TITLE: Icatibant for Patients with Type III Hereditary Angioedema: A Review of Clinical Effectiveness and Harms

DATE: February 6, 2014

CONTEXT AND POLICY ISSUES

Hereditary angioedema (HAE) is a rare genetic disorder, characterized by recurrent and unpredictable episodes of angioedema over a patient’s lifetime including in the gastrointestinal tract, such as abdominal attack; skin, such as peripheral, facial, and genital attack; as well as the upper airways such as laryngeal attack.1-4 While the episodes of facial, peripheral subcutaneous edema, and abdominal attack are recurrent and self-limiting,1,5 laryngeal attacks are potentially fatal due to the risk of airway obstruction.3,6 The estimated prevalence of HAE is one out of 50,000 without major sex or ethnic differences (range: from 1:10,000 to 1:150,000).3,4,7 In HAE, deficiency of C1-esterase inhibitor (C1-INH), a key regulator of human immune system (the kallikrein–kinin plasma cascade system and classical complement pathway), activates kallikrein and subsequently leads to an over production of the vasoactive peptide bradykinin.8 Bradykinin is an important mediator of HAE, which binds to endothelial B2 receptors causing vasodilatation, increasing vascular permeability and resulting in angioedema.2,5 HAE can be classified into three types: type I HAE characterized by deficiency of the C1-esterase inhibitor (C1-INH), type II HAE characterized by normal but dysfunctional C1-INH, and type III HAE characterized with a normal C1-INH protein level and normal C1-INH activity function.2,9,10

Type III HAE occurs mainly in women.9,10 It is also called familial angioedema with normal C1-INH or HAE with normal C1-INH.9 The etiology of type III HAE appears to be more heterogeneous, with some patients having a gain-of-function mutation in the F12 gene which encodes factor XII, a coagulation factor that is also integral to bradykinin.9 Two subtypes of type III HAE were further reported, one is called HAE with normal C1-INH and a factor XII (FXII) mutation; the other is HAE with normal C1-INH of unknown cause.9 The diagnosis of type III HAE is based on recurrent attacks of subcutaneous or submucosal edema, no chronic relapsing urticarial, family history, and normal C1-INH level and function.10

Optimal management of HAE includes both treatment of acute attacks and short or long term prophylactic therapy to prevent acute attacks.2,11 A short term prophylactic treatment has been used prior to some surgical, dental or invasive medical procedures to prevent the acute attack of...
HAE potentially triggered by those procedures.\textsuperscript{12} There are two pharmacotherapeutic approaches to treat acute attack. One is the C1-INH replacement therapy. The other is to use medications to inhibit bradykinin either by blocking the enzyme kallikrein or preventing the binding of bradykinin with B2 receptor.\textsuperscript{2,6,13} The available pharmacological treatment options for type I HAE and type II HAE includes C1-INH concentrate,\textsuperscript{9} ecallantide, a kallikrein-bradykinin inhibitor,\textsuperscript{9} tranexamic acid, an antifibrinolytic agent; and icatibant, a selective bradykinin B2 receptor antagonist.\textsuperscript{4,8,10} The management options for type III HAE are overall similar to those for types I and type II HAE, which are primarily based on observational studies and expert opinions.\textsuperscript{3,9}

Icatibant, a selective bradykinin B2 receptor antagonist, has been approved in many countries worldwide for the symptomatic treatment of acute attacks of types I and II HAE in adults since 2008.\textsuperscript{2,6} It was reported that icatibant was successful in the prevention of angioedema after thyroid biopsy in HAE type I.\textsuperscript{12} Icatibant has also reportedly been used for type III HAE, although it is not licensed for this indication.\textsuperscript{5,10} The objective of this report is to review the therapeutic and prophylactic effectiveness and harms of icatibant in the treatment of type III HAE.

RESEARCH QUESTIONS

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 small observational study showed that icatibant appeared effective and safe in the treatment of type III HAE acute attack. However, it is inconclusive and needs to be interpreted with caution due to the important methodological limitations of the body evidence. No evidence for the prophylactic effectiveness of icatibant for patients with type III HAE was found. No evidence on harms associated with long-term use of icatibant is found. Better designed RCTs or larger scale observational studies in Canadian settings are needed to further determine the therapeutic or prophylactic effectiveness and harms of icatibant for patients with type III HAE.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), 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 methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and January 8, 2014.
Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with type III Hereditary Angioedema (HAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Icatibant</td>
</tr>
<tr>
<td>Comparator</td>
<td>Steroids, antihistamines, tranexamic acid, C1 esterase inhibitors, or no comparator</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Resolution of acute attack</td>
</tr>
<tr>
<td></td>
<td>Reduction in the need for tracheotomy, intubation, hospital admissions</td>
</tr>
<tr>
<td></td>
<td>Harms</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessment, systematic review / meta-analysis, randomized controlled trial or non-randomized studies.</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria.

Critical Appraisal of Individual Studies

The non-randomized study was assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist (SIGN 50 checklist 3). A numeric score was not calculated for each study. Rather, the strengths and limitations of the included study were summarized and described. No critical appraisal was done for the selected case serial report as this study design is considered to be inferior quality.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search from January 1, 2004 to January 8, 2014, yielded 93 citations. Upon screening titles and abstracts, 86 citations were excluded, and seven potentially relevant articles were retrieved for full-text review. Of the seven potentially relevant reports, five did not meet the inclusion criteria, and thus two non-randomized study reports were included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of the individual studies are presented in Table 2.

What is the evidence for the clinical effectiveness and harms of icatibant in the treatment of patients with type III hereditary angioedema?
Two non-randomized studies\textsuperscript{6,10} were identified. Both were conducted in France. One\textsuperscript{6} was a single arm prospective cohort study. In this cohort study, there were total 15 patients included. Among them, seven were with type I HAE and eight with type III HAE. For efficacy data, only data on type III HAE was extracted in this review. However, the reported adverse events were from both type I and type III HAE since there was no subgroup data for type III HAE. In the eight patients with type III HAE, seven patients were female and one was male. Age (year) ranged from 20 to 42 (median: 30.5). The median age at diagnosis of type III HAE was 25.5 (range: 18 to 32). The effectiveness of icatibant self-administration in eight patients with type III HAE for 32 severe or very severe acute attacks was observed. Among the 32 acute attacks, 11 were abdominal attacks; eight were laryngeal; nine were laryngeal and abdominal; three were laryngeal and facial; and one was abdominal, laryngeal and facial attack. Icatibant (30 mg, 3 ml solution) was self-administered by subcutaneous (s.c.) injection in the abdomen. The outcomes observed were the resolution of acute attack, the time to first symptom improvement after icatibant injection, the time to symptom complete resolution after icatibant injection, the number of icatibant injections, quality of life, and the adverse events.

The other report\textsuperscript{10} was a case series report, in which, three type III HAE patients with acute attacks were presented. Two patients presented with severe abdominal attack. The third one was with severe abdominal and facial edema. Age (year) ranged from 32 to 43. Ages at first HAE symptom ranged from 28 to 41. One patient received long term prophylaxis treatment with tranexamic acid, and one with danazole. The third had no long term history prophylaxis treatment. Two patients received one dose of icatibant injection (s.c) and one received two icatibant injections. The resolution of acute attack and the time to symptom resolution after icatibant injection and the adverse events were reported.

Table 2: Characteristics of Included studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccon-Gibod,\textsuperscript{6} 2012, France</td>
<td>Cohort study\textsuperscript{a} N = 8 pts</td>
<td>Type III HAE pts with acute attack\textsuperscript{b}</td>
<td>Icatibant, (30mg) s.c. injection\textsuperscript{c}</td>
<td>None</td>
<td>●Resolution of acute attack ●AE ●QOL</td>
</tr>
<tr>
<td>Bouillet,\textsuperscript{10} 2009, France</td>
<td>Case series N = 3 pts</td>
<td>Type III HAE pts with acute attack\textsuperscript{d}</td>
<td>Icatibant (30mg) s.c. injection\textsuperscript{c} - Pt 1: 1 dose - Pt 2: 1 dose - Pt 3: 2 doses (with 6 hours apart)</td>
<td>None</td>
<td>●Resolution of acute attack ●AE ●QOL</td>
</tr>
</tbody>
</table>

HAE= hereditary angioedema; Pt = patient; s.c. = subcutaneous.
\textsuperscript{a}The cohort study included 15 patients with HAE in total. Among them, seven were with type I HAE and eight with type III HAE. Only data on type III HAE was extracted in this review.
\textsuperscript{b}HAE acute attacks included abdominal, laryngeal, laryngeal and abdominal, laryngeal and facial or abdominal, laryngeal and facial attacks. Mostly were severe or very severe.
\textsuperscript{c}Self-administer a single dose of icatibant (30 mg, 3 ml solution) by s.c. injection in the abdomen
\textsuperscript{d}HAE acute attacks included severe or unusual severe abdominal attack, or abdominal and facial edema.

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

No evidence was identified for the prophylactic effectiveness of icatibant for patients with type III hereditary angioedema.
Summary of Critical Appraisal

The details on the critical appraisal of individual studies are presented in Table 3.

Methodological quality of the cohort study was considered poor due to the limitations of the nature of the observational study itself. There was no control arm. The sample size was very small (n=8). The patient selection process was not clearly described. No statistical analysis was performed and confounding factors were not addressed. The methodological quality of the case series report was not assessed, as these types of study are considered to be of inferior quality.

Table 3: Critical Appraisal of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccon-Gibod, 2012, France</td>
<td>• Research question (objectives) was stated</td>
<td>• Single arm study, no control group</td>
</tr>
<tr>
<td></td>
<td>• Prospective cohort study</td>
<td>• Small sample size</td>
</tr>
<tr>
<td></td>
<td>• Population baseline demographic characteristics were reported</td>
<td>• Patient selection process was not clearly described</td>
</tr>
<tr>
<td></td>
<td>• Outcomes and main findings were clearly stated</td>
<td>• No blind analysis process</td>
</tr>
<tr>
<td></td>
<td>• Outcome measurement was valid and reliable</td>
<td>• 95%CI was not provided</td>
</tr>
<tr>
<td></td>
<td>• Conflict of interest reported</td>
<td>• Statistical analyses were not performed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confounding factors were not addressed</td>
</tr>
<tr>
<td>Bouillet, 2009, France</td>
<td>Case serial report: critical appraisal not performed</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Findings

The results of the effectiveness and safety are presented in Table 4.

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

In the cohort study, the efficacy and safety of icatibant self-administration was assessed in eight patients with type III HAE. It was found that all eight patients experienced a full or partial response after icatibant treatment. It was also reported that the first symptom improvement occurred in eight minutes (min) to one hour (h) for abdominal attacks (n = 9 evaluable attacks) and 10 min to 12 h for laryngeal attacks (n = 6 evaluable attacks). Complete symptom resolution occurred in 15 min to 48 h for abdominal attacks (n = 9 evaluable attacks) and 8h to 48 h for laryngeal attacks (n = 5 evaluable attacks). No patient required emergency hospitalization. The only adverse events were injection site reactions (ISR) including erythema, swelling, and itching, which were all mild and spontaneously resolved within 0.5 h to 3 h. The ISR occurred in 14 patients with either type I HAE or type III HAE (for 48 of the 55 self-treated attacks). The authors also reported that patients with HAE (both type I and type III HAE) had greater confidence in managing acute attacks when carrying icatibant with them. Neither adverse event, nor QOL information was reported only for the subgroup of type III HAE. The author indicated that icatibant self-administration was generally effective in the management of severe HAE acute attack.
In the case series report, two patients with abdominal attack reported symptom resolution in one hour after icatibant injection. But one of the two patients received the second icatibant injection when the symptom relapsed six hours after the first injection. The third patient with abdominal and facial attack experienced the symptom resolution in two hours after icatibant injection. Local ISRs were reported in all three patients. The author concluded that icatibant was safe and effective in the treatment of severe acute attack in patients with HAE type III.

Table 4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccon-Gibod, France 2012</td>
<td>(Only data for type III HAE was extracted, N = 8 patients) ● Response rate: All patients experienced a full or partial response after icatibant treatment. ● Time to first symptom improvement after treatment: - for abdominal attacks (9 attacks): 8 min – 1 h; - for laryngeal attacks (6 attacks): 10 min – 12 h ● Time to complete symptom resolution after treatment: - for abdominal attacks (9 attacks): 15 min – 48 h - for laryngeal attacks (5 attacks): 8 h – 48 h ● Emergency hospitalization: 0 ● Number of icatibant injection: 1 injection: for 62.5% attacks (number of pts.: NR) 2 injections: for 4 pts. (at 6 h – 9 h after first injection) 3 injections: for 2 pts. (injection time interval not reported) ● AEs: ISRs including erythema, swelling and itching: reported in 48 out of 55 self-treated HAE attacks from 14 pts including HAE type I and HAE type III. No subgroup HAE type III AEs data was reported. ● QOL: Patients felt more confident in managing their condition when carrying icatibant with them.</td>
<td>No conclusion was made by the author. It was summarized that icatibant self-administration was generally effective and the only AE was mild and spontaneously resolving ISR. Patients carrying icatibant showed greater confidence in managing their HAE symptoms.</td>
</tr>
<tr>
<td>Bouillet, France 2009</td>
<td>● Response rate: All 3 pts responded to the icatibant treatment ● Time to complete symptom resolution after treatment - Pt 1: 1 h for abdominal attack - Pt 2: 2 h for abdominal and facial attack - Pt 3: 1 h for abdominal attack ● AEs: ISR observed in all 3 patients</td>
<td>On page 448: “Icatibant is a safe and effective symptomatic treatment for severe attacks in patients with HAE type III.”</td>
</tr>
</tbody>
</table>

AE = adverse event; h=hour; HAE= hereditary angioedema; ISR= injection site reactions; Min=minutes; NR= not reported; Pt = patient; QOL= quality of life;

*All the attacks requiring a second or third icatibant injection showed an initial response, but for some the response was partial after ~6 h (n = 7), and for others (n = 4) attack recurrence (or worsening) occurred after the initial response.

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

No evidence was identified for the prophylactic effectiveness of icatibant for patients with type III hereditary angioedema.

Limitations

The methodological quality of the cohort study was considered poor due to the limitations of the nature of the observational study itself. There was no control arm, therefore it is not clear whether any observed effect is attributable to icatibant or other factors including natural resolution with time. There was no comparative effectiveness and safety data comparing icatibant with other existing active treatments. The sample size was very small; and no statistical analysis was performed. The patient selection process was not clearly described, and confounding factors
such as comorbidity and other concomitant medications were not addressed. No long term observational data is identified. Furthermore, the evidence obtained from the studies was generated outside Canada may not be transferable to Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Type III HAE is a rare genetic disease. Icatibant is indicated for the treatment of patients with type I and type II HAE. Icatibant has been sometimes used for the treatment of type III HAE in some jurisdictions as off-label use; however, no systematic reviews or randomized controlled trials were identified investigating the clinical effectiveness and harms of icatibant in the treatment of acute attack of type III HAE. The primary observational data from a total of 11 patients with type III HAE showed the icatibant subcutaneous injection appeared effective and safe in the treatment of type III HAE acute attack. But, the findings reported in this review are not conclusive and need to be interpreted with caution because of the sparse data and the important methodological limitations of the included studies. No evidence for the prophylactic effectiveness of icatibant for patients with type III HAE was found. Better designed RCTs or larger scale observational studies in Canadian settings are needed to further determine the therapeutic or prophylactic effectiveness and harms of icatibant for patients with type III hereditary angioedema.

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REFERENCES


APPENDIX 1: Selection of Included Studies

- 93 citations identified from electronic literature search and screened
- 86 citations excluded
- 7 potentially relevant articles retrieved for scrutiny (full text, if available)
- 0 potentially relevant reports retrieved from other sources (grey literature)
- 7 potentially relevant reports
- 5 reports excluded: 
  - Irrelevant population (not type III HAE) (4)
- 2 reports included in this review