BRIEF COMMUNICATION

Long-term safety of icatibant treatment of patients with angioedema in real-world clinical practice

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Abstract

The Icatibant Outcome Survey (IOS) is an observational study monitoring safety and effectiveness of icatibant in the real-world setting. We analyzed safety data from 3025 icatibant-treated attacks in 557 patients (enrolled between July 2009 and February 2015). Icatibant was generally well tolerated. Excluding off-label use and pregnancy, 438 patients (78.6%) did not report adverse events (AEs). The remaining 119 (21.4%) patients reported 341 AEs, primarily gastrointestinal disorders (19.6%). Of these, 43 AEs in 17 patients (3.1%) were related to icatibant. Serious AEs (SAEs) occurred infrequently. A total of 143 SAEs occurred in 59 (10.6%) patients; only three events (drug inefficacy, gastritis, and reflux esophagitis) in two patients were considered related to icatibant. Notably, no SAEs related to icatibant occurred in patients with cardiovascular disease, nor in those using icatibant at a frequency above label guidelines. Additionally, no major differences were noted in AEs occurring in on-label *vs* off-label icatibant users.

Icatibant has demonstrated tolerability and efficacy in patients with hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) type I/II (1–5). Icatibant phase 3 studies included around 200 patients (228 attacks) and follow-up periods ≤24 weeks (1, 2). No icatibant-related serious adverse events (SAEs) were reported (1, 2). Nevertheless, considering the limited number of patients enrolled and the short follow-up, additional data are desirable.

Patient registries provide useful sources of additional data on rare conditions. The Icatibant Outcome Survey (IOS; NCT01034969) is an ongoing, international, prospective, observational registry monitoring efficacy and safety of icatibant in the real-world setting. Preclinical studies have suggested that icatibant-associated adverse events (AEs) may relate to its mechanism of action (6, 7). The current analysis evaluated incidence of cardiovascular-related AEs, as well as other common AEs in icatibant-treated patients. The objective was to assess safety data from the IOS database.

Patients and methods

Eligible patients were currently receiving or were candidates for icatibant use. Data were collected by physicians completing electronic forms with information from patients' follow-up visits; the protocol recommended every 6-month visits, but visit frequency was not mandated. IOS is conducted per

local ethics committees and/or health authorities at participating sites, the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines, and all patients provided written informed consent prior to participation. Additional details regarding the IOS registry have been previously described (8).

Safety data from the IOS reported herein were collected between July 2009 and February 2015 from 47 participating centers in 11 countries. Adverse events were categorized per Medical Dictionary for Regulatory Activities (MedDRA) system organ classification and analyzed by number/percentage of patients reporting a safety event and number/percentage of the occurrence of any safety event. The MedDRA term 'general disorders and administration site conditions' encompassed the following: application site pain, chest discomfort, chills, drug ineffective, drug intolerance, edema, fatigue, feeling hot, gait disturbance, hyperhidrosis, hyperplasia, influenza-like illness, infusion site pain, injection site erythema, injection site pain, injection site urticaria, localized edema, local swelling, malaise, noncardiac chest pain, pain, peripheral edema, pyrexia, and therapeutic product ineffective. Although pregnancy and off-label use (defined as patients with angioedema other than HAE type I/II or occurrence of AEs in patients <18 years) were documented as AEs in the IOS registry from a regulatory standpoint, these events were not considered clinically meaningful AEs and therefore were analyzed separately from our safety analysis.

Results

Patients

As of February 2015, ≥1 dose of icatibant was used to treat 3025 attacks in 557 patients. Mean age [standard deviation (SD)] at enrollment was 41.6 (15.2) years, with a female/male gender distribution of 63.6/36.4%.

Of patients with documented ethnicity (n = 540), most were white (93.3%). A total of 378 (69.9%) and 23 (4.3%) patients had C1-INH-HAE type I/II, respectively; the remaining patients (n = 140, 25.9%) had HAE with normal C1-INH, angiotensin converting enzyme (ACE) inhibitor-induced angioedema, idiopathic angioedema, acquired angioedema (CI-INH-AAE), or other (missing diagnoses, n = 16). Demographic parameters varied across HAE types. For instance, mean (SD) age at diagnosis was lower for patients with C1-INH-HAE type I/II [24.0 (16.0) years] and HAE with normal C1-INH [36.0 (14.3) years] *vs* those with idiopathic angioedema [44.7 (13.7) years], CI-INH-AAE [59.2 (9.7) years], and ACE inhibitor-induced angioedema [73.2 (6.1) years]. However, patients with CI-INH-AAE and ACE inhibitor-induced angioedema had a shorter mean (SD) delay between symptom onset and diagnosis [1.0 (1.2) and 1.7 (2.6) years, respectively] *vs* those with idiopathic angioedema [8.4 (10.8) years], C1-INH-HAE type I/II [10.1 (13.5) years], or HAE with normal C1-INH [11.1 (11.3) years].

Since entry into the IOS, the overall patient population was followed for a mean (SD) of 2.97 (1.42) years (<1 year, 10.2%; 1–2 years, 19.4%; 2–3 years, 17.2%; 3–4 years, 24.1%; 4–5 years, 26%, and ≥5 years, 3.1%). Follow-up times were similar across HAE subtypes. In total, patients were followed for 1655.2 icatibant-treated patient years.

AEs overall

Most icatibant-treated patients (n = 438, 78.6%) did not report an AE; the remaining 119 (21.4%) reported 341 AEs. The most commonly reported events were gastrointestinal (GI) disorders (19.6%), general disorders and administration site conditions (13.8%), infections and infestations (11.1%), respiratory, thoracic, and mediastinal disorders (8.8%), musculoskeletal and connective tissue disorders (6.5%), and skin and subcutaneous tissue disorders (6.5%). All other AEs represented <5% of total events. No major differences were noted in AEs occurring in on-label *vs* off-label icatibant users.

AEs related to icatibant

A total of 17 patients (3.1%) reported 43 treatment-related events (Table 1). Of these, 19 events (44.2%) in five patients were considered possibly related, and 24 events (55.8%) in 12 patients probably related. The most common treatment-related AEs were general disorders and administration site conditions (53.5%), GI disorders (11.6%), investigations (weight or blood pressure decreases, 11.6%), vascular disorders (hyperemia, 9.3%), and nervous system disorders (7.0%).

Serious adverse events

A total of 59 patients (10.6%) reported 143 SAEs (Table 2). The most common events were GI disorders (28%), respiratory, thoracic, and mediastinal disorders (12.6%), neoplasms (benign, malignant, or unspecified, 8.4%), general disorders and administration site conditions (7.7%), and infections and infestations (7.7%). Three SAEs (drug inefficacy, gastritis, reflux oesophagitis) in two patients were considered possibly or probably related to icatibant.

AEs in patients with cardiovascular disease

Cardiovascular disease (CVD) was reported in 95 icatibant-treated patients. At time of enrollment, patients reported: hypertension (n = 80), transient ischemic attack (TIA) or stroke (n = 5), angina (n = 4), and ischemic heart disease (n = 3). At follow-up, the following new onset CVDs were reported: hypertension (n = 5), angina (n = 1), ischemic heart disease (n = 1), and TIA or stroke (n = 1). Additionally at follow-up, hypertension was reported in three patients whose CVD history was missing at baseline.

A total of 22 (23.2%) patients with CVD reported 49 AEs, most commonly general disorders and administration site conditions (eight events, 16.3%), respiratory, thoracic, and mediastinal disorders (seven events, 14.3%), and GI disorders (five events, 10.2%). Of AEs occurring in patients with CVD, 13 events in three patients were considered possibly or

Table 1 AEs (excluding off-label use* and pregnancy) considered by the investigator to be possibly or probably related to icatibant

	Icatibant-treated patients (n = 557)	
	Number of events related to icatibant use (%)	Number of patients experiencing icatibant-related events (%)
Any event	43 (100.0)	17 (3.1)
Drug ineffective	6 (14.0)	5 (0.9)
Injection site erythema	6 (14.0)	1 (0.2)
Blood pressure decreased	4 (9.3)	1 (0.2)
Hyperemia	4 (9.3)	3 (0.5)
Pain	3 (7.0)	2 (0.4)
Gastritis	2 (4.7)	1 (0.2)
Application site pain	1 (2.3)	1 (0.2)
Chest discomfort	1 (2.3)	1 (0.2)
Cholelithiasis	1 (2.3)	1 (0.2)
Depression	1 (2.3)	1 (0.2)
Dizziness	1 (2.3)	1 (0.2)
Epigastric discomfort	1 (2.3)	1 (0.2)
Feeling hot	1 (2.3)	1 (0.2)
Headache	1 (2.3)	1 (0.2)
Herpes zoster	1 (2.3)	1 (0.2)
Infusion site pain	1 (2.3)	1 (0.2)
Injection site pain	1 (2.3)	1 (0.2)
Injection site urticaria	1 (2.3)	1 (0.2)
Nausea	1 (2.3)	1 (0.2)
Noncardiac chest pain	1 (2.3)	1 (0.2)
Therapeutic product ineffective	1 (2.3)	1 (0.2)
Postherpetic neuralgia	1 (2.3)	1 (0.2)
Reflux oesophagitis	1 (2.3)	1 (0.2)
Weight decreased	1 (2.3)	1 (0.2)

AEs, adverse events.
*Off-label use refers to patients with angioedema other than HAE type I or II or those in whom AEs occurred prior to 18 years of age.

probably related to icatibant, with the majority being general disorders and administration site conditions (eight events, 61.5%). Sixteen patients reported 24 SAEs, none of which were considered related to icatibant.

AEs in patients who used icatibant at a frequency above label guidelines

Per the icatibant summary of product characteristics, ≤8 icatibant injections per month have been administered in clinical trials (9). In the IOS registry, of 10 patients who received ≥9 icatibant injections in 1 month, drug ineffectiveness was reported in two patients. The icatibant package information recommends an interval of ≥6 h between doses and no more than three doses in 24 h (10). In the IOS registry, no AEs were reported by 13 patients whose intervals between icatibant doses were <6 h, nor in four patients who received icatibant more frequently than three times in 24 h.

Table 2 SAEs (excluding off-label* use and pregnancy) occurring with a frequency of >1% of total events

	Icatibant-treated patients (n = 557)	
	Number of events (%)	Number of patients (%)
Any event	143 (100.0)	59 (10.6)
Abdominal pain	8 (5.6)	7 (1.3)
Angioedema	4 (2.8)	4 (0.7)
Diarrhea	4 (2.8)	2 (0.4)
Peripheral edema	4 (2.8)	2 (0.4)
Abdominal distension	3 (2.1)	3 (0.5)
Face swelling	3 (2.1)	3 (0.5)
Laryngeal edema	3 (2.1)	3 (0.5)
Abdominal hernia	2 (1.4)	2 (0.4)
Abdominal pain (upper)	2 (1.4)	2 (0.4)
Colonic polyp	2 (1.4)	1 (0.2)
Cough	2 (1.4)	2 (0.4)
Dyspnoea	2 (1.4)	2 (0.4)
Hematochezia	2 (1.4)	1 (0.2)
Hereditary angioedema	2 (1.4)	2 (0.4)
Legionella infection	2 (1.4)	1 (0.2)
Local administration site swelling	2 (1.4)	2 (0.4)
Myelodysplastic syndrome	2 (1.4)	1 (0.2)
Pyrexia	2 (1.4)	2 (0.4)
Respiratory failure	2 (1.4)	1 (0.2)
Suicide attempt	2 (1.4)	2 (0.4)

SAEs, serious adverse events.
*Off-label use refers to patients with angioedema other than HAE type I or II or those in whom adverse events occurred prior to 18 years of age.

Discussion

Overall, no unexpected safety signals emerged in this large database, and AEs were similar in off-label *vs* on-label users. General disorders and administration site conditions occurred in 13.8% of icatibant-treated patients, including but not limited to local injection site reactions. Occurrence of these reactions was notably lower than their 97% incidence in icatibant clinical trials (10), especially since the 13.8% incidence may be an overestimation (given that these reactions were recorded as part of a larger bucket of events). This discrepancy may reflect multiple factors, including differences in the processes followed for reporting and documenting such reactions in a real-world setting *vs* a controlled environment. Whereas in a clinical trial setting investigators proactively document occurrence of all (including very minor and transient) injection site reactions in a detailed manner upon their immediate occurrence, in a drug registry setting, such reactions are documented retrospectively, possibly leading to recall bias. Patients may fail to report a well-tolerated local reaction, or the investigators may choose not to document this expected, minor reaction as an AE. The extended time lapse between occurrences of angioedema attacks and when patients report AEs during follow-up visits may further

contribute to underreporting. Nonetheless, our findings present a real-world perspective with regard to icatibant tolerability, which may indeed differ somewhat from findings in clinical trials.

Serious adverse events occurred infrequently, and none were cardiovascular-related. Studies have shown that bradykinin B2 receptor blockade might impair endothelial repair after an acute cardiovascular event (6, 7). However, icatibant has a short half-life (9) and the effect of intermittent treatments is likely transient.

Potential limitations of the IOS study were the uncontrolled clinical environment inherent in an observational study design, as well as possible inconsistences in patient and physician-based reporting of AEs across registry study sites. Nonetheless, observational registries offer valuable insights into the safety and efficacy of treatments in real-world settings.

Our results show that icatibant was generally well tolerated; incidence and severity of AEs was not greater than was expected in this patient population. No major differences were noted in on-label *vs* off-label icatibant users, and no SAEs occurred in patients with CVD using icatibant.

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Author contributions

Andrea Zanichelli contributed to study conception and design, data acquisition, analysis and interpretation, drafting the manuscript and critical content revisions, as well as final content approval for submission; Marcus Maurer contributed to study conception and design, data acquisition, analysis and interpretation, drafting the manuscript and critical content revisions, as well as final content approval for submission; Werner Aberer contributed to data acquisition, analysis and interpretation, drafting the manuscript and critical content revisions, as well as final content approval for submission; Teresa Caballero contributed to study conception and design, data acquisition, analysis and interpretation, drafting the manuscript and critical content revisions, as well as final content approval for submission; Hilary J. Longhurst contributed to data acquisition, analysis and interpretation, drafting the manuscript and critical content revisions, as well as final content approval for submission; Laurence Bouillet contributed to data acquisition, drafting the manuscript and critical content revisions, as well as final content approval for submission; Vincent Fabien contributed to study conception and design, analysis and interpretation of data, drafting the manuscript and critical content revisions, as well as final content approval for submission; and Irmgard Andresen contributed to study conception and design, analysis and interpretation of data, drafting the manuscript and critical content revisions, as well as final content approval for submission.

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Conflicts of interest

Dr Andrea Zanichelli has received speaker fees from CSL Behring, Shire, and Sobi; consultancy fees from CSL Behring and Shire; and has acted on the medical/advisory boards for CSL Behring and Shire. Prof Marcus Maurer has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, and Shire/Jerini AG. Prof Werner Aberer has acted as a medical advisor and speaker for BioCryst, CSL Behring, Pharming, and Shire, and has received funding to attend conferences/educational events, and donations to his departmental fund from and participated in clinical trials for Shire. Dr. Teresa Caballero has received speaker fees from CSL Behring, GlaxoSmithKline, MSD, Novartis, and Shire; consultancy fees from BioCryst, CSL Behring, Novartis, Shire, and Sobi; funding for travel and meeting attendance from CSL Behring, Novartis, and Shire, and has participated in clinical trials/registries for CSL Behring, Dyax, Novartis, Pharming, and Shire. She is a researcher from the IdiPaz Program for promoting research activities. Dr Hilary J. Longhurst has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, Shire, and SOBI-Biovitrum. Prof Laurence Bouillet has received honoraria from BioCryst, CSL Behring, Novartis, Pharming, and Shire, and her institute has received research funding from CSL Behring, GlaxoSmithKline, Novartis, Roche, and Shire. Dr Irmgard Andresen is a full-time employee of Shire, Zug, Switzerland. Vincent Fabien was a Shire employee at time of analysis.

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