angioedema: Potential role of icatibant. *Vasc Health Risk Manag* 6:795–802, 2010.
- Johnston DT. Diagnosis and management of hereditary angioedema. *J Am Osteopath Assoc* 111:28–36, 2011.
- Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: Consensus report of an International Working Group. *Allergy* 67:147–157, 2012.
- Leach JK, Spencer K, Mascelli M, et al. Pharmacokinetics of single and repeat doses of icatibant. *Clin Pharm Drug Dev* 10.1002/cpdd.138, 2014.
- Lumry W, Levy R, Li H, et al. Icatibant for the treatment of repeated attacks of hereditary angioedema: FAST-3 trial open-label extension study phase. *Allergy* 68(suppl. 97):254–255, 2013. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.