

Brand Name: Firazyr

Generic Name: icatibant

Manufacturer¹: Shire Orphan Therapies, Inc.

Drug Class^{1,2,3}: selective bradykinin B2 receptor antagonist, cardiovascular agent

Uses:

Labeled^{1,2,3,4}: Treatment of acute attacks of hereditary angioedema in adults 18 years of age and older.

Mechanism of Action^{1,2,3,4}:

Icatibant is a selective, competitive inhibitor of the bradykinin B2 receptor.

Pharmacokinetics:

Absorption:

T _{max}	0.75 hours
V _d	29 L
t _{1/2}	1.4 hours
Clearance	245 ml/min
Protein binding	Not reported
Bioavailability	97%

Metabolism: Icatibant is extensively metabolized by proteolytic enzymes to inactive metabolites. Icatibant is not degraded by oxidative metabolic pathways. Icatibant is not an inhibitor or an inducer of major cytochrome P450 isoenzymes

Elimination: Icatibant is excreted in the urine with less than 10% of the dose is eliminated unchanged.

Efficacy:

Cicardi M, Banerji A, Bracho F, Malbran A, Fan W, et al. Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema. *New England Journal Of Medicine (USA)*. n.d.;363(Jun):532. Available from: International Pharmaceutical Abstracts, Ipswich, MA.

Study design: Multi-center, double-blind, placebo-controlled, randomized, prospective study

Description of study: Methods: After being accepted into the study, subjects were instructed to go to the study site within 6 hours after an acute attack of angioedema became at least moderately severe, to be reassessed and randomized. Fifty-six patients who were screened and enrolled were randomly assigned to receive either subcutaneous icatibant injection, at a dose of 30mg, or a placebo injection. Blinding was maintained by identical appearance of the active drug and placebo. After receiving medication, patients were then hospitalized for up to 15 hours. During hospitalization, symptoms were assessed at scheduled times. After discharge,

patients assessed their own symptoms until symptoms had subsided and follow-up visits were scheduled. Blood samples were obtained before study-drug administration and after administration on Days 1, 2, and 14, Week 5, and Week 24. Concomitant medication for other conditions was permitted as long as there was no interference with the objectives of the study. Rescue therapy for relief of any symptoms was permitted but withheld, ideally for 8 or 9 hours after study-drug administration. Data for patients who required rescue therapy were not excluded from analyses. The primary efficacy end point was the median time to clinically significant relief of an index symptom identified during screening. Clinically significant symptom relief was defined as a minimum decrease in the score on the visual-analogue scale. The index symptom was defined for each patient as one of the 3 main symptoms, cutaneous swelling, cutaneous pain, or abdominal pain. Secondary efficacy end points included the median times to first symptom improvement, the median time to almost complete relief of symptoms, and the proportion of patients reaching the median time to clinically significant relief of the index symptom within 4 hours after the start of the study drug. Safety was evaluated by means of adverse event reporting, documentation of local tolerability, measurement of vital signs, electrocardiography, clinical laboratory testing, urinalysis, and assessment of complement activation. Testing for anti-icatibant antibodies was performed using enzyme-linked immunosorbent assays. The primary analysis was based on the intent-to-treat population. *Outcome results:* The median time to clinically significant relief of the index symptom was 2.5 hours in the icatibant group compared to 4.6 hours in the placebo group ($p=0.14$). In a post hoc analysis which excluded data from patients who received rescue medication, icatibant showed a significant benefit over placebo. On the basis of a composite symptom score, the median time to symptom relief was 2.5 hours with icatibant compared to 7.0 hours with placebo ($p=0.02$). Secondary endpoints were also analyzed. The median time to almost complete relief of symptoms was 8.5 hours with icatibant compared to 19.4 hours with placebo ($p=0.08$). The percentage of patients with clinically significant relief of the index symptom at 4 hours after the start of study treatment was 67% in the icatibant group compared to 46% in the placebo group ($p=0.18$). The median time to first symptom improvement was significantly shorter with the icatibant compared to placebo when assessed by the patient (0.8 vs. 16.9 hours; $p<0.001$) and the investigator (1.0 vs. 5.7 hours; $p<0.001$). In this study, 8 patients had laryngeal symptoms and received open-label icatibant. Four hours after the administration of icatibant, 7 of the 8 patients had no symptoms and the remaining patient had mild symptoms. Injection site reactions were reported by 96% of subjects. Other drug-related adverse events that were reported by 15% of study subjects, including dizziness, nasal congestion, and abnormal liver function tests.

Limitations: The FAST-1 trial was partially supported by and many of the authors were associated with Jerini, the manufacturer of Firazyr. These associations could potentially be a source of bias. Another limitation is that the index symptom that was identified during screening was not identical for all subjects. A limitation of the analysis of this study exists because data from patients who required rescue medication were included. The inclusion of the subjects who received icatibant as rescue treatment who were in the placebo group could have contributed to the statistically non-significant difference between the groups receiving icatibant and placebo.

Conclusions: The rate of the primary endpoint in this study, median time to clinically significant relief of an index symptom identified during screening, was not found to be statistically significant. Post hoc analysis that was not based on the intent-to-treat population showed a

significant benefit of icatibant compared to placebo. Although this study provided evidence that icatibant is more effective compared to placebo, further studies are needed to determine its benefit compared to current standard therapy.

Cicardi M, Banerji A, Bracho F, Malbran A, Fan W, et al. Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema. *New England Journal Of Medicine (USA)*. n.d.;363(Jun):532. Available from: International Pharmaceutical Abstracts, Ipswich, MA.

Study design: Multi-center, double-blind, active-control, randomized, prospective study

Description of study: *Methods:* This study was done by the same authors with a very similar study design. The only difference was that this study had an active-control experimental design, comparing icatibant to tranexamic acid. Seventy-four patients were randomly assigned to receive either icatibant (n=36) or tranexamic acid (n=38). *Outcome results:* The median time to clinically significant relief of the index symptom was 2.0 hours with icatibant compared to 12.0 hours with tranexamic acid ($p<0.001$). In a post hoc analysis of the primary endpoint which excluded data from patients who received rescue medication, icatibant showed a significant benefit over placebo. On the basis of a composite symptom score, the median time to symptom relief was 2.0 hours with icatibant compared to 15.0 hours with tranexamic acid ($p<0.001$). Secondary endpoints were also analyzed. The median time to almost complete relief of symptoms was 10.0 hours with icatibant compared to 51.0 hours with tranexamic acid ($p<0.001$). The percentage of patients with clinically significant relief of the index symptom at 4 hours after the start of study treatment was 80% in the icatibant group compared to 31% in the tranexamic acid group ($p<0.001$). The median time to first symptom improvement was significantly shorter with icatibant than with tranexamic acid when assessed by the patient (0.8 vs. 7.9 hours; $p<0.001$) and when assessed by the investigator (1.5 vs. 6.9 hours; $p<0.001$). In this study, 3 patients had laryngeal symptoms and received open-label icatibant. Four hours after the administration of icatibant, 2 of the 3 patients had no symptoms and the remaining patient had mild symptoms. Adverse events that were reported by study subjects include injection-site reactions, abdominal pain, nausea, worsening of attack, asthenia, and rash; however, none were considered to be related to the study drug.

Limitations: The major limitation of this trial is that the active-control is not a medication that is used first-line to treat acute attacks of HAE. The active-control used was tranexamic acid, while current first-line therapies include purified human C1 inhibitor or ecallantide⁹. The FAST-2 trial was designed and sponsored by Jerini, the manufacturer of Firazyr. Additionally, many of the authors were associated with Jerini. These associations could potentially be a source of bias. Another limitation is that the index symptom that was identified during screening was not identical for all subjects.

Conclusions: In this study, the median time to clinically significant relief of the index symptom was significantly shorter for patients given icatibant compared to those given tranexamic acid. Given that no drug-related adverse effects were suspected, icatibant is a safe medication that has shown to be more effective than tranexamic acid.

Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *Journal of Allergy*

and Clinical Immunology (USA). n.d.;119(Jun 2007):1497-1503. Available from: PubMed, Bethesda, MD. PMID: 17418383.

Study design: uncontrolled pilot study

Description of study: *Methods:* Five sequential groups, consisting of four subjects each, received icatibant as a single intravenous infusion or a single subcutaneous injection. Group 1 received 0.4 mg/kg body weight administered by an intravenous infusion over a period of 2 hours. Group 2 received the same dose of icatibant administered by an intravenous infusion over a period of 0.5 hours. Group 3 received 0.8 mg/kg body weight administered by an intravenous infusion over a period of 0.5 hours. Groups 4 and 5 received 30mg and 45mg of icatibant, respectively, administered subcutaneously in the lower abdominal region. Patients were analyzed with respect to the period from initiation of treatment to onset of symptom relief as reported by the patient and as documented by using a standardized and clinically validated visual analog scale. Furthermore, the time to onset of relief of the treated attacks was compared with untreated edema attacks that had occurred previously in the same patient. This was possible due to the regular monitoring of the patients' symptoms and courses of individual attacks. Adverse events were recorded from admission until 120 hours after the end of icatibant infusion or injection. Additionally, patients were provided with diaries upon discharge to record any symptoms of angioedema or drug-related adverse events until the next visit to the study center. For efficacy analysis, a Wilcoxon for paired data was used for the combining the visual analog scales data from all treatment groups. *Outcome results:* Intravenous icatibant was administered in a total of 12 attacks, and resulted in a median time to onset of symptom relief of 1.50 hours in Group 1, 1.42 hours in Group 2, and 1.13 hours in Group 3. Subcutaneous icatibant was administered in a total of 8 attacks, and resulted in a median time to onset of symptom relief of 0.58 hours in Group 4 and 0.45 hours in Group 5. In all groups, icatibant administration resulted in a mean (SD) time to onset of symptom relief of 1.16 hours (0.95 hours). Improvement of symptoms from baseline to 4 hours after icatibant administration was similar between the subcutaneous and intravenous groups. The median differences in the visual analog scale values are as follows: 5.31cm in Group 1, 1.92cm in Group 2, 5.61cm in Group 3, 3.15cm in Group 4, and 4.31cm in Group 5. The median difference (lower, upper 95%CI) in the visual analog scales after 4 hours was 4.11cm (1.72, 6.07) in all 15 patients ($p < 0.01$). Treatment led to a 97% reduction concerning the time to relief of symptoms when compared to historical data of untreated attacks. Local injection site reactions were noted in all patients in the subcutaneous groups, and resolved spontaneously and did not require medical attention. Headache was the only other adverse event reported during the study. In all attacks, plasma bradykinin levels had a median 7-fold increase in all attacks. At 4 hours after administration of intravenous icatibant, a decrease from 48.5 to 18.0 pmol/L was noted. At 4 hours after administration of subcutaneous icatibant, a decrease from 75.0 to 30.5 pmol/L was noted, but not significant.

Limitations: A major limitation of this study is that it was not the gold standard study design. Other limitations dealing with study design are the small number of patients and the several different treatment groups in the study. Another limitation is that many symptoms were logged in a diary by the patient. This could have been done inconsistently among the individual patients in the study, and the authors failed to report the findings of the diaries.

Conclusions: In this study, a beneficial effect of icatibant in patients with hereditary angioedema. Icatibant improved skin swelling and abdominal pain attacks. Larger, randomized, placebo-controlled trials are needed to further study the treatment of hereditary angioedema with icatibant.

Contraindications^{1,2}: There are no contraindications listed in the manufacturer's labeling.

Precautions^{1,2,3,4,5}:

Laryngeal Attacks: Laryngeal attacks of hereditary angioedema may lead to airway obstruction. Patients with laryngeal attacks should seek medical attention immediately in addition to icatibant injections.

Adverse effects^{1,2,3,4,5}:

Occurring in >10% of patients:

Dermatologic:

Injection site reactions; such as bruising, hematoma, burning, erythema, hypoesthesia, irritation, numbness, edema, pain, pressure sensation, pruritis, swelling, urticaria, and warmth (97%)

Occurring in >1 to < 10% of patients:

Central Nervous System:

Pyrexia (4%)

Dizziness (3%)

Hepatic:

Transaminase increased (4%)

Dermatologic:

Rash (>1%)

Other:

Fever (4%)

Drug Interactions^{1,2,3,4,5}:

ACE Inhibitors: Icatibant has the theoretical potential to interact with ACE inhibitors. Icatibant may attenuate the antihypertensive effects of ACE inhibitors due to the antagonism due to its antagonism of the bradykinin B2 receptor.

Cytochrome P450 inducers, inhibitors, and substrates: Metabolic drug interactions between icatibant and CYP-450 inducers, inhibitors, and substrates are not expected. Icatibant is not metabolized by the CYP-450 isoenzymes. In vitro studies have shown no significant inhibition or induction of CYP-450 isoenzymes.

Dosing/Administration^{1,2,3,4,5}:

Adult Dosing:

The recommended dose of icatibant is 30mg administered by subcutaneous injection in the abdominal area. Additional doses of 30mg may be administered at intervals of 6

hours if the response of the previous dose is inadequate or if symptoms recur. No more than 3 doses may be administered in a 24 hour period.

Pediatric Dosing:

The safety and efficacy icatibant have not been established in infants and children younger than 18 years of age.

Elderly:

Refer to adult dosing. No dosage adjustments are recommended. No identified differences in efficacy and safety between elderly and younger patients have appeared in clinical experience.

Hepatic Impairment:

No dosage adjustments are necessary.

Renal Impairment:

No dosage adjustments are necessary.

Use in special circumstances:

Pregnancy: Pregnancy Category C. There are currently no adequate and well-controlled studies of the use of icatibant in pregnant women. Animal studies have been done on the use of icatibant showing no teratogenic effects, but some other harmful effects, such as delayed parturition, fetal death, and pre-implantation loss. Icatibant should only be used in pregnant women if the potential therapeutic benefit outweighs the potential risk to the fetus.

Labor and Delivery: There are currently no human studies on the effects of icatibant on preterm labor or labor at term.

Lactation: Caution should be exercised when icatibant is administered to nursing women. It is unknown if icatibant is excreted in human breast milk; however, icatibant has been shown to be excreted in the milk of lactating rats.

Conclusion:

Icatibant is a tolerable and effective treatment for acute attacks of hereditary angioedema. Multiple clinical trials have demonstrated the efficacy and safety of icatibant when used to treat this condition. The FAST-2 trial provided evidence that icatibant is more effective than tranexamic acid, which is a possible treatment for acute exacerbations of HAE. However, as tranexamic acid is not a first-line therapy for this condition, further studies comparing icatibant with first line treatment for HAE attacks are needed to determine icatibant's true place in therapy. Minimal side effects and adverse events have been reported with the use of icatibant. A disadvantage of this medication is that it is very expensive, costing around \$6800 per injection⁸. Due to the tolerability, lack of contraindications, minimal drug interactions, and clinical benefit provided by icatibant, it appears to be a useful medication in the treatment of acute attacks of hereditary angioedema.

References:

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