

FRESH FROM THE PIPELINE

Icatibant

Konrad Bork, Uma Yasothan and Peter Kirkpatrick



Icatibant

In July 2008, icatibant (Firazyr; Jerini), a bradykinin B₂ receptor antagonist, was granted market authorization by the European Commission for the symptomatic treatment of acute attacks of hereditary angioedema.

Hereditary angioedema (HAE) is a rare autosomal dominant disease that typically manifests as intermittent swelling in the skin, the upper airways, the genitourinary tract and the gastrointestinal mucosa^{1,2}. HAE attacks are often painful, and angioedema of the upper airways can be fatal^{1,2}.

HAE is caused by an absence or dysfunction of C1 esterase inhibitor (C1INH), which regulates several important biological pathways, including the complement pathway and the kinin cascade^{1,2}. Increased levels of bradykinin — a kinin peptide that has a wide range of biological effects including increasing vascular permeability — is thought to be central to the clinical symptoms of HAE^{1,3}.

In Europe, intravenous infusion of purified C1INH has been used to treat acute HAE attacks for more than two decades, and has also been used for short-term prophylaxis^{1,2}. Attenuated androgens such as danazol and antifibrinolytic agents such as tranexamic acid are also used to treat acute attacks, and for prophylaxis in some cases^{1,2}.

As well as additional C1INH products, there have also been efforts to develop other drugs that target the downstream pathways involved in HAE^{1,2}. Icatibant is the first such agent to receive regulatory approval.

Basis of discovery

The biological effects of bradykinin, which is produced by cleavage of precursor kininogens by proteolytic enzymes known as kallikreins, are mediated by two related G-protein-coupled receptors, termed the B₁ and B₂ receptors⁴. The B₂ receptor is constitutively expressed on many cell types, and is considered to be the major mediator of the effects of bradykinin involved in HAE^{4,5}.

The development of antagonists of the B₁ and B₂ receptors has been pursued for many years⁴. The first generation of B₂-selective antagonists, based on [D-Phe⁷]bradykinin, were discovered in the mid-1980s, although

their potency and metabolic stability were limited^{4,5}. Studies involving the introduction of several unnatural amino acids into bradykinin analogues with the aim of addressing these issues resulted in the discovery of Hoe 140, now known as icatibant^{4,6}.

Drug properties

Icatibant (FIG. 1), a synthetic decapeptide, is a competitive and selective B₂ receptor antagonist^{3,7}. It has been shown to inhibit the biological effects of bradykinin in a wide range of disease models^{4,6}, and was found to be effective in treating acute attacks of HAE in a small pilot clinical study⁸, which provided support for full-scale clinical trials.

Clinical data

The safety and efficacy of icatibant were assessed in two randomized, double-blind controlled Phase III studies: one with oral tranexamic acid as the comparator (study 1) and one that was placebo-controlled (study 2)⁷. The two studies were otherwise identical in design⁷. A total of 130 patients were randomized to receive either icatibant (30 mg as a subcutaneous injection; 63 patients) or comparator — either tranexamic acid (38 patients) or placebo (29 patients)⁷. Subsequent episodes of HAE were treated in an open-label extension study⁷. Patients with symptoms of laryngeal angioedema received open-label treatment with icatibant⁷. The primary efficacy end point in both studies was time to onset of symptom relief using a visual analogue scale⁷.

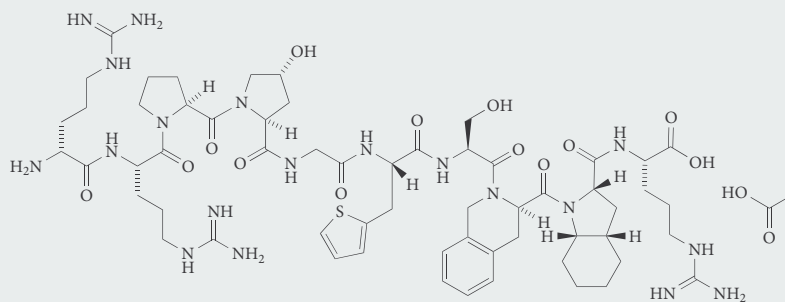
In both studies, patients receiving icatibant had a more rapid median time to onset of symptom relief (2.0 hours in study 1, and 2.5 hours in study 2) compared with tranexamic acid (12.0 hours in study 1) and placebo (4.6 hours in study 2)⁷. The treatment effect of icatibant was confirmed by secondary efficacy end points. For example, the median time to almost complete relief of symptoms for patients receiving icatibant was 10.0 hours in study 1 and 8.5 hours in study 2, compared with 51.0 hours with tranexamic acid in study 1, and 23.3 hours with placebo in study 2 (REF. 7).

A total of 118 patients were treated in the open-label extension phase for a total of 597 separate attacks⁷. The efficacy results were similar to those seen in the controlled phase of the studies⁷. The majority of attacks (89.3% and 90.9%, respectively) in both studies required only a single dose of icatibant⁷.

A total of 36 patients were treated for a total of 61 attacks of HAE affecting the larynx⁷. The results were similar to patients with non-laryngeal attacks of HAE, with a median time to start of regression of symptoms of 0.6–1.0 hours (controlled phase)⁷.

Indications

Icatibant is approved by the European Commission for the symptomatic treatment of acute attacks of HAE in adults (with C1INH deficiency)⁷.



Icatibant acetate

D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg acetate;
M_r = 1364.6; C₅₉H₈₉N₁₉O₃S • C₂H₄O₂

Figure 1 | **Icatibant**. Icatibant (originally known as Hoe 140) is a synthetic decapeptide with a structure similar to bradykinin, but with five non-proteinogenic amino acids^{5,7}.

ANALYSIS | HEREDITARY ANGIOEDEMA

- Analysing issues in the treatment of hereditary angioedema is Konrad Bork, M.D., Ph.D, Professor of Dermatology in the Department of Dermatology, Johannes Gutenberg University, Mainz, Germany.

Hereditary angioedema (HAE) that is due to C1 esterase inhibitor (C1INH) deficiency — the most common form of the disorder — is clinically characterized by unpredictable relapsing episodes of oedema at various body sites, followed by disease-free intervals of variable duration⁹. Despite an increase in the awareness of HAE, it continues to represent an unmet clinical need, with cases of laryngeal oedema sometimes leading to mortality.

The aims of HAE treatment are either treating acute attacks or avoiding attacks by a prophylactic treatment. As maximal symptoms for acute HAE attacks usually occur within 24 hours of onset, treatment for acute attacks should start within the first hours of the attacks. In treating abdominal attacks with purified C1INH, it has been shown that delayed treatment is less effective and needs a greater amount of drug¹⁰. So, not only efficacy and safety but also prompt availability of the medication is an important need for treatment of HAE.

Given this, self-injection or home treatment could considerably improve the situation for some patients with HAE. Benefits include improved quality of life, reduced attack frequency, and greater patient

independence and convenience. With regard to treating acute attacks with purified C1INH, home-treatment programmes are currently being established. Some countries are introducing training programmes to include practical aspects of C1INH administration. However, concerns and practical problems have to be considered, including the management of side effects, the medical and legal responsibility, and problems associated with incorrect intravenous injections and vein obstruction.

Icatibant has recently been approved in Europe for the treatment of acute attacks of HAE due to C1INH deficiency. It represents a new approach for the treatment of HAE — antagonizing the bradykinin B₂ receptor — and is the first drug for acute attacks of HAE that can be injected subcutaneously. Principally, this is a considerable advantage over drugs given intravenously. At present, however, icatibant is not available for self-injection by patients, but hopefully this can be achieved within the next few years.

In addition to another C1INH product purified from human plasma (produced by Lev Pharmaceuticals), two other drugs are presently in late-stage development: ecallantide (Dyax) and a recombinant human C1INH (rhC1INH; Pharming) produced in transgenic rabbits. Ecallantide (also known as DX-88), a 60-amino-acid protein identified by phage display technology, is a potent and selective kallikrein inhibitor that

is produced as a recombinant protein in the yeast *Pichia pastoris*. This agent, which can be administered by subcutaneous injection, has been proven effective in the treatment of acute attacks of HAE in clinical studies¹¹. Intravenous delivery of rhC1INH has also been shown to be effective and safe in acute attacks of HAE¹².

Icatibant, ecallantide and rhC1INH all have a relatively short half-life, ranging from 2–4 hours, so their use in prophylactic long-term treatment of HAE seems to be questionable at present. Nevertheless, it is hoped that all these new drugs, which have shown encouraging clinical results, will contribute to diminishing the burden of HAE.

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Competing financial interests

K.B. declares competing financial interests: see web version for details.

Box 1 | Market for hereditary angioedema

Analysing the market for drugs for hereditary angioedema is Uma Yasothan, IMS Health, London, UK.

It is estimated that ~1 in 50,000 people are affected by hereditary angioedema (HAE), a rare genetic disease for which treatment of acute attacks and prophylaxis, long and short term, is needed². There are no approved treatments yet in the United States for this orphan disorder, although in Europe, plasma-derived C1 esterase inhibitor (C1INH) infusions have been used for many years. In 2007, worldwide sales of purified C1INH were US\$1.5 million¹³, with the class showing a 3.5% growth over the previous year.

Icatibant (Firazyr; Jerini), a subcutaneous bradykinin B₂ receptor antagonist, received European approval in July 2008 for the treatment of acute attacks of HAE (with C1INH deficiency) and is anticipated to be available in the market in the third quarter of 2008. Icatibant received a non-approvable letter from the US FDA for this indication in April 2008, and the regulatory situation surrounding potential US approval is not clear at present. Bearing in mind that the drug would launch into the acute HAE market, with a potential for self-administration, analyst estimates for peak sales of icatibant range from \$213 million by 2014 globally¹⁴ to \$100 million¹⁵ for Europe alone.

In August 2008, UK-based Shire acquired Jerini, which could provide the marketing boost needed for an orphan drug such as icatibant. Icatibant is also in clinical trials for drug-induced angioedema, capillary leak syndromes and other inflammatory disorders, which if all approved could significantly expand its market potential. However, possible competitors for icatibant are also in late-stage development, including Pharming's recombinant C1INH, and a kallikrein inhibitor, ecallantide (Dyax), which is also administered subcutaneously.