CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Icatibant for Patients with Type III Hereditary Angioedema: An Updated Review of Clinical Effectiveness and Harms

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Icatibant for Patients with Type III Hereditary Angioedema

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Context and Policy Issues
Hereditary angioedema (HAE) is a rare familial disorder with autosomal dominant inheritance, affecting approximately 1 in 50,000 people in the United States. The world-wide prevalence of the disease is estimated to vary between 1 in 10,000 and 1:150,000. HAE presents itself typically as recurrent edema attacks in different body parts including extremities, face, gastrointestinal tract, and upper respiratory tract. The frequency and severity of attacks can vary among patients. Gastrointestinal (GI) attacks are common in HAE and may manifest with severe abdominal pain and other GI symptoms that mimic a surgical emergency. Untreated laryngeal attacks may result in asphyxiation and death. Swelling in other body parts may also cause significant morbidities that can interfere with patients’ daily activities, resulting in an impaired quality of life.

HAE attacks are attributed to an over-production of a vasoactive mediator, bradykinin, which can lead to a rapid increase in vascular permeability, and cause acute edema in subcutaneous and sub-mucosal tissues. Some attacks may be triggered by trauma, psychological stress situations, the use of medications, especially inhibitors of angiotensin-converting enzyme (ACE) and estrogens, and infectious diseases.

HAE has been classified into three types, mainly based on the level and activity of C-1 esterase inhibitor (C1-INH). C1-INH is a protein with a significant role in the regulation of the complement and proteolytic pathways. Deficiency or dysfunction of C1-INH can result in the activation of the kallikrein-kinin and complement systems and lead to excessive release of bradykinin. Type I HAE is the most common type of HAE, accounting for approximately 85% of HAE cases, and is defined by low levels or absence of C1-INH. In type II HAE, the C1-INH levels are normal, but the function of C1-INH is impaired. Type II HAE accounts for approximately 15% of HAE cases. HAE with normal C1-INH (previously known as Type III) is not associated with C1-INH quantitative or qualitative deficiency, but shares similar signs and symptoms with Type I and Type II HAE attacks. The estimated proportion of HAE patients who are affected by Type III HAE has not been reported in the literature, possibly due to the rarity of this condition. Unlike HAE types I and II which are equally common in men and women, Type III HAE is more common in women. Two subtypes of Type III HAE have been described: HAE with factor XII mutation (FXII-HAE), and HAE with normal C1-INH of unknown genetic origin (U-HAE). The clinical signs and symptoms and the suggested management strategies are similar in these two subtypes.

Three main therapeutic management strategies are indicated for HAE patients: treatment of acute attacks (on-demand therapy), short-term prophylaxis to prevent angioedema attacks, and long-term prophylaxis to decrease the number and severity of angioedema attacks. The available therapeutic options for the treatment of Type I and Type II HAE include: concentrated C1-INH, ecallantide, icatibant, tranexamic acid, and fresh frozen plasma. Presently, there is a lack of approved treatment options for Type III HAE. However, limited clinical evidence, based uncontrolled studies and case reports, suggests that the drugs recommended for HAE with C1-INH deficiency (including icatibant) may be effective in Type III HAE as well. Therefore, general treatment strategies for this type of HAE are similar to those in Type I and Type II HAE.

Icatibant is an antagonist of the bradykinin B2 receptor and has been shown to be effective in the treatment of acute attacks in HAE patients. Clinical studies have shown that treatment with icatibant can result in a statistically significant reduction in
the time to symptom relief in Type I and Type II HAE patients, when compared to those treated with placebo (2.0 hours versus 19.8 hours)\textsuperscript{11} or tranexamic acid (2.0 hours versus 12.0 hours).\textsuperscript{12} It has been licensed in Canada, Europe and the USA, for the treatment of acute attacks in adult patients with Type I and Type II HAE.\textsuperscript{1,13,14} The purpose of this report is to review the clinical effectiveness and safety of icatibant when it is used in patients with Type III HAE. This report is an update of a previous CADTH Rapid Response report (2014),\textsuperscript{15} which found inconclusive evidence from two observational studies to support the use of icatibant in Type III HAE patients.

**Research Question**

1. What is the evidence for the clinical effectiveness and harms of icatibant in the treatment of patients with type III hereditary angioedema?

2. What is the evidence for the prophylactic effectiveness and harms of icatibant for patients with type III hereditary angioedema?

**Key Findings**

One single-arm cohort study, three case series, and three case reports were identified regarding the clinical effectiveness and safety of icatibant for the treatment of acute attacks in patients with Type III HAE. The studies were descriptive in nature and small in size. The limited evidence from this review suggests that icatibant may be considered as a potentially safe and effective treatment option in patients with acute attacks of type III HAE. However, the findings of this review should be interpreted with caution, as they are derived from low-quality evidence. No relevant evidence was found regarding the prophylactic use of icatibant in Type III HAE.

**Methods**

**Literature Search Methods**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 7, 2017.

**Selection Criteria and Methods**

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td><strong>Population</strong></td>
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<td><strong>Intervention</strong></td>
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<td><strong>Comparator</strong></td>
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<td><strong>Outcomes</strong></td>
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<td><strong>Study Designs</strong></td>
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Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014.

Critical Appraisal of Individual Studies
The included non-randomized observational studies were critically appraised using the Scottish Intercollegiate Guidelines Network (SIGN 50) checklist for cohort studies. The methodological quality of the included case series studies was assessed using a checklist developed by Moga et al. This tool consists of 18 items relating to different methodological components of a study (i.e., study objectives, population, interventions, follow-up, outcomes, statistical analysis, results, and competing interests). Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively. No critical appraisal was performed for the included case reports, given the fact that they represent a low level of evidence.

Summary of Evidence
Quantity of Research Available
A total of 63 citations were identified in the literature search. Following the screening of titles and abstracts, 47 citations were excluded, and 16 potentially-relevant reports from the electronic search were retrieved for full-text review. Seven potentially-relevant publications were retrieved from the grey literature search. Of the 23 potentially-relevant articles, 13 publications were excluded for various reasons. Of the 10 publications which met the inclusion criteria, three articles were further excluded during the data extraction process because they did not provide sufficient data on the outcomes of interest, leaving a total of seven publications for inclusion in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics
The body of evidence included seven observational studies addressing the effectiveness and safety of icatibant in the treatment of Type III HAE patients. No systematic reviews or randomized controlled trials were identified. Two of the studies were published as conference abstracts. General characteristics of the included studies are summarized below. More details are available in Appendix 2, Table A2.

Study Design
One of the included studies had a single arm cohort design, while three were case series studies, and three were case reports.

Country of Origin
Two of the included studies originated from Italy, and one study each from Spain, France, Germany, Brazil, and the United States.

Patient Population, Interventions and Comparators
In the prospective cohort study by Pinero-Saavedra et al., the study participants were identified through screening of close relatives of nine index female cases diagnosed with FXII mutations. Thirty-five individuals with a positive test for FXII were enrolled in the study. Clinical and treatment-related data were collected prospectively from the identified symptomatic FXII-HAE cases and asymptomatic FXII mutation carriers for a minimum follow-up period of 12 months. During the study period, a total of nine patients developed acute attacks requiring therapeutic interventions; of
which, five patients received C1-INH concentrate, and two patients were treated with first line icatibant therapy. One of the patients who failed to respond to C1-INH concentrate was also treated with icatibant. No comparison groups had been defined a priori and no comparative analyses were conducted. A descriptive analysis of the therapeutic options used for the treatment of symptomatic patients during the study period was presented.

Bouillet et al.\(^{21}\) retrospectively analyzed data from a total of 182 French HAE cases (153 with Type I, 7 with Type II, and 22 with Type III HAE) who were registered in the Icatibant Outcome Survey (IOS) database. IOS was an international prospective observational study that enrolled symptomatic HAE patients and collected data on their demographic variables, angioedema attacks (frequency, site, and severity of attacks) and outcome variables at the baseline and every 6 months thereafter. Full intervention and outcome data were available for five Type III HAE patients.

The case series by Mansi et al.\(^{22}\) reported the results of a retrospective analysis of the data from 377 (including 24 Type III) HAE cases who had been treated in one referral hospital during a 20 year time period. Of the 24 Type III HAE cases, two patients (one with FXII-HAE and one with U-HAE) received on-demand icatibant therapy, five were treated with tranexamic acid, one with C1-INH concentrate, and one with fresh-frozen plasma. No comparison groups had been defined a priori and no comparative analyses were conducted.

Firinu et al.\(^{23}\) described the clinical, genetic and laboratory features of two separate series of FXII-HAE and idiopathic non-histaminergic acquired angioedema cases. The FXII-HAE cases were identified through screening the relatives of nine apparently unrelated index cases with FXII mutations.

Icatibant was not a primary exposure variable of interest in three of the four aforementioned studies.\(^{20,22,23}\) However, the case series by Bouillet et al.\(^{21}\) exclusively included HAE patients who had been treated with icatibant, with an specific objective of evaluating icatibant-related treatment outcomes. Icatibant was administered for the treatment of acute attacks in all of the included studies. Each of the three included case reports\(^{24-26}\) described the characteristics of an individual Type III HAE case, along with their outcomes following icatibant therapy.

**Outcomes**

The included studies reported on the impact of icatibant on clinical outcomes measured as: time to administration,\(^{21,24}\) time to onset of symptom relief,\(^{20,24,26}\) time to objective symptom relief,\(^{20}\) time to resolution,\(^{20-25}\) and duration of treated attacks.\(^{21,24}\) As a part of their study method, Bouillet et al.\(^{21}\) defined time to administration as a measure for the ‘duration from symptom onset to first subcutaneous icatibant injection’, time to resolution as a measure for the ‘duration from icatibant injection to complete symptom resolution’, and attack duration as a measure for the ‘time from symptom onset to complete symptom resolution’. The study outcomes were not clearly defined in the other included studies.

Safety outcomes were reported in one case series study\(^{21}\) and two case reports.\(^{23,24}\)

**Summary of Critical Appraisal**

Detailed summaries of the critical appraisal of included cohort and case series studies are provided in Appendix 3, Table A2 and A3, respectively.
Overall, the methodological quality of the included cohort study\textsuperscript{20} was poor. The objectives, data collection methods, and study outcomes were explicit and participants were recruited during the same period of time. However, it seemed to suffer from a lack of predefined treatment groups, small numbers of patients who received the study treatments, unmasked assessment of treatment results, negligence of confounding factors (such as natural resolution of self-limiting attacks, self-administration versus health care practitioner administration, or effect of time to administration on the duration of the attack), and lack of a statistical analysis. Such flaws might be explained by the fact that the primary goal of the study was to describe phenotypic features of FXII-HAE and the related enzyme polymorphism, rather than evaluating the effects of icatibant and other study treatments in FXII-HAE patients.

All of the included case series studies\textsuperscript{21-23} provided a clear description of population from which the study participants were enrolled, along with the eligibility criteria for inclusion in the studies. One case-series\textsuperscript{21} selected the participants based on their icatibant treatment status (the intervention of interest in this review), while in the other two\textsuperscript{22,23} icatibant was administered to a subset of the participants on an on-demand basis. This can be a source of selection bias, considering that the choice of treatment option could have been influenced by the severity, site, or prognosis of the HAE attacks. The follow-up durations were not reported in two of the case series\textsuperscript{22,23} and, in one study\textsuperscript{21}, the length of follow up was variable depending on the physician’s and patient’s preferences. Estimates of random variability (e.g., confidence intervals) were not provided in two studies.\textsuperscript{22,23} One study provided a clear definition of the outcome measures in the text.\textsuperscript{21} None of the studies reported sufficient information on the cases lost-to-follow up, and two of them excluded patients with incomplete follow ups or missing outcome data from their analyses.\textsuperscript{21,22}

Summary of Findings
The overall findings of the review are summarized below. Additional details are available in Appendix 4, Tables A4-A6.

What is the evidence for the clinical effectiveness and harms of icatibant in the treatment of patients with type III hereditary angioedema?

Non-randomized Studies
In the cohort study by Pinero-Saavedra,\textsuperscript{20} single doses of icatibant were used to treat a total of nine acute attacks in two FXII-HAE patients. C1-INH concentrate and tranexamic acid were administered in five (11 attacks) and two (2 attacks) patients, respectively. The time to the first improvement was comparable between the patients receiving icatibant and C1-INH concentrate. In all three groups, objective symptom relief was observed in less than 2 hours. Although not statistically tested, the time to complete resolution of symptoms appeared to be shorter in the C1-INH concentrate group (3-24 hours), than the icatibant (24 hours) and tranexamic acid (24-48) groups. In this study, two participants received more than one drug for the treatment of a single attack. One patient who failed to respond to C1-INH concentrate responded well to icatibant; and one patient whose symptoms did not improve after an icatibant injection, was treated successfully with fresh frozen plasma. Administration of icatibant in this latter case was considered, by the authors, to be late (>6 hours after the onset of the symptoms). The authors believed that icatibant and C1-INH concentrate could play a role in resolution of acute attacks in patients with FXII-HAE.

Case Series Studies
In the study by Bouillet el al.,\textsuperscript{21} icatibant treatment outcomes were assessed in 22 Type III HAE patients (the largest sample of icatibant-users among the included
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Garro et al. reported that the patient's response to on-demand icatibant therapy was satisfactory, without providing any objective outcome measures.

In the study by Mansi et al., icatibant was administered to one case of U-HAE with an abdominal attack, and the symptoms were resolved with four hours after treatment. One patient with FXII-HAE received subcutaneous icatibant (30 mg) injections for two attacks of facial angioedema. The symptoms were resolved within 72 hours and the treatment was deemed ineffective in this case. No definitive conclusions about the clinical effectiveness of icatibant were made by the authors of this study.

In the study by Firinu et al., three moderate to severe attacks (2 abdominal and 1 facial angioedema) were treated with icatibant (30 mg subcutaneous injections) in three different FXII-HAE cases. The abdominal attacks were completely resolved in 2.5 and 11 hours, and the facial attack was resolved in 12 hours. The authors attempted to demonstrate the effectiveness of icatibant by comparing the aforementioned outcome measures with those related to similar untreated attacks that the same patients had had in the past (time to resolution of untreated symptoms > 48 hours).

Case Reports

Bork et al. reported a case of a 31-year-old woman with U-HAE who received icatibant (30 mg subcutaneous injections) for the treatment of a total of 29 (22 abdominal and 7 facial) acute HAE attacks. The mean time from the onset of each attack to administration of icatibant was 1.9 ± 2.7 hours. The first symptom relief was 0.5 ± 0.1 hour. Total duration of treated abdominal attacks (8.0 ± 6.5 hours) seemed to be slightly longer than that for facial attacks (5.6 ± 6.6 hours). The untreated abdominal and facial attacks in this patient lasted an average of 42.6 ± 9.9 and 74.1 ± 20.7 hours, respectively. The authors concluded that icatibant was an effective treatment in this case.

The case report by Cuhlen et al. presented results of icatibant therapy in a 26-year-old woman with Type III HAE and a history of recurrent episodes of tongue swelling that lasted for at least 24 hours. The patient had been referred to the study centre from an outpatient setting following unsuccessful treatment with ecallantide. She was treated with multiple doses of icatibant during hospitalization, and with five on-demand doses over the following 9-month period. Two concomitant doses of C1-INH concentrate were also administered during the early hospital days. The authors reported that the patient's response to on-demand icatibant therapy was satisfactory, without providing any objective outcome measures.

Garro et al. reported a case of 33-year-old female Type III HAE patient with a history of recurrent oro-facial attacks, who was admitted to the emergency room with symptoms
of severe airway closure. She was treated with a single dose of subcutaneous icatibant (30mg), and the symptoms improved in less than one hour. This case report, published as a conference abstract, did not provide any objective outcome measures.

*What is the evidence for the prophylactic effectiveness and harms of icatibant for patients with type III hereditary angioedema?*

No studies addressing prophylactic use of icatibant in patients with Type III HAE were identified.

**Limitations**

This review included descriptive observational studies, case series and case reports, which generally provide low quality evidence. The studies used no control groups to compare the effect of icatibant therapy with other viable alternatives or no treatment, and no statistical analyses were performed. In addition, they rarely reported the outcomes of untreated HAE attacks in the study patients to account for the confounding effect of time. The included studies were generally of small sample size. The number of patients who were included in the analysis in each of the included cohort and case series studies was small enough (≤5 patients) that these studies could have been considered as case reports, for the purpose of this review. The majority of the included studies used retrospective data collection methods and excluded patients with missing data from their descriptive analysis. This can be considered a potential threat to the generalizability of the findings of these studies. None of the studies were conducted in Canada. Therefore, it is not clear to what extent the results will be applicable to a Canadian setting.

**Conclusions and Implications for Decision or Policy Making**

While substantial progress has been made in the understanding of the pathophysiology of Type III HAE and the related treatment options, challenges exist in the therapeutic management of patients with this condition, mainly due to paucity of evidence on the comparative effectiveness and safety of available treatment options. As a result, the current practice of treating patients with Type III HAE remains largely based on the results of observational studies and expert opinion. The current review, which was conducted with the objective of updating a previous CADTH rapid response review, summarizes the results of seven uncontrolled observational studies and case reports. Despite the variation in study type, clinical settings, and characteristics of study populations across the included studies, consistent patterns were found in the reported results. The limited evidence from the included observational studies suggests that icatibant may be considered as a potentially safe and effective treatment option in patients with acute attacks of type III HAE. However, the findings of this review should be interpreted with caution, as they derived from low-quality evidence lacking appropriate controls. No relevant evidence was found regarding the prophylactic use of icatibant in Type III HAE. Although this review did not demonstrate definitive results regarding the efficacy and safety of icatibant for Type III HAE, it strengthens the evidence base reported in the previous Rapid Response report, by identifying and describing additional relevant studies. Nonetheless, further well-controlled observational studies and randomized controlled trials, preferably in a Canadian setting, are needed to confirm the clinical effectiveness and safety of icatibant in patients with Type III HAE.
References


Appendix 1: Selection of Included Studies

63 citations identified from electronic literature search and screened

47 citations excluded

16 potentially relevant articles retrieved for scrutiny (full text, if available)

16 potentially relevant reports retrieved from other sources (grey literature, hand search)

7 potentially relevant reports included in review
Uncontrolled observational studies (4)
Case reports (3)
### Appendix 2: Characteristics of Included Publications

#### Table A1: Characteristics of Included Publications

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Study Design (sample size†)</th>
<th>Study Populations</th>
<th>Icatibant ‡‡</th>
<th>Comparator</th>
<th>Reported Outcomes</th>
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</thead>
</table>
| Pinero-Saavedra 2016<sup>20</sup> Spain | Prospective cohort (n=35) | – Carriers and symptomatic patients from 9 unrelated families carrying FXII gene mutations  
– Recruited between January 2009 and April 2015 and followed up until April 2016 (minimum follow-up= 12 months) | Female 80%  
Age, mean (range), y @ disease onset  
– females: 19.9 (14.0-28.0)  
– males: 61.5 (55.0-68.8)  
Common sites of attack: abdomen 62%; facial area 25% | – Single injection per attack  
– (Dose not reported) | C1-INH concentrate Tranexamic acid  
– Time to onset of improvement  
– Time to objective symptom relief  
– Time to complete resolution |
| Bouillet 2017<sup>21</sup> France | Case series (n=22) | – Symptomatic HAE  
– Treated with HCP- or self-administered icatibant between July 2009 and September 2013  
– Lack of response to antihistamines and corticosteroids  
– Criteria for normal C1INH (Type III) group: C1-INH level (≥15-50mg/dl); C1-INH function (≥70-130%), confirmed FXII mutation or a family history of HAE | Female 82%  
Age, median (IQR), y @enrollment: 35.1 (28.0-42.8)  
@ disease onset: 21.0 (16.0-29.0)  
@ diagnosis: 29.4 (23.5-40.2)  
Confirmed FXII mutations: 25%  
Common sites of attack:  
– abdomen 80%;  
– larynx 23% | Injections per attack:  
– One 70.0%  
– Two 24.4%  
– Three 5.6%  
(Dose not reported)  
Method of administration:  
HCP: 3.9%  
self-administered: 96.1% | No relevant comparator  
– Time to administration  
– Time to resolution  
– Attack duration  
– Adverse events |
<table>
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<tr>
<th>First Author Year Country</th>
<th>Study Design (sample size†)</th>
<th>Study Populations</th>
<th>Eligibility Criteria</th>
<th>Baseline Characteristics†</th>
<th>Icatibant ††</th>
<th>Comparator</th>
<th>Reported Outcomes</th>
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| Mansi 2015 Italy          | Case series FXII-HAE (n=6) U-HAE (n=18) | FXII-HAE (n=6) U-HAE (n=18) | - Angioedema with or without wheals  
- Referred to the study centre between 1993 and 2012  
- History of recurrent angioedema in a 1st or 2nd degree relative  
- C1-INH level > 50% normal values | Female  
- FXII-HAE: 83%  
- UI-HAE: 33%  
Age, median (range), y @ disease onset  
- FXII-HAE: 26.0 (24.0-27.0)  
- U-HAE: 25.0 (2.0-69.0) @ diagnosis  
- FXII-HAE: 26.0 (25.0-34.0)  
- U-HAE: 38.0 (8.0-76.0) | – Single injection per attack  
(30 mg subcutaneously) | None | – Time to resolution of symptoms |
| Firinu 2015 Italy         | Case series FXII-HAE (n=14) U-HAE (n=7) | FXII-HAE (n=14) U-HAE (n=7) | – Symptomatic patients with recurrent angioedema without wheals from 9 unrelated families  
- Normal C1-INH  
- Lack of response to daily prophylaxis with high-dose antihistamines or to steroids | Female  
- FXII-HAE: 75%  
- U-HAE: 57%  
Age, median (range), y @ disease onset  
- FXII-HAE: 20.5 (9.0-76.0)  
- U-HAE: 22.0 (16.0-47.0) | – Single injection per attack  
(30 mg subcutaneously) | None | – Time to resolution of symptoms |
| Bork 2015 Germany         | Case report (n=1) | HAE with normal C1 INH level without a FXII gene mutation  
- Positive family history | Gender: female  
Age: 31 y  
Sites of attack: Facial and abdominal | – Single injection per attack  
(30 mg subcutaneously) | None | – Time to administration  
– Time to first symptom relief  
– Time to resolution of symptoms  
– Attack duration |
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<tr>
<th>First Author Year</th>
<th>Study Design (sample size†)</th>
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<th>Comparator</th>
<th>Reported Outcomes</th>
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| Kuhlen 2014 | Case report (n=1) | - HAE with normal C1 INH level without wheals  
- Positive family history  
- Lack of response to high-dose prophylactic antihistamines | Gender: female  
Age: 26 y  
Sites of attack: Oro-facial and abdominal | Multiple injections during hospitalizations  
Single injection per attack during follow-up period (Doses not reported) | None  
- Adverse events |
| Garro 2014 | Case report (n=1) | - Recurrent episodes of angioedema with normal C1 INH level, without pruritus  
- Lack of response to prophylactic antihistamines and corticosteroids | Gender: female  
Age: 26 y  
Site of attack: Larynx | – Single injection (30 mg subcutaneously) | None  
- Time to improvement of symptoms |

C1 INH= C1 esterase inhibitor; FXII-HAE= angioedema with FXII mutation; HCP= healthcare provider; HAE= hereditary angioedema; IOS= Icatibant Outcome Survey; U-HAE= hereditary angioedema with unknown origin; USA= United States of America; y= year  
† Number of type III hereditary angioedema cases (the studies may include other types of angioedema cases, as well)  
†† Icatibant was administered for the treatment of acute attacks (on-demand therapy) in all of the included studies
### Appendix 3: Critical Appraisal of Included Publications

**Table A2: Strengths and Limitations of Cohort Studies using SIGN 50 checklist**

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<th>Strengths</th>
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<td>Pinero-Saavedra et al, 2016&lt;sup&gt;22&lt;/sup&gt;</td>
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<tr>
<td>– Research questions were stated</td>
<td>– The comparison groups were not specified a priori (single arm cohort with internal comparison groups)</td>
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<tr>
<td>– Characteristics of the study participants were clearly described</td>
<td>– It is unclear if the reported treatment (comparison) groups were comparable in all respects other than the treatment they received</td>
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<tr>
<td>– Basic information regarding study design, patient selection process, follow up and data collection methods was provided</td>
<td>– The assessors of outcomes were not blind to the exposure (treatment) status</td>
</tr>
<tr>
<td>– The outcomes were adequately defined</td>
<td>– It is not clear if the knowledge of exposure (treatment type) could have influence the outcome report.</td>
</tr>
<tr>
<td>– Competing interests were stated.</td>
<td>– No statistical comparisons were made between the treatment groups</td>
</tr>
<tr>
<td></td>
<td>– Estimates of the random variability were not provided</td>
</tr>
<tr>
<td></td>
<td>– Potential confounders were not addressed</td>
</tr>
<tr>
<td></td>
<td>– Source of funding was not reported</td>
</tr>
</tbody>
</table>
Table A3: Strengths and Limitations of Case Series Studies using the Quality Appraisal Tool by Moga et al.\textsuperscript{17}

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bouillet et al, 2017\textsuperscript{21}</strong></td>
<td>- Type III HAE cases were available from only one centre.</td>
</tr>
<tr>
<td>- The aim and objectives if the study were clearly stated</td>
<td>- It is unclear if the participants were recruited consecutively</td>
</tr>
<tr>
<td>- Characteristics of the study participants were described</td>
<td>- It is unclear if the patients entered the study at a similar point in the disease</td>
</tr>
<tr>
<td>- Eligibility criteria to participate in the study were clearly stated</td>
<td>- Details (e.g., dose) of the intervention of interest were not described</td>
</tr>
<tr>
<td>- Study outcomes are clearly defined</td>
<td>- Follow up data was collected for variable periods of time depending on the physician’s and patient’s preferences</td>
</tr>
<tr>
<td>- Limitations of the study and potential sources of bias were described</td>
<td>- Patients with missing data on any of the study outcomes were excluded from the analysis</td>
</tr>
<tr>
<td>- Estimates of the random variability were provided in the analysis of relevant outcomes</td>
<td>- Length of follow up was not reported</td>
</tr>
<tr>
<td>- The conclusions of the study were supported by the results</td>
<td>- No information on adverse events was provided</td>
</tr>
<tr>
<td>- Competing interests and sources of support were reported</td>
<td>- Estimates of the random variability were not provided in the analysis of relevant outcomes</td>
</tr>
</tbody>
</table>

| **Mansi et al, 2015\textsuperscript{22}** | - Patients with auto-immune diseases, missing follow-up visits or incomplete data were excluded from the analysis |
| - The aim and objectives if the study were clearly stated | - Length of follow up was not reported |
| - Characteristics of the study participants were described | - No information on adverse events was provided |
| - Eligibility criteria to participate in the study and the details of intervention of interest were clearly stated | - Estimates of the random variability were not provided in the analysis of relevant outcomes |
| - The study participants were recruited in a consecutive manner | - The report does not have a clear conclusion. |
| - The conclusions of the study were supported by the results | - It is unclear if the patients entered the study at a similar point in the disease |
| - Competing interests and sources of support were reported | - Length of follow up was not reported |

| **Firinu et al, 2015\textsuperscript{23}** | - Estimates of the random variability were not provided in the analysis of relevant outcomes |
| - The aim and objectives if the study were clearly stated | - The report does not have a clear conclusion. |
| - Characteristics of the study participants were described | - Length of follow up was not reported |
| - Eligibility criteria to participate in the study and the details of intervention of interest were clearly stated | - No information on adverse events was provided |
| - The study participants were recruited in a consecutive manner | - Estimates of the random variability were not provided in the analysis of relevant outcomes |
| - The conclusions of the study were supported by the results | - The report does not have a clear conclusion. |
| - Competing interests and sources of support were reported | - It is unclear if the patients entered the study at a similar point in the disease |
| | - Length of follow up was not reported |
## Appendix 4: Main Study Findings and Author’s Conclusions

### Table A4: Summary of Findings of the Included cohort study

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type III HEA subtypes (sample size)</th>
<th>Main Study Findings</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinero-Saavedra, 2016</td>
<td>FXII-HAE (n=35; 17 symptomatic, 5 pauci-symptomatic, and 13 asymptomatic)</td>
<td>Treatment of acute attacks in FXII-HAE patients</td>
<td>Improvement in symptoms after a single dose of icatibant was observed in 2 cases. In one case icatibant was administered &gt;6 hours after the onset of the attack and was ineffective. A similar positive response was observed in patients receiving plasma-driven C1-INH concentrate. The authors concluded that the study results supported existing evidence suggesting general effectiveness these two medications in resolution of acute attacks in Type III HAE.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Icatibant</th>
<th>C1-INH concentrate</th>
<th>Tranexamic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>2†</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td># attacks</td>
<td>9</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Time to onset of improvement, min</td>
<td>15-30</td>
<td>20-30</td>
<td>–</td>
</tr>
<tr>
<td>Objective symptom relief, h</td>
<td>1-2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Time to complete response, h</td>
<td>24</td>
<td>3-24</td>
<td>24-48</td>
</tr>
</tbody>
</table>

† A third case, for whom icatibant was given late (>6h after attack), was not included in the analysis of the outcomes.

C1-INH= C1 esterase inhibitor; FXII-HAE= angioedema with FXII mutation; h= hour(s); HEA= hereditary angioedema; min= minute(s)
### Table A5: Summary of Findings of Included Case Series Studies

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type III HEA subtypes (sample size)</th>
<th>Number of icatibant-treated patients (attacks)</th>
<th>Main Study Findings</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
</table>
| Bouillet, 2017<sup>1</sup> | FXII-HAE or U-HAE (n=22) | 22 (90) | Time to administration, med (IQR), h  
- all patients: 2.0 (0.8, 3.5)  
Time to resolution, med (IQR), h  
- all patients: 20.0 (8.0, 43.5)  
- abdominal attacks: 27.0 (9.7, 43.5)  
- cutaneous attacks: 16.5 (7.5, 37.0)  
- laryngeal attacks: 26.9 (13.3, 44.1)  
- severe/very severe attacks: 23.5 (8.0, 43.5)  
Duration of treated attacks, med (IQR), h  
- all patients: 32.5 (12.0, 47.3)  
Safety  
- patients reported AEs [unspecified]: 44 events (in 11/22 patients)  
- icatibant-related AEs: 3 events (in 2 patients)  
- death: none | The authors concluded that the limited treatment outcomes and safety data from this study indicate that icatibant could be considered as a potentially safe and effective option for treating acute attacks in HAE patients with normal C1-INH (type III). |
| Mansi, 2015<sup>2</sup> | FXII-HAE (n=6) U-HAE (n=18) | 2 (3) | Resolution of symptoms:  
- one U-HAE patient with an abdominal attack <4h  
- one FXII-HAE patient with two facial attacks: within 72 h | Treatment with icatibant was considered to be effective in one case (resolution <4h) and ineffective in a second one (resolution with 72h). The authors did not make a conclusion on the effectiveness and safety of icatibant, possibly due to paucity of data. |
| Firinu, 2015<sup>3</sup> | FXII-HAE (n=14) U-HAE (n=7) | 3 (3) | Resolution of symptoms:  
- 2 FXII-HAE patients with abdominal attacks: within 2.5-11 h  
- one FXII-HAE patient with a facial attack: within 12 h  
Local or systematic AEs: none | The authors compared the time to resolution of attacks from this study with that of similar untreated attacks reported historically by the same patients (>48h), and concluded that off-label use of icatibant was safe and effective for treatment of acute attacks in all three of the FXII-HAE participants. |

AEs= adverse events; C1-INH= C1 esterase inhibitor; FXII-HAE= angioedema with FXII mutation; h= hour(s); HEA= hereditary angioedema; IQR= inter-quartile range; SD= standard deviation; U-HAE= hereditary angioedema with unknown origin.
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type III HEA subtypes (sample size)</th>
<th>Number of attacks</th>
<th>Main Study Findings</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
</table>
| Bork, 2015<sup>24</sup> | U-HAE (n=1) | 29 | Time to administration, mean(SD), h: 1.9 (2.7)  
Time to first symptom relief, mean(SD), h: 0.5 (0.1)  
Duration of treated attacks mean(SD), h  
- face: 5.6 (6.6)  
- abdomen: 8.0 (20.7)  
Duration of untreated attacks mean(SD), h  
- face: 74.1 (6.6)  
- abdomen: 42.6 (9.9)  
Most frequent AEs: mild injection site reactions | The authors concluded that icatibant was an effective treatment for acute attacks in the reported case of U-HAE. |
| Kuhlen, 2014<sup>25</sup> | Unspecified subtype (n=1) | ≥6 | Improvement of symptoms after on-demand icatibant injections  
Re-hospitalization: none | The authors used the reported case as an example to demonstrate the off-label use of icatibant in HAE patients with normal C1-INH. However, no general comments have been made on the effectiveness and safety of icatibant in this type of HAE. |
| Garro, 2014<sup>26</sup> | Unspecified subtype (n=1) | 1 | Time to resolution of symptoms: <1h | The authors concluded that the immediate response to icatibant in the reported case supported the existing clinical evidence and its importance in early diagnosis of type III HAE. |

AEs= adverse events; C1-INH= C1 esterase inhibitor; h= hour(s); HEA= hereditary angioedema; SD= standard deviation; U-HAE= hereditary angioedema with unknown origin.