Treatment of acute attacks of hereditary angioedema (HAE) with the bradykinin B2 receptor antagonist icatibant

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ABSTRACT

Icatibant is a selective and competitive bradykinin B2 receptor antagonist. It was approved in 2008 for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with a deficiency of the C1 esterase inhibitor. Icatibant is the first subcutaneous treatment for HAE. The efficacy of icatibant in the treatment of moderate to very severe cutaneous and abdominal attacks in patients with HAE was investigated in two Phase III trials in comparison with tranexamic acid and with placebo, respectively. The time to onset of symptom relief, the primary end point of the trial, was significantly shortened with icatibant compared to tranexamic acid. Icatibant demonstrated a favourable safety profile in clinical trials with no drug-related serious adverse events.

Key-words: *Bradykinin, hereditary angioedema, icatibant.*

Hereditary angioedema (HAE) is a rare disease with dominant autosomal inheritance[1]. According to some estimations, there are around 550 patients diagnosed with hereditary angioedema in Spain and Portugal. The disease is likely to be underdiagnosed, so the real figures are probably higher, with estimations up to 900 patients. Patients suffer from repeated attacks of subcutaneous or mucosal swellings. The swelling usually starts gradually over a period of up to 24 hours and resolves, without treatment during the following 48 to 72 hours. The regions most commonly affected are the face and limbs, as well as the gastrointestinal tract and genitalia. Oropharyngeal and laryngeal swelling is much rarer, although such attacks are potentially life-threatening. This lifelong condition generally manifests in early childhood or puberty. The frequency of the attacks and the severity of the symptoms vary notably from one individual to another. Approximately 30% of patients report a frequency of greater than one attack per month; 40% of patients experience on average 6 to 11 attacks per year; and the remaining 30% are infrequently symptomatic[2]. In most cases, the symptoms of HAE are transient, progressing over 12 to 36 h and then subsiding gradually over the next 2 to 5 days. However, some patients may experience attacks that last over a week[2,3]. During puberty and adolescence, a worsening of the clinical situation is frequently noted.

Attacks usually appear without any recognizable trigger. On the other hand, physical/mechanical trauma, mental stress, infectious diseases and, in women, oestrogens (for example, pregnancy, use of oral contraceptives) have all been reported to induce attacks in some patients.

The cause of hereditary angioedema is a congenital lack of the C1-esterase inhibitor (C1-INH), due to mutations in the C1-INH gene of chromosome 11. Two types of hereditary deficiency of C1-INH can be differentiated:

- Type I (classic form, 85% of cases) is due to a defect in the synthesis of C1-INH. The concentration of C1-INH in serum is significantly decreased.
- Type II (variant, 15% of cases) corresponds to a functional defect of C1-INH. Serum concentration of C1-INH is normal or slightly elevated and the C1-INH activity is decreased.

Another type of HAE which is referred to as type III is characterized by normal serum concentrations and normal C1-INH activity. Some of these patients affected by HAE type III present a mutation of the factor XII gene. It often affects women, so a link with oestrogens is suspected[4].

C1-INH is a serine protease inhibitor blocking the activation of the complement system, the kallikrein-kinin-system and the fibrinolytic system (Figure 1).

Studies have shown that these systems are activated in patients during HAE attacks. Various vasoactive mediators are released, including bradykinin as the key mediator determining the increase of vascular permeability and the symptoms of hereditary angioedema[5].

Bradykinin is a nonapeptide that binds to and acts on constitutionally expressed bradykinin B_2 receptors. This G protein coupled surface receptor is present in most tissues and highly expressed by endothelial cells. After binding of the ligand and activation of the receptor, endothelial cells undergo a release of phospholipase C dependent inositol phosphate, an increase in intracellular Ca^{2+} and a stimulation of phospholipase A_2 that activate the metabolism of arachidonic acid and release vasoactive substances (e.g. NO, prostaglandins): this results in vasodilatation, increased vascular permeability and the onset of pain.

The therapy of patients with hereditary angioedema is based on treating acute attacks and preventing further attacks (Table 1).

The treatment of choice for acute attacks (particularly pharyngeal or laryngeal or those of the gastrointestinal tract) until now was the intravenous replacement of C1-INH concentrate, where available. Alternatively, fresh frozen plasma (FFP) or (in some European countries) tranexamic acid were used for treatment. One of the major downsides of using FFP for treateing HAE attacks is

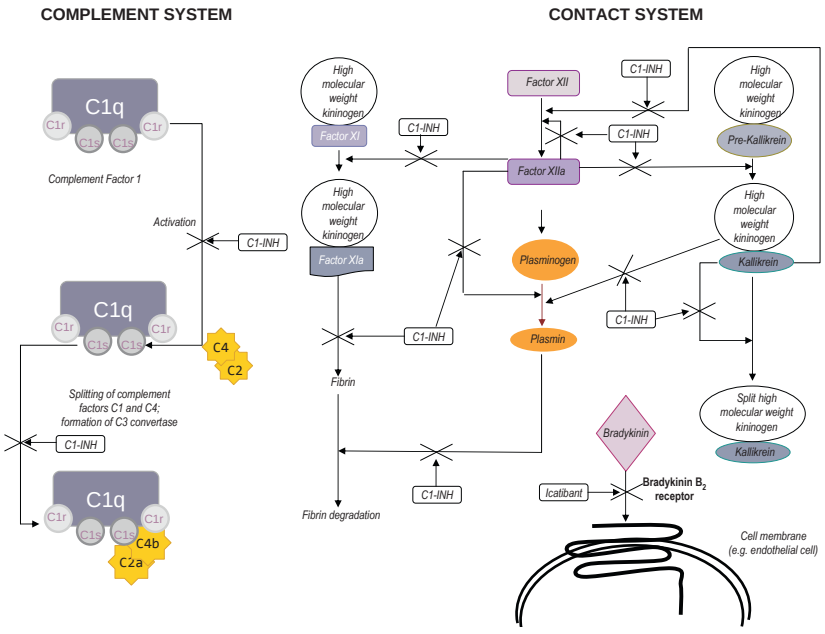

Figure 1. Physiological effects of the C1-esterase inhibitor (C1 INH) on the complement and contact system (as per 1). C1 INH inhibits the activation of the complement system by blocking the activation of complement factor 1 (C1 at the start of the classic complement activation pathway). Factors C2 and C4 are split by the activated C1-complex (marked with asterisks on the respective molecules), resulting in C2a, C2b, C4a and C4b. Binding of C2a and C4b to C3 convertase results in cleavage of factor C3 into C3a and C3b. The complement fractions, such as C3a, may cause vasodilatation and an increase in vascular permeability, for instance through their binding to endothelial cells. C1 INH also inhibits the start phase of the kallikrein-kinin system and the fibrinolytic system. In the pathogenesis of hereditary angioedema, the release of bradykinin from high molecular weight kininogen is decisive: by binding to its receptor (bradykinin B2 receptor) on the endothelial cells, bradykinin induces vasodilatation and increases vascular permeability with subsequent oedema formation

Table 1. Therapeutic options for the prophylaxis and treatment of hereditary angioedema attacks (HAE)

Substance	Mechanism of action
Acute treatment	
Icatibant (Firazyr®)	Antagonist of bradykinin B2 receptors
C1-INH concentrate	Replacement of C1-INH
Fresh frozen plasma	Replacement of components
Prophylaxis	
Short-term treatment (ordinarily prior to surgery or dental treatments)	
C1-INH concentrate*	Replacement of C1-INH
Androgens such as danazol	Stimulation of C1-INH synthesis in the liver (?)
Fresh frozen plasma	Replacement of components
Long-term treatment	
Androgens such as danazol**	Stimulation of C1-INH synthesis
Tranexamic acid (e.g. Cyklokapron®)$	Anti-fibrinolytic effect: inhibition of plasminogen binding to fibrin or fibrinogen, blocking the degrading effect of the plasmin

* The administration of C1 INH concentrate as short-term prophylaxis is advised in the current consensus algorithm [Bowen T, *et al.* Ann Allergy Asthma Immunol 2008 Jan; 100 (1 Suppl 2):S30-40. Review. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema]

** During treatment, there may be several adverse reactions (e.g. weight gain, depression, virilization of females, hypertension increased LDL cholesterol, liver damage)

$ Withdrawal from current consensus algorithm recommended, particularly before and during puberty

that, together with C1-INH, substrates of the complement system and the kinin system are also infused and these may exacerbate the attacks through activation of vasoactive peptides. On July 11th, 2008, icatibant (Firazyr®), a competitive antagonist of bradykinin B_2 receptors, was approved in the EU member states for the symptomatic treatment of acute attacks of hereditary angioedema in adults (with a lack of C1-INH).

PHARMACOLOGY

Pharmacodynamics

The synthetically manufactured decapeptide icatibant is a selective and competitive antagonist of bradykinin B2 receptors with a tertiary structure similar to that of bradykinin (Figure 1)[6]. As such, icatibant antagonizes bradykinin mediated reactions such as vasodilatation, increased vascular permeability, and the onset of pain.

Pharmacokinetics

The pharmacokinetic data (Table 2) on icatibant were obtained in clinical trials with healthy individuals and patients who received intravenous or subcutaneous injections[6,7]. Icatibant is metabolized by proteolytic enzymes to inactive metabolites that are mainly excreted in the urine. Only limited data are available from the icatibant-treated patients with altered liver or kidney function but no dosage adjustment appears necessary. There is no data on pharmacokinetics in children nor is there information about the influence of race on pharmacokinetic parameters. The data available indicate that patients' weight and gender have no significant effect on the pharmacokinetics of icatibant.

Table 2. Pharmacokinetic characteristics of icatibant[6,7]

Absolute bioavailability	97% following subcutaneous injection
Time to maximum plasma concentration (tmax)	Approximately 0.5 h
Distribution volume (Steady State)	20 to 25 l
Plasma protein binding	44%
Clearance	Approximately 15 to 20 l/h*
Terminal plasma half life (t1/2)	Approximately 1 to 2 h

* Data suggest an age-related decline in clearance resulting in about 50-60% higher exposure in the elderly (75-80 years) compared to a patient aged 40 years

Efficacy

Two international Phase III, randomized, double blind trials (FAST-1 and FAST-2, *For Angioedema Subcutaneous Treatment*) assessed the efficacy and safety of icatibant as a treatment for moderate, severe or very severe cutaneous and abdominal attacks in patients with hereditary angioedema[7]. FAST-1 was conducted in 26 study centers in North America, Argentina, and Australia, FAST-2 in 31 study centers in Europe and Israel.

In these trials, icatibant (30 mg s.c., n = 63) was compared to placebo (n = 29) or tranexamic acid (3x2 tablets of 500 mg for 2 days, n = 38). The European Medicines Agency had recommended tranexamic acid as comparator, as it is administered for treatment of HAE attacks in some European countries, i.e. France and Spain.

The treatment of subsequent attacks could be performed with up to 3 s.c. injections of 30 mg icatibant in an open-label extension phase (OLE) of the trials. Patients with laryngeal attacks were treated open-label with 30 mg icatibant s.c. in both trials.

The primary end point in both studies was the time to onset of symptom relief after administration of the study drug, assessed by an visual analogue scale (VAS) (0 = no symptoms; 100 = worst possible symptoms). Regarding the primary endpoint only the improvement of one main symptom was taken into account (cutaneous swelling, abdominal pain or cutaneous pain). The primary efficacy endpoint was the time to significant symptom relief based on VAS scoring with values of 20-30 mm depending upon

initial symptom severity. Clinically significant symptom relief was documented at three consecutive measurements based on VAS, with the earliest of these being defined as the time point of clinically significant symptom relief.

The time to onset of symptom relief of the first attack was significantly shorter with icatibant than with tranexamic acid (2.0 hrs vs 12.0 hrs; p<0.001) but not compared to placebo (2.5 hrs vs 4.6 hrs; p=0.142) (Table 3).

After 4 and 12 hours following administration of the study medication, significant differences were seen between icatibant, tranexamic acid and placebo, respectively (Table 3).

Table 3. Efficacy of icatibant for the treatment of moderate, severe or very severe attacks in patients with hereditary angioedema according to the results of two randomized, double-blind, controlled trials (FAST-1 and FAST-2) (placebo; tranexamic acid)[6,7]

	FAST-2			FAST-1		
	Icatibant	**Tranexamic acid**	**p value**	**Icatibant**	**Placebo**	**p value**
Patients in the ITT group [n]	36	38		27	29	
Baseline value according VAS (mm)]	63.7	61.5		69.3	67.7	
Primary end-point: Median time to onset of symptom relief (hours)	2.0	12.0	<0.001	2.5	4.6	0.142
Change from baseline to 4 hours	-41.6	-14.6	Difference between treatment groups: 27.8 (95% CI 39.4; 16.2) <0.001	-44.6	-23.5	Difference between treatment groups: 22.3 (95% CI 36.1; 9.3) 0.002
Change from baseline to 12 hours	-54.0	-30.3	Difference between treatment groups: 24.1 (95% CI 33.6; 14.8) <0.001	-53.9	-41.0	Difference between treatment groups: 14.0 (95% CI 27.7; 0.3) 0.046
Median time to onset of symptom relief, for all symptoms[h]*						
Cutaneous swelling	2.6	18.1	0.001	3.1	10.2	0.039
Cutaneous pain	1.5	12.0	0.003	1.6	9.0	0.007
Median time to regression of symptoms, according to the patient[h]*	0.8	7.9	<0.001	0.8	16.9	<0.001
Median time to almost complete symptom relief (hours) [h]*	10.0	51.0	<0.001	8.5	23.3	0.069

95% CI: 95% confidence interval; ITT: intention-to-treat; * Secondary endpoint;

In both trials, a total number of 36 patients with 61 laryngeal attacks were treated with icatibant. The results were similar to those in patients with cutaneous and abdominal attacks. The initial symptomatic improvement in most patients occurred within the first hour.

The efficacy data obtained during the open-label phase of the trial were similar to those in the double blind phase. In total, 118 patients with 597 attacks were treated with icatibant during the open-label phase of the trial. Furthermore, one single application of icatibant was sufficient to adequately treat most of the attacks (FAST-1: 89.3%; FAST-2: 90.9%) in this phase of the trial. Unlike in the double-blind phase of the trial, during the OLE phase, icatibant could be administered in multiple doses: up to 3 injections, without exceeding 30 mg/day or up to 8 injections, each of 30 mg, over a period of 4 weeks.

The reason for not meeting the primary endpoint in FAST-1 can be most likely explained by the small number of patients and a high placebo response, especially in those patients with abdominal pain. In addition, patients in the placebo group used "rescue medication" (i.e. analgesics) to a higher percentage but were not censored in the primary analysis. As such the effect of rescue medication largely contributed to the placebo response.

Tolerance

Most of the patients who received icatibant in the clinical trials presented with local reactions at the injection site (e.g. erythema, swelling, burning, itching and/or pain in the skin). Most of the reactions were mild and short-lasting, resolving spontaneously without any further intervention. Other common adverse reactions (≥ 1/100; < 1/10) comprised:

- Nausea, abdominal pain
- Fatigue
- Dizziness, headache
- Rash
- Nasal congestion
- Increased creatine phosphokinase in the blood, abnormal values for liver function test.

Interactions

Interactions between icatibant and other medicinal products are unlikely. *In vitro* studies have shown that icatibant is not metabolized by the cytochrome P450 enzyme system (CYP) and does not inhibit major CYP-P450 isoenzymes such as CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 and 3A4 nor does it induce CYP1A2 or 3A4.

Indication, dosage, administration and handling

According to the information from the European Medicines Agency, icatibant is approved for the symptomatic treatment of acute attacks of hereditary angioedema in adults with a deficiency of C1-INH. The recommended dose of 30 mg of icatibant is to be injected subcutaneously by a health-care professional preferably in the abdominal area.

In the vast majority of cases a single injection of icatibant is sufficient to treat an attack. In case of insufficient relief or recurrence of symptoms, a second injection of icatibant can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of icatibant can be administered after a further 6 hours. No more than 3 injections of icatibant should be administered in a 24 hour period.

Caution is advised[6]

- in patients with acute ischaemic heart disease or unstable angina (theoretically deterioration of cardiac function and a decrease in coronary blood flow could arise from antagonism of bradykinin receptor type 2 under ischemic conditions) and
- in patients who have suffered a stroke in the preceding weeks (possible antagonism of the late phase neuroprotecting effect of bradykinin through the blockade of B_2 receptors by icatibant).

Icatibant may have a slight to moderate effect on the ability to drive vehicles and operate machinery.

SUMMARY, EVALUATION, CONCLUSION

During the last 30 years the treatment of choice for acute attacks of HAE was the intraveneous application of C1-INH concentrate in countries where it was available (= replacement therapy). With the approval of the bradykinin B_2 receptor antagonist, icatibant (Firazyr®) a novel treatment option for acute HAE attacks (due to C1-INH deficiency) is now available:

- Icatibant targets the last step in the kallikrein-kinin cascade by specifically blocking the bradykinin B2 receptor and thus inhibiting the action of the key mediator of symptoms, bradykinin.
- Icatibant is the first drug for subcutaneous administration in HAE attacks.
- Icatibant is not a blood derived product and, in accordance with the legislation on transfusions, it is exempt from any obligatory documentation.

Other characteristics of icatibant are:

- Icatibant can be administered for treatment of all kinds of HAE attacks (cutaneous, abdominal, laryngeal)
- short time to first symptom improvement
- Shortening of the duration of HAE attacks
- Maintenance of efficacy in the treatment of repeated attacks
- Favourable safety profile
- Possibility of storage at room temperature

Despite its subcutaneous application and is packaging as a pre-loaded syringe, icatibant is not currently indicated for self-injection but has to be administered by a healthcare professional. An ongoing study assessing the safety of self-administration of icatibant by patients may lead to a label change in the near future.

Efficacy of icatibant was demonstrated in phase II and phase III clinical trials. The median time until onset of symptom relief was significantly shorter with icatibant compared to tranexamic acid (2.5 hrs vs 12.0 hrs). A similar time to onset of symptom relief was recorded for icatibant in the FAST-1 trial but the difference compared to placebo was not significant (2.5 hrs vs 4.6 hrs; p=0.142). This may be best explained by the high placebo response especially in abdominal attacks. Results from secondary endpoints in the FAST-trials support the efficacy of icatibant.

As icatibant is indicated for the treatment of HAE attacks due to C1-inhibitor deficiency only (type I and II) HAE type III - being characterised by normal C1-INH levels - is currently not an indication. Nevertheless, in non-allergic angioedema i.e. ACE-inhibitor induced angioedema, where bradykinin is held to be the key mediator, the bradykinin B2 receptor antagonist icatibant may be a treatment option. Clinical trials in these conditions have to provide proof-of-principle.

Like C1-INH concentrate, icatibant should only be administered after the diagnosis of HAE has been confirmed. Patients arriving with symptoms of angioedema (and no reports of HAE in the family history) should in principle receive treatment with anti-histamines and, where appropriate, glucocorticoids at first, as histamine-mediated angioedemas (often occurring with a pruriginous rash) are most common. If the swelling does not cease or resolve after repeated administration of antiallergic drugs, treatment with icatibant or C1-INH may be taken into consideration.

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