

BRIEF COMMUNICATION

Icatibant treatment for acquired C1-inhibitor deficiency: a real-world observational study

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To cite this article: Zanichelli A, Bova M, Coerezza A, Petraroli A, Triggiani M, Cicardi M. Icatibant treatment for acquired C1-inhibitor deficiency: a real-world observational study. *Allergy* 2012; DOI: 10.1111/j.1398-9995.2012.02853.x.

Keywords

acquired angioedema; C1-inhibitor deficiency; icatibant.

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Accepted for publication 01 May 2012

DOI:10.1111/j.1398-9995.2012.02853.x

Edited by: Hans-Uwe Simon

Abstract

Icatibant, a bradykinin B₂ receptor antagonist, is an established treatment for acute attacks of hereditary angioedema (HAE) with C1-inhibitor (C1-INH) deficiency. We describe our experience with icatibant in eight patients with angioedema because of acquired C1-INH deficiency (AAE). Forty-eight moderate-to-severe attacks were treated with subcutaneous icatibant 30 mg; two moderate attacks resolved without treatment. The median (range) duration of treated attacks (onset to complete resolution) was 9.33 (1.67–39.00) h; durations of the untreated attacks were 72 and 96 h. Symptom improvement following icatibant treatment occurred in 0.5 (0.25–2.10) h and complete resolution in 6.75 (0.50–30.75) h. A single icatibant injection achieved complete symptom resolution in 47 attacks; one facial attack required a second injection. One peripheral attack responded less quickly than other treated attacks. Five patients reported transient injection site reactions. Icatibant appeared to provide effective symptom relief and was generally well tolerated.

Angioedema with acquired C1-inhibitor (C1-INH) deficiency, or acquired angioedema (AAE), is a rare syndrome that is frequently associated with lymphoproliferative disorders. Clinically, AAE is broadly similar to hereditary angioedema (HAE), although involvement of the face and limbs is more frequent in AAE and symptom onset differs within the second decade of life for >90% of patients with HAE, and after the fourth decade in AAE (1). Unlike most patients with HAE, family history of angioedema is absent in patients with AAE (1).

C1-inhibitor deficiency in AAE is caused by increased C1-INH catabolism because of the presence of lymphoproliferative disorders, including monoclonal gammopathies of undetermined significance (MGUS) and non-Hodgkin's lymphoma and/or anti-C1-INH neutralising autoantibodies (1). Reduced C1-INH function activates the classical complement pathway and contact system, leading to elevated bradykinin levels, increased vascular permeability and angioedema (2–5). Standard treatment for AAE attacks is replacement therapy with plasma-derived C1-INH concentrate (pdC1-INH). However, some patients with AAE become progressively less responsive

to pdC1-INH treatment (6,7), possibly due to anti-C1-INH autoantibody development (a disease characteristic) (2).

Icatibant (Shire Orphan Therapies GmbH, Berlin, Germany), a selective bradykinin B₂ receptor antagonist registered in 38 countries worldwide for the symptomatic treatment of acute attacks of HAE in adults with C1-INH deficiency, has been evaluated in three Phase III controlled studies in patients with HAE (8,9) and is a recommended option for on-demand therapy of HAE attacks (10–12). Unlike pdC1-INH, icatibant is not affected by the presence of anti-C1-INH autoantibodies. Three case reports have described successful acute treatment of AAE with icatibant (13–15). On the basis of these positive data and clinical experience in HAE, we examined the use of icatibant in AAE (icatibant is not licensed for AAE, and such use is therefore off-label and experimental).

Patients and methods

Consecutive adult patients with AAE who did not respond to high doses (up to 40 U/kg) of pdC1-INH concentrate (i.e. no

symptom improvement within 4 h) with moderate-to-severe angioedema attacks at any location were treated with subcutaneous icatibant (30 mg). Acquired angioedema was defined as history of recurrent angioedema without major urticaria, onset of symptoms after the age of 40 years, absence of family history of angioedema and functional C1-INH plasma levels >50% of normal on two separate determinations. Plasma C1-INH functional levels were measured by chromogenic assay (Technochrom C1-inhibitor, Technoclone GmbH, Vienna, Austria). Antigenic C1-INH, C4 and C1q measurements were performed by radial immunodiffusion (NOR-Partigen, LC-Partigen; Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). C1-inhibitor autoantibodies were detected by ELISA (16).

All patients gave written informed consent. For each attack, patients recorded the date/time of onset; attack location (categorised according to the location with the most severe symptom[s] for attacks in multiple locations) and

severity (11); and date/time of treatment, first improvement and complete resolution of symptoms. Angioedema attacks initially treated with pdC1-INH, as well as subsequent attacks, were eligible for icatibant treatment.

Results

Eight patients (seven men, one woman) with AAE (median age 73.5 years; range 62.0–86.0) were monitored during 50 acute angioedema attacks (August 2009–January 2010) at two sites (Milan, Naples; Italy). All patients had C1-INH functional levels and C4 levels below 50% of normal. C1-inhibitor antigen and C1q were below 50% in five patients (62.5%). Neutralising autoantibodies to C1-INH were detected in seven patients. Four patients had MGUS; none had lymphoma at diagnosis or during follow-up (Table 1).

In total, 48 moderate-to-severe attacks (one cutaneous, four oro-pharyngeal-laryngeal, 18 facial and 25 abdominal)

Table 1 Patient characteristics, complement parameters, anti-C1-INH autoantibodies, associated diseases and summary of angioedema attacks

	Sequential patient number							
	1	2	3	4	5	6	7	8
Age, years	74	62	64	67	84	76	86	73
Gender	M	M	F	M	M	M	M	M
BMI, kg/m ²	25.5	25.2	33.4	31.9	24.2	23.7	22.9	27.5
Complement parameters (% values indicate activity relative to normal human plasma)								
C1-INH antigen (%)	14	72	36	66	25	25	56	23
C1-INH activity (%)	10	46	8	30	30	30	14	16
C4 (%)	10	36	4	25	10	25	36	19
C1q (%)	10	88	10	88	10	10	122	6
Anti-C1-INH	IgA	IgG	IgA	IgG	IgG	IgG-IgM	IgM	Negative
Associated diseases	MGUS	None detected	MGUS	MGUS	None detected	None detected	None detected	MGUS
Number of icatibant-treated/untreated angioedema attacks								
	1/0	1/0	3/0	5/1	15/1	1/0	20/0	2/0
Localisation of icatibant-treated angioedema attacks								
Peripheral	–	–	–	–	–	–	1	–
Abdominal	–	–	–	5	1	–	19	–
Oro-Pharyngeal-Laryngeal	–	–	1	–	3	–	–	–
Facial	1	1	2	–	11	1	–	2

BMI, body mass index; F, female; IgG, immunoglobulin G; IgM, immunoglobulin M; M, male; MGUS, monoclonal gammopathy of undetermined significance.

Table 2 Times from attack onset to icatibant treatment and from icatibant treatment to first symptom relief and complete resolution of symptoms

Attack category (number of attacks)	Median (range) duration, h		
	From attack onset to icatibant treatment	From icatibant treatment to first relief of symptoms	From icatibant treatment to complete resolution of symptoms
Overall (48)	1.62	0.50 (0.25–21.00)	6.75 (0.50–30.75)
Peripheral (1)	3.00	21.00	28.00
Abdominal (25)	2.00	0.50 (0.25–1.25)	1.00 (0.50–30.50)
Oro-Pharyngeal-Laryngeal (4)	0.75	0.50 (0.25–2.00)	11.00 (4.00–18.00)
Facial (18)	1.00	0.50 (0.25–4.00)	16.25 (2.0–30.75)

were treated with icatibant (Table 1). Two moderate attacks (one cutaneous and one abdominal) in two patients remained untreated and resolved spontaneously. Patients were treated for 1–20 acute attacks. Three patients received icatibant for more than five consecutive attacks.

The median (range) duration (from onset to complete resolution) of the 48 treated attacks was 9.33 (1.67–39.00) h; the two untreated attacks had durations of 72 h (abdominal) and 96 h (cutaneous). Times from attack onset to icatibant treatment and from icatibant treatment to first symptom relief and complete resolution are summarised in Table 2. For 47 attacks, a single icatibant injection achieved complete symptom resolution. In one of these patients who responded to a single icatibant injection (Patient 7), one peripheral attack responded less quickly than other treated attacks (but still resolved more quickly than the two untreated attacks). Only one patient (Patient 8), who had a severe facial attack, required a second injection because of symptom rebound 17 h after first administration; complete symptom resolution was achieved 14 h thereafter. Patients 7 and 8 were both also successfully treated with a single injection for other attacks during the study.

Burning sensation and erythema at the site of icatibant injection were reported by five patients (24 attacks). These events were transient and resolved spontaneously. Three patients did not report any adverse events.

Summary and conclusions

Several studies have reported pdC1-INH concentrate resistance in patients with AAE or HAE (6, 17–21), and even in patients who initially respond to treatment, the number of C1-INH-anti-C1-INH antibody complexes can increase several-fold within minutes (17).

In our study, median times to onset of symptom relief and complete symptom resolution were rapid (within 1 h and 6 h, respectively). The peripheral attack that responded less quickly to icatibant treatment than other treated attacks occurred in a patient who was also successfully treated for 19 abdominal attacks. This patient (an 86-year-old man) had no other conditions that could explain the delayed response and was on no concomitant medications other than danazol. The facial attack that required a second icatibant injection occurred in a patient who was also successfully treated with icatibant for another facial attack.

Our findings suggest that icatibant may have an efficacy and safety profile in AAE similar to that reported in HAE (9,10) and may be an effective option for patients not responding to pdC1-INH concentrate (although neither treat-

ment is currently licensed for AAE). Moreover, icatibant was efficacious irrespective of attack location, including potentially fatal oro-pharyngeal-laryngeal angioedema (1), suggesting a possible role for icatibant in emergency AAE attack management.

Acknowledgments

Medical writing support was provided by Mark Waterlow BSc. at Prime Medica Ltd during the preparation of this article, supported by Shire Human Genetic Therapies Inc. Responsibility for opinions, conclusions and interpretation of data lies with the authors, and such perspectives do not reflect those of Shire Human Genetic Therapies Inc.

Authors contributions

AZ involved in acquisition of data (patient recruitment, treatment and follow-up); analysis and interpretation of data; critical review of the manuscript. MB involved in treatment and follow-up of patients; acquisition of data.

AC involved in acquisition of data (patient recruitment, treatment and follow-up); analysis and interpretation of data; critical review of the manuscript.

AP involved in patient recruitment and acquisition of data. MT contributed to study design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript. MC contributed to study design; patient recruitment; analysis and interpretation of data; critical revision of the manuscript.

Conflict of interest

AZ is an advisor for Shire Human Genetic Therapies Inc. and has been an invited speaker for Shire Human Genetic Therapies Inc. and CSL Behring. MC has consultancy agreements with Dyax, Pharming and Shire Human Genetic Therapies Inc., is an advisor for Dyax, Shire Human Genetic Therapies Inc. and CSL Behring and has been an invited speaker for Dyax, Shire Human Genetic Therapies Inc., CSL Behring, Pharming and ViroPharma.

MB and AP have received research support from Shire Human Genetic Therapies Inc. and CSL Behring. MT has consultancy agreements and has been an invited speaker for Shire Human Genetic Therapies Inc. and CSL Behring.

Data from this study were presented at the *American Academy of Asthma Allergy and Immunology 2012 Annual Meeting, Orlando, FL, USA (2–6 March 2012)*.

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