Icatibant and its Therapeutic Indications

Christian Longley 1*

1 Emergency Registrar, St Vincent’s Emergency Department, Melbourne, Australia
* Corresponding author’s email: christian.longley@googlemail.com

Date published: 15/05/2016

Angioedema is a localised dermal and subcutaneous swelling. There are multiple causes for angioedema, including allergic reactions, angiotensin-converting enzyme inhibitor (ACE inhibitor) use and hereditary angioedema (HAE). ACE inhibitor angioedema and HAE are both mediated by an excess of bradykinin, while angioedema secondary to an allergic reaction is mediated by histamine. In these instances, oropharyngeal swelling may occur unpredictably, requiring immediate treatment to prevent airway obstruction. Recent randomised controlled trial evidence suggests early use of 30 mg subcutaneous icatibant, a synthetic bradykinin B2 receptor antagonist, is an effective treatment in HAE. Its potential use in ACE inhibitor angioedema is recognised, but, as yet, less well evidenced. Additionally, its superiority to other therapies is also unclear. This article examines the use of icatibant for hereditary angioedema and ACE inhibitor angioedema.

Keywords: Icatibant; angiotensin-converting enzyme inhibitors; hereditary angioedema; angioedema

Introduction

In recent years icatibant (Firazyr®) has been increasingly recognised as a therapeutic option for HAE. Interest has also developed in its use for ACE inhibitor angioedema, as it shares a common pathway mediated by bradykinin. The financial cost of this medication is high and its efficacy, like other drugs in this area, is not well studied. Initial trials and case series were encouraging, leading to its licensing for use in HAE attacks in adults over eighteen in the United States and European Union. In the emergency setting it is hoped it may be an excellent addition to the clinician’s armament when faced with cases of angioedema. Other benefits in this setting may also include reduced duration of symptoms and reduced hospital length of stay (LOS). With various novel treatments becoming available, and difficult management decisions facing clinicians who deal with angioedema, it remains a challenging condition to treat. This article will examine icatibant within the larger context of angioedema.

Angioedema

Angioedema is a localised and self-limiting oedema involving deeper layers of the dermis, including the subcutaneous tissue and occasionally the bowel wall. It occurs due to increased vascular permeability caused by release of vasoactive mediators.[1] The swelling affects a variety of areas of the body and presents the most serious threat to life when oedema occurs in the oropharynx (lips, tongue) and larynx.[2] It may occur as a distinct entity, or in addition to urticaria, which only involves the superficial portion of the dermis, and is usually seen in histaminergic mediated angioedema. The episode is considered acute if it lasts less than six weeks, and can occur at any time of life.

The aetiology of this condition is largely dictated by its underlying cause, with common pathways at play (Table 1). In 2014, Moellman et al. produced a consensus document for management in the emergency department, classifying angioedema as anaphylaxis, histaminergic angioedema without anaphylaxis and non-histaminergic angioedema.[3] The best-known
mediators are histamine and bradykinin. This simple distinction in pathogenesis is of key clinical importance when treating acute attacks of angioedema. Clinical endpoints are similar, but emergency treatment takes one of two distinct pathways. Angioedema can be idiopathic, but recognised causes are multiple, including: allergy and anaphylaxis, HAE, acquired C1 esterase inhibitor deficiency, adverse reaction to ACE inhibitors and some viral, bacterial and parasitic infections (especially in children).

If the cause is known, treatment should be tailored to the individual mechanism. For instance, in anaphylaxis where the underlying cause for angioedema is histamine release, immediate intramuscular or intravenous adrenaline is the mainstay of treatment. If an immune-mediated IgE response triggers a lesser clinical manifestation, steroids and antihistamines can be given. However, if HAE or ACE inhibitors are known to be responsible, or adrenaline fails to improve the situation in angioedema of unknown cause, excess circulating bradykinin is likely to be the causative factor and the medication icatibant is amongst treatment options. Several consensus guidelines suggest adrenaline, corticosteroids and antihistamines have no effect on HAE or ACE inhibitor angioedema. Several drugs have been considered in the past decade for the treatment of acute HAE, including ecallantide (a kallikrein inhibitor), icatibant and C1-inhibitor concentrate. Due to its similar bradykinin pathway, interest has also developed in whether similar medications will work in ACE inhibitor angioedema.

### Bradykinin Pathway

Bradykinin is a vasoactive peptide formed at the endpoint of kallikrein-kinin system, and acts as the primary mediator in non-allergic angioedema. Factor XIIa from the coagulation cascade converts prekallikrein to kallikrein. Subsequently, kallikrein converts high-molecular-weight kininogen to produce bradykinin. Usually bradykinin concentration is very low, with a half-life less than thirty seconds. Genes for two bradykinin receptors (B1, B2) are found on chromosome 14. When bradykinin activates endothelial cells via B2 receptors, vascular permeability increases and oedema results.

### Hereditary Angioedema

Hereditary angioedema is a rare autosomal dominant condition usually due to a quantitative or functional deficiency of C1 esterase inhibitor (C1-INH). Low levels of C1-INH result in uninhibited action of vasoactive mediators, especially bradykinin, causing vasodilatation, smooth muscle contraction, submucosal and subcutaneous oedema without urticaria. The underlying

| Table 1. Comparison of histamine- and bradykinin-mediated angioedema (Adapted from Moellman et al. A Consensus parameter for the evaluation and management of angioedema in the Emergency Department).[3] |
|---|---|
| **Features** |  |
| Histamine-mediated | Associated urticaria  
Swelling typically resolves in 24-48 hours |
| Bradykinin-mediated | No urticaria  
Swelling onset is varied but typically quick (hours)  
May have a family history or previous bouts of abdominal pain  
Related to menstruation  
Resolves in 2-7 days  
Poor/no response to traditional therapy aimed at histamine-mediated aetiology (steroids/antihistamine) |
| **Mechanism** |  |
| Histamine-mediated | Immunoglobulin-mediated IgE antibodies  
Allergic – drugs, food, latex, insect bites  
Idiopathic |
| Bradykinin-mediated | Bradykinin excess due to decreased metabolism (ACE inhibitor)  
Abnormal C1-inhibitor gene results in overproduction of bradykinin  
Triggers for attacks include surgery and stress |
| **Causes** |  |
| Histamine-mediated | HAE (type I and II)  
ACE inhibitors  
Acquired C1 esterase inhibitor deficiency  
Idiopathic |
| Bradykinin-mediated | Allergic – drugs, food, latex, insect bites  
Idiopathic |
| **Management** |  |
| Histamine-mediated | Monitoring  
Invasive airway management  
H1 and H2 antagonists  
Corticosteroids  
Adrenaline |
| Bradykinin-mediated | Monitoring  
Invasive airway management  
Discontinue ACE inhibitor  
Options – Fresh frozen plasma, ecallantide, plasma-derived C1-Inhibitor concentrate, Icatibant, Recombinant C1-Inhibitor |
cause is a mutation of the gene encoding the C1-INH, inherited in an autosomal pattern with high penetrance. Recent estimates place its prevalence at 1:50,000.[11] Three subtypes are defined:

- type I, due to low levels of C1-INH (85%),
- type II, due to normal C1-INH levels, but abnormal C1-INH function (15%), and
- type III, an extremely rare, poorly understood HAE, involving normal C1-INH levels.[12]

Due to its autosomal dominant nature, a family history is expected; however, de novo mutations are found in 25% cases. Clinical expression may differ significantly, even in members of the same family. Attacks can result in gastrointestinal, subcutaneous or oropharyngeal swelling. Gastrointestinal attacks range from mild to severe and usually result in recurrent pain, generally resolving without serious complication. Diagnosis can be difficult in this instance and patients may undergo multiple medical investigations including spectroscopy before diagnosis. Cutaneous attacks are clinically more apparent but also not usually associated with serious complication. However, when the attack involves the larynx, it poses a definite risk of asphyxiation and death. Fortunately, most attacks present with mild symptoms, which develop over twenty-four hours or so and resolve over two to five days. Signs and symptoms may include tingling followed by a non-itchy macular rash, abdominal pain, diarrhoea, vomiting and swelling of the limbs, face, or genitals.[13] If cases of HAE are suspected, blood testing may confirm diagnosis. Occasionally, genetic testing may be required.

Treatment of acute attacks depends on clinical presentation. There has been significant recent evolution of the pharmacological treatment for acute attacks and longer-term prophylaxis. Therapies aim to provide C1 inhibitor protein replacement or to antagonise bradykinin or kallikrein (Figure 1). Depending on a specific

patient’s pattern of attacks, they may be able to initiate treatment themselves at home. However, patients who suffer a laryngeal attack are always advised to seek immediate medical assistance. In cases of airway compromise, endotracheal intubation, or even a surgical airway, may be required. It is hoped that novel agents may prevent this critical intervention in some circumstances and reduce symptom duration. Symptoms of dysphonia, dysphagia, stridor and globus pharyngeus must be taken very seriously as airway obstruction has been reported as early as twenty minutes from the onset of symptoms.[14]

Angiotensin-Converting Enzyme Inhibitor Angioedema

ACE inhibitors are commonly prescribed medications used to treat congestive cardiac failure, diabetic nephropathy and hypertension.[16] ACE inhibitors prevent the conversion of angiotensin I to angiotensin II. The angiotensin-converting enzyme is also the principal enzyme responsible for the breakdown of bradykinin. Several side-effects of ACE inhibitors are recognised, including cough and rash. Angioedema is a serious complication of their use, usually occurring within the first month of treatment but may occur years later.[17,18] Why some people are affected in this way is not fully understood, but may be related to genetic variations producing altered function in other enzymes that also help metabolise bradykinin.[19] ACE inhibitor use results in excess circulating bradykinin levels. Patients with decreased ability to metabolise bradykinin, via one of the other redundant mechanisms, are at increased risk of developing angioedema. Angioedema is estimated to occur in 0.1-0.7% of patients taking ACE inhibitors, classically presenting with facial, tongue or lip swelling, in the absence of urticaria.[20,21] ACE inhibitor angioedema can be severe, and with limited treatment options, fatal cases have been reported.[22] As ACE inhibitors are such a widely prescribed medication in cardiovascular and renal disease, ACE inhibitor angioedema is a relatively common cause of angioedema presenting the emergency department.[23] In a retrospective review at a large community hospital over a five-year period, 11% of patients who presented with ACE inhibitor angioedema required definitive airway intervention (5/45), with 2% requiring a surgical airway (1/45).[24] Another study found 30% (15/50) required ventilation, with 4% requiring a surgical airway (2/50). [25] With angioedema being so unpredictable, the decision of when and how to secure the airway in the cases of ACE inhibitor angioedema is challenging.

The standard treatment of ACE inhibitor angioedema is to secure the airway when clinically indicated and

<table>
<thead>
<tr>
<th>Medication (trade name)</th>
<th>Route</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Approval status</th>
<th>Cost per dose (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-Inhibitor concentrate (Berinert®, Cinryze®)</td>
<td>Intravenous</td>
<td>20 units/kg or 1000 units for Cinryze®</td>
<td>C1-INH protein replacement</td>
<td>Berinert® is approved in Europe and USA for all HAE attacks in adults and adolescents. Cinryze® is approved for all attacks in Europe.</td>
<td>$6377</td>
</tr>
<tr>
<td>Ecallantide (Kalbitor®)</td>
<td>Subcutaneous</td>
<td>30 mg</td>
<td>Plasma-kallikrein inhibitor</td>
<td>Approved in USA for all acute facial and abdominal attacks in patients &gt;16 years old. Not approved in Europe.</td>
<td>$11,130</td>
</tr>
<tr>
<td>Icatibant (Firazyr®)</td>
<td>Subcutaneous</td>
<td>30 mg</td>
<td>Bradykinin 2-receptor antagonist</td>
<td>Approved in Europe and USA for all acute attacks in adults</td>
<td>$8,004</td>
</tr>
<tr>
<td>Recombinant C1-Inhibitor (Ruconest®)</td>
<td>Intravenous</td>
<td>50 units/kg</td>
<td>C1-INH protein replacement</td>
<td>Approved in Europe for all acute attacks in adults. Approved in USA for acute attacks of HAE in adult and adolescent patients.</td>
<td>$7,917</td>
</tr>
</tbody>
</table>
provide supportive management whilst stopping the causative medication. Unfortunately, there are no approved medical treatments for ACE inhibitor angioedema and no widely accepted consensus algorithm exists. Again, cases will not respond to steroids, antihistamines or adrenaline, as ACE inhibitor angioedema is bradykinin mediated, as opposed to histaminergic. This bradykinin pathway, shared with HAE, has stimulated interest in the use of icatibant. Evidence currently stems from isolated case reports and case series.[26-31] Similar interest has been shown in the potential of ecallantide and CI-INH concentrates. Improvement of symptoms following the cessation of the ACE inhibitor is usually enough to confirm diagnosis.

**Icatibant (Firazyr ®)**

Icatibant (Firazyr®, Shire) is a synthetic decapeptide similar in structure to bradykinin and acts as a competitive antagonist at the bradykinin (B2) receptor (Figure 2).

In Europe, Icatibant was approved by the Committee for Medicinal Products for Human Use (CHMP) in 2008 for angioedema in adults linked to C1 esterase inhibitor deficiency. The Therapeutic Goods Association (TGA) approved its use for symptomatic attacks of HAE in adults in Australia in 2010 and it has been FDA (U.S. Food and Drug Administration) approved in the United States since 2011 for treatment of acute attacks of HAE in people aged eighteen years and older.

Product information and characteristics of icatibant are detailed in material produced by the pharmaceutical company Shire.[32] Icatibant is available as a fixed dose preparation, in a 3 ml (30 mg) pre-filled syringe. It is administered as a slow subcutaneous injection into the abdominal area. A single injection is currently thought to be sufficient to reduce oedema, but if needed, a second and third injection can be given at six-hour intervals to a maximum of three doses in a twenty-four hour period. The most commonly reported adverse effects include local injection site skin reactions and pain. Its bioavailability is 97% and time to maximum concen-
tration is approximately 30 minutes. Ninety percent is metabolised by enzymes to inactive metabolites and excreted via the kidneys whilst 10% is excreted unchanged. It is not metabolised by the cytochrome P450 system and no dose adjustment is needed in hepatic or renal impairment. There is relatively little experience worldwide with this medication; therefore caution is advised in concomitant acute coronary syndrome, stroke and pregnancy. It is not recommended in children. It is not known whether icatibant is excreted in breast milk. Currently, it is recommended that breastfeeding should be delayed by a minimum of 12 hours after icatibant administration.

Its use is recommended in known cases of HAE. It may also be used in suspected cases of ACE inhibitor angioedema. It can be considered for empiric use in cases of angioedema when the cause is unknown, and a response has not been seen with adrenaline. Icatibant is not universally available and remains an expensive drug, therefore its use in the emergency setting is suggested when swelling is seen in the tongue, neck, oropharynx or larynx (to avoid an airway obstruction). It should not be given for minor peripheral swelling, where simple observation may be appropriate. Whilst expensive, it may preserve the airway from life threatening compromise, avoiding costly admissions to the intensive care unit. It is easily administered and repeatable if needed.

Self-administration of icatibant for HAE attacks was assessed in a small case series of fifteen patients. Whilst limited by small sample size and no comparator group, the authors were encouraged by the ease of use and low side effect profile patients’ experienced with icatibant. No patients required hospitalisation following use of icatibant.[33]

**Current Evidence**

**Icatibant in acute HAE attacks**

In 2007, icatibant was given intravenously or subcutaneously in an open label pilot study involving fifteen patients with HAE attacks.[34] There was an improved median time to symptom relief in the subcutaneous group compared to the intravenous group (30 minutes vs. 1 hour); therefore, further research used the subcutaneous route. When compared to untreated attacks, time to resolution of symptoms was quicker (reducing mean time to onset of symptom relief by 97%).

This phase II study paved the way for subsequent phase III trials, sponsored by the original manufacturer, Jerini. Three randomised, double blind, control trials (FAST-1, FAST-2, FAST-3 - “For Angioedema Subcutaneous Treatment”) have been published. FAST-1 and FAST-3 were placebo-controlled trials, while in FAST-2 icatibant was compared to oral tranexamic acid. The primary endpoint in all three FAST trials was assessed using a three-point visual analogue scale (VAS) assessment of symptoms – skin swelling, skin pain and

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Study groups (number of patients)</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST-1 (2010)</td>
<td>Icatibant (27) vs. placebo (29)</td>
<td>Time to 30% decrease in VAS score</td>
<td>2.5 hours vs. 4.6 hours (p=0.14)</td>
</tr>
<tr>
<td>FAST-2 (2010)</td>
<td>Icatibant (36) vs. tranexamic acid (38)</td>
<td>Time to 30% decrease in VAS score</td>
<td>2 hours vs. 12 hours (p&lt;0.001)</td>
</tr>
<tr>
<td>FAST-3 (2011)</td>
<td>Icatibant (43) vs. placebo (45)</td>
<td>Time to 50% decrease in VAS score</td>
<td>2 hours vs. 19.8 hours (p=0.001)</td>
</tr>
</tbody>
</table>

Table 3. Primary endpoint results for FAST trials

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Study groups (number of patients)</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST-1 (2010)</td>
<td>Icatibant (27) vs. placebo (29)</td>
<td>Onset of primary symptom relief</td>
<td>0.8 hours vs. 16.9 hours (p&lt;0.001)</td>
</tr>
<tr>
<td>FAST-2 (2010)</td>
<td>Icatibant (36) vs. tranexamic acid (38)</td>
<td>Onset of primary symptom relief</td>
<td>0.8 hours vs. 7.9 hours (p&lt;0.001)</td>
</tr>
<tr>
<td>FAST-3 (2011)</td>
<td>Icatibant (43) vs. placebo (45)</td>
<td>Onset of primary symptom relief</td>
<td>1.5 hours vs. 18.5 hours (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Table 4. FAST trial outcomes using onset of primary symptom relief as endpoint
abdominal pain. To reach the primary endpoint, a 30% reduction in symptoms was needed on three consecutive scores in the FAST-1 and FAST-2 trials and a 50% reduction in the FAST-3 trial.

FAST-1 compared icatibant with placebo in patients with moderate to severe cutaneous, laryngeal or abdominal attacks of HAE. This showed a non-statistically significant improvement in the time to reduction of symptoms. The FAST-2 trial reported a ten-hour quicker recovery time with icatibant, compared to oral tranexamic acid at a dose of 3 g orally daily for three days. The results of FAST-1 and FAST-2 were published together.[35] The FAST-3 trial compared icatibant with placebo in moderate to severe attacks of HAE and showed the strongest statistically significant improvement.[36]

To improve the safety of these trials, laryngeal attacks were not included in the FAST 1 and 2 trials. Instead, patients with laryngeal symptoms were included in an open label study. In FAST-3, patients with mild laryngeal symptoms were included, whereas patients with severe symptoms were treated in an open label study, resulting in a total of 40 unblinded patients who received icatibant. This provides further limited information on how icatibant fares when dealing with a threatened airway. It is unlikely studies in this area will proceed due to obvious ethical barriers. The unblinded data for laryngeal attacks showed median times for 50% reduction in symptoms were 2.5 and 3.2 hours for icatibant and placebo, respectively. These results emphasise that, in the emergency setting of a laryngeal attack of HAE, it may be appropriate to trial a dose of icatibant, although administration should never supersede the proactive securing of a patient’s airway.

As a result of these trials, icatibant gained approval status in Europe and the U.S. The European CMHP used data from FAST-1 and FAST-2 to decide that “Firazyr’s benefits are greater than its risk”. The FDA cited data from all the FAST trials to provide approval in 2011 for adults over eighteen with HAE.

Prior to the publication of the FAST-3 trial, an international working group met to assess the evidence base for current HAE treatments.[37] The FAST-1 and -2 trials were reviewed favourably, suggesting the available evidence shortened attacks of HAE, with approximately 10% requiring a second dose and 1% requiring a third dose. There were no major safety concerns with the medication, with the main side effect registered being local site irritation. Icatibant compares well with the other angioedema therapies in terms of safety. Allergy, or possible anaphylaxis, has been reported in the other available drugs – ecallantide, recombinant human C1 inhibitor and plasma-derived C1 inhibitors, but not with icatibant. In conclusion, the group reported patients should have access to one of the medications available to treat HAE (which includes icatibant), but do not assign superiority to any of these agents.

The major breakthrough of the FAST trials is that they managed to collate international data on the use of icatibant in a rare condition. Whilst FAST-1 did not show statistical improvement on its primary endpoint, FAST-2 and FAST-3 showed benefit when compared to tranexamic acid and placebo, respectively. Multiple end-points suggest consistent and beneficial results (Tables 3 and 4).[38]

Although the FAST trials have resulted in licensing in the US and EU, certain weakness and unanswered questions remain. The study populations were small. FAST-2 compared icatibant to tranexamic acid, a medication already considered to be of very limited benefit in HAE. No head-to-head trials are currently available comparing icatibant to other treatments such as C1 inhibitor concentrate, ecallantide or fresh frozen plasma (FFP). Clinicians therefore have a range of options when faced with HAE presentations, with little evidence to support superiority of any treatment. The 2012 international working group reviewed all phase 3 trials for acute treatment of HAE, comparing mainly time for improvement of symptoms and complete resolution of symptoms.[37] Whilst no specific medication was definitively superior, the group made a number of consensus statements regarding an acute attack, suggesting all HAE patients should have access to one of the available medications and that all attacks are eligible to administration of one of the medications either by the patient or healthcare professional as soon as symptoms are recognised. Based on this consensus, it appears the clinician may be justified in giving a novel therapy, such as icatibant, in any patient with HAE, not only one presenting with a threatened airway.

No other published major phase 3 trial data is currently available. There is no data on the efficacy and safety in children (0-18 years old) or use in pregnancy. Currently, there is a multi centre, open label study running involving thirty paediatric subjects with HAE.
using subcutaneous icatibant 30 mg in the U.S. The results are expected in 2017.[39]

Icatibant in ACE Inhibitor angioedema

The use of icatibant for ACE inhibitor angioedema is, as yet, neither well tested nor established. Most evidence is available in the form of case reports or small series.

In 2010, Bas et al. published the first small case series of eight patients with ACE inhibitor angioedema who were treated with icatibant.[27] The mean time to initial improvement of symptoms was 50.6 minutes, and to resolution of symptoms, 4.4 hours. No patient required intubation or tracheostomy. In comparison, their historic control group showed an average of 33 hours for resolution of symptoms in patients treated with steroid and antihistamine.

Bas et al. subsequently published a randomised phase two trial in The New England Journal of Medicine in January 2015. This study included 27 patients with ACE inhibitor angioedema of the upper aerodigestive tract treated with either icatibant 30 mg subcutaneously or intravenous prednisolone 500 mg and clemastine 2 mg.[40] Patients presented within ten hours from symptom onset. Icatibant shortened the time to both improvement of oedema (2 hours vs. 11.7 hours) and resolution of symptoms (8 hours vs. 27.1 hours). Three patients in the steroid and antihistamine group needed rescue treatment with icatibant and one required tracheostomy. This small study seems to support the anecdotal evidence so far, that icatibant is useful in ACE inhibitor angioedema. However, it has drawn criticism for describing prednisolone and clemastine as “standard therapy”. It is generally recognised that steroids and antihistamine actually have little or no effect on ACE inhibitor angioedema, and therefore comparing icatibant to this therapy may be doing little more than comparing icatibant to placebo.

Another case series from Italy reported the treatment of thirteen patients with ACE inhibitor angioedema with icatibant.[41] All patients had shown no response to treatment with adrenaline, steroids and antihista-mines. After treatment with icatibant 30 mg subcutaneously, the median time to symptom relief was thirty minutes and time to complete resolution was five hours. No patient required a definitive airway and all were discharged within 24 hours of presentation.

Results from the first phase III, double blind, placebo-controlled trial examining icatibant in cases of ACE inhibitor angioedema are expected shortly (CAMEO trial).[42] One hundred and eighteen adult patients have been enrolled in a 1:1 ratio to examine the safety and efficacy of icatibant in patients presenting within twelve hours of the development of suspected ACE inhibitor angioedema. Two primary outcomes are under examination - time to meeting discharge criteria and safety and tolerability of icatibant. In addition, a number of secondary outcomes, including time to onset of symptom relief and occurrence of airway intervention, will be considered.

Discussion Points

Clinicians currently face difficult decisions when managing angioedema, regardless of its aetiology. Firstly, if possible, they must establish what the likely cause may be, and subsequently what treatment may be most effective. Once decided, the type of intervention required is often a judgement decision. One of the most important questions is when to secure the airway in the presence of oropharyngeal angioedema. This remains a complex clinical decision and one taken on a case-by-case basis. It remains unclear at what time point expensive drugs, such as icatibant, should be considered and administered. As clinician awareness of these medications increases, there is a risk that clinical usage patterns will change, in the absence of robust evidence of benefit from large clinical trials.[43] In a condition which is not particularly conducive to guideline-based management, there is concern this medication could be used at lower and lower thresholds. Angioedema patients who may have been reasonably managed by observation could now be treated on a “just in case” basis.

Ishoo proposed a simple staging system based on eighty patients with angioedema requiring admission to ICU over a ten year period (Table 5).[44] This may help clinicians to risk-stratify patients and identify those most at risk of requiring an active airway intervention. It has also been suggested patients presenting to the emergency department with head and neck oedema may benefit from flexible fibreoptic laryngoscopy to identify the extent of oedema.[45]

Other suggested therapies for treating ACE inhibitor angioedema, such as FFP and C1 esterase concentrate, have limited study data. Again, the main body of
Evidence is currently from case reports. No randomised control trials have been published comparing icatibant to these therapies. FFP contains multiple enzymes that degrade bradykinin, yet no prospective trials have looked at its use in ACE inhibitor angioedema. Successful use has been reported in several case reviews.[46-50] Whilst FFP has limitations, including viral transmission, fluid overload and is unsuitable as an out-of-hospital treatment, its relative availability and overall safety profile suggests it could be a therapeutic option.

Conclusions

Icatibant is now available as an easily used treatment in certain forms of angioedema. Its use in severe HAE and ACE inhibitor angioedema appears to be supported by the small-scale data available. It remains expensive and high quality randomised control trials comparing its use to other therapies are absent.

If available, icatibant 30 mg subcutaneously may be a viable treatment in attacks of HAE, especially in the emergency setting when a patient’s airway is threatened. Current evidence suggests more rapid improvement than with oral tranexamic acid, however, it is unclear whether it is superior to other available treatments, such as C1 esterase inhibitor concentrate, ecallantide or human plasma.

Its use in ACE inhibitor angioedema is also theoretically strong but evidence is limited. Case series and a single phase II randomised trial suggest efficacy in comparison to steroids and antihistamines, but no published trial evidence is available comparing it to FFP or other novel medications. The results of the first phase III randomised control trial are expected shortly.

Table 5. Ishoo Classification for Monitoring Severity of Upper Airway Oedema [44]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical findings</th>
<th>Disposition</th>
<th>Airway intervention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Facial rash, facial oedema, lip oedema</td>
<td>Home or admission</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate oedema</td>
<td>Home or admission</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>Lingual oedema</td>
<td>Intensive Care Unit</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>Laryngeal oedema</td>
<td>Intensive Care Unit</td>
<td>24</td>
</tr>
</tbody>
</table>

References

10. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis


39. A Multicenter, Open-Label, Non-Randomized Study
to Assess the Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Administration of Icatibant in Children and Adolescents With Hereditary Angioedema [Internet]. Available from: http://adisinsight.springer.com/trials/700242659


42. CAMEO A study evaluating the safety and efficacy of icatibant as a treatment of Angiotensin-Converting Enzyme Inhibitor (ACE-I) induced angioedema in adults [Internet]. Shire; [cited 2015 Nov 3]. Available from: https://clinicaltrials.gov/show/NCT0191980


