NHS Commissioning Board

Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema

April 2013

Reference: NHSCB/B09/P/b

THE NHS CONSTITUTION
the NHS belongs to us all

NHS Commissioning Board Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema

First published: April 2013

Prepared by the NHS Commissioning Board Clinical Reference Group for

Allergy and Immunology

First published April 2013
Published by the NHS Commissioning Board, in electronic format only.

Contents

Policy Statement

The NHS Commissioning Board (NHS CB) will commission treatments for acute attacks in hereditary angioedema in accordance with the criteria outlined in this document.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

Hereditary angioedema (HAE) is a rare condition, arising from a genetic deficiency of C1-inhibitor, a regulator of inflammatory pathways. At times of physiological or psychological stress, people with HAE have insufficient functional C1-inhibitor to regulate inflammatory pathways, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings.

All clinical and consensus opinion agree that early treatment with C1-inhibitor replacement therapy is the only appropriate treatment for severe HAE attacks. Practice varies in different countries but in the UK such treatment is reserved for severe attacks causing intolerable pain or risk of suffocation from airway obstruction, and in individuals judged to be at high risk of progression to that state because of the severity and/or frequency of their swellings. Less commonly, planned single dose prophylaxis is used to cover risk of fatal angioedema during selected surgical/dental or obstetric procedures judged to be a high risk for airway obstruction.

1. Introduction

Hereditary angioedema (HAE) is a rare condition, arising from a genetic deficiency of C1-esterase inhibitor, also called C1-inhibitor, a regulator of inflammatory pathways. Most people with HAE have low concentrations of C1-inhibitor (HAE Type I); around 15% have normal or high concentrations of non-functional C1-inhibitor protein (HAE Type II). Acquired angioedema (AAE) is essentially HAE which has occurred later in life due to an autoimmune process usually triggered by a tumour, it is included as part of HAE for the purposes of this definition. It is a much rarer condition which may represent 10% of the C1inhibitor deficient population, but many of these people may be cured and will not need to use the acute treatments described in this policy. Most people with AAE are effectively cured by treating the underlying condition which causes the syndrome and have very few if any attacks; a few continue to be at risk. Patients who cannot be cured are treated in a similar way to HAE, because the swellings are mostly due to dysfunctional or absent C1inhibitor in the same manner as HAE. The condition is so rare that there is not and is never likely to be subjected to controlled trials comparing treatment strategies and it is clinically appropriate that they are not denied access to the same treatments as HAE. In the rest of this document HAE will mean (HAE and AAE)

At times of physiological or psychological stress, people with HAE have insufficient functional C1-inhibitor to regulate inflammatory pathways, resulting in localised oedematous swellings. These can affect any part of the body but most commonly affect subcutaneous tissue, causing swellings of the limbs, face, trunk or genitals, and the mucous membranes of the gastro-intestinal tract. Less than 10% of episodes involve the oral mucous membranes; angioedema of the brain, joints and abdominal viscera occur less often [1]. Patients may have swellings occurring simultaneously at more than one site.

Most episodes result in reversible effects lasting between one and five days. Swellings, which develop over several hours, are often preceded by a period of up to 16 hours involving erythema marginatum (prodromal transient pink rings on the skin), fatigue or local discomfort. Peripheral swellings are usually moderately painless. Intra-abdominal swellings generally start with low-level discomfort, abdominal distension and nausea, before progressing to more severe pain with vomiting or diarrhoea. Symptoms are at their maximum intensity for up to twenty-four hours before spontaneously resolving in a further day. Facial swellings affect approximately half of patients with HAE. These may involve severe swelling and carry significant risk of asphyxiation from extension to the larynx if untreated.

The number of people in the UK with C1 INH deficiency is not known, but based on an estimated incidence of 1:50,000 for HAE and 1:500,000 people for AAE, there are likely to be about 1000-1,500 affected people in the UK(15).

The angioedema that characterises HAE develops over hours and it may affect any part of the body, but if it involves the larynx it is potentially life threatening. Swelling involving the viscera is severely incapacitating and can be clinically indistinguishable from acute surgical emergencies such as appendicitis, where as involvement of the hands or the feet often prevents a patient from being able to do their job. An acute episode of angioedema can require the patient to attend A&E and in some cases a hospital or even an ITU admission is necessary. However, because these conditions are rare and unfamiliar to non-specialist medical staff patients frequently report long

delays while senior assistance is sought and sometimes inappropriate treatment is administered [15].

The degree to which healthcare commissioners are prepared to fund the relatively expensive treatments is reported to be variable by clinicians and patients. There is evidence that treatment administered very early in an attack is more effective, and for this reason, and because it precludes the need to attend A&E, many patients prefer to self-administer their acute treatments at home. However, not all patients have access to a centre with specialist nurses able to provide and support this service. Hence, the treatment available to a patient with C1INH deficiency depends on where they happen to live [5] and the availability of support for home care through Specialist Immunology (or allergy) centres with the necessary facilities.

2. Definitions

C1-inhibitor, injected intravenously, is a blood product, extracted from pooled donated plasma, which is then purified to eliminate the risk of contamination with pathogens, especially blood-borne viruses. Two forms of C1-inhibitor derived from humans are licensed in the United Kingdom: Berinert®, a highly purified, virus-inactivated C1-inhibitor concentrate, and Cinryze®, a newer product which uses cryoprecipitation, ion-exchange chromatography and polyethylene glycol precipitation nano-filtration to eliminate viruses.

Conestat alfa (trade names Ruconest®, Rhucin®), is a form of C1-inhibitor extracted from the milk of genetically modified rabbits. This eliminates the risk of viral contamination from human plasma.

Icatibant, (Firazyr®) by contrast, is a synthetic peptide which blocks the bradykinin-2 receptor, thus mitigating the increase in capillary permeability which is a near-final stage in the pathogenesis of HAE. Unlike the C1-inhibitors, icatibant is injected subcutaneously.

The C1-inhibitors and icatibant are licensed for the treatment of acute attacks of HAE, but only Cinryze is licensed for prophylaxis. Icatibant is not suitable for prophylaxis due to its short half-life. Berinert®, Cinryze® and icatibant are all licensed for self-administration.

3. Aim and objectives

The aim of this policy is to describe the indications that the NHS Commissioning Board will approve the use of injected treatments for acute severe attacks in Hereditary Angioedema (all ages) due to C1inhibitor deficiency/dysfunction and for acute prophylaxis for surgical/obstetric/dental interventions where there is a risk of procedure induced morbidity/mortality

This policy does not apply to the more common and different condition called idiopathic angioedema which is not caused by C1inh deficiency/dysfunction.

4. Criteria for commissioning

1. Any patient with HAE/AAE will be eligible for access to acute treatment with the specified drugs for an HAE/AAE patient under care of specialist centre as defined in the Immunology Specialist Service Definition – drug costs for emergency use in other hospitals will be reimbursed through the Specialist Centre

2. C1inhibitor replacement or Bradykinin receptor antagonists will be funded (via home treatment where clinically appropriate) for:
    a. Acute attacks of HAE/AAE of sufficient severity to require admission/injected treatment on clinical and risk assessment (e.g. pain due to internal swelling or any risk of blockage of the airway)Administration for prophylaxis in HAE/AAE patient undergoing planned surgery, obstetric (including pregnancy) or dental work or similar trauma with a risk of upper airway blockage (intubation or trauma to mouth/throat) or significant morbidity or mortality risk from uncontrolled swellings.

The product with the lowest procurement cost should be used unless otherwise clinically indicated.

3. Icatibant will be available as an alternative to C1inh where suitable for the patient, dependent on clinical judgement, who meet the following criteria:
    a. Are unsuitable for C1inhibitor replacement because of adverse reactionsor ineffectiveness of C1inhibitor
    b. For home treatment, where the patient meets the criterion for home self-administered therapy of acute attacks, but is unable to successfully administer the intravenous C1inhibitor because of inability to master the technique or inadequate venous access or other barriers
    c. Where the Specialist clinician determines that Icatibant is the most suitable or cost-effective preparation for the patient
4. Recombinant C1inhibitor (Ruconest, Conestat alpha) will be available for use where there is a contraindication to the use of C1inh derived from blood products (for obstetric, religious or medical reasons) or where the Specialist determines that it will be more cost effective or clinically effective than the alternatives.

Although there is some evidence to suggest that prophylaxis has a place in the management of a severe subset of patients, long term regular prophylaxis with any of these products will currently require prior approval by an Individual Funding Requestor Group Prior Approval from commissioners where there is a clinical indication for its use, and the evidence for clinical and cost-efficacy can be reviewed for future iterations of the policy.

5. Patient pathway

Initial referrals may have originated from a variety of clinicians. Most of these referrals would be via GPs to secondary care and then onwards to Specialist Immunology or Allergy Centres.

Once the diagnosis of C1inhibitor deficiency is established the patient will have been given information on the condition, an emergency treatment plan, and training in the circumstances and use of rescue medication and how to recognise attacks of sufficient severity to require C1inh or Icatibant treatment as part of their individualised risk assessment and treatment plan.

Prophylactic treatment with attenuated androgens will have been instituted where the patient is symptomatic. Asymptomatic patients may receive no prophylactic treatment in the absence of known triggers, but will be given prophylaxis for risky procedures such as dental extractions or during surgical/obstetric procedures. In the UK Tranexamic acid is generally used only where attenuated androgens cannot be tolerated or are contraindicated, or used as an additional treatment to attenuated androgens where control is poor.

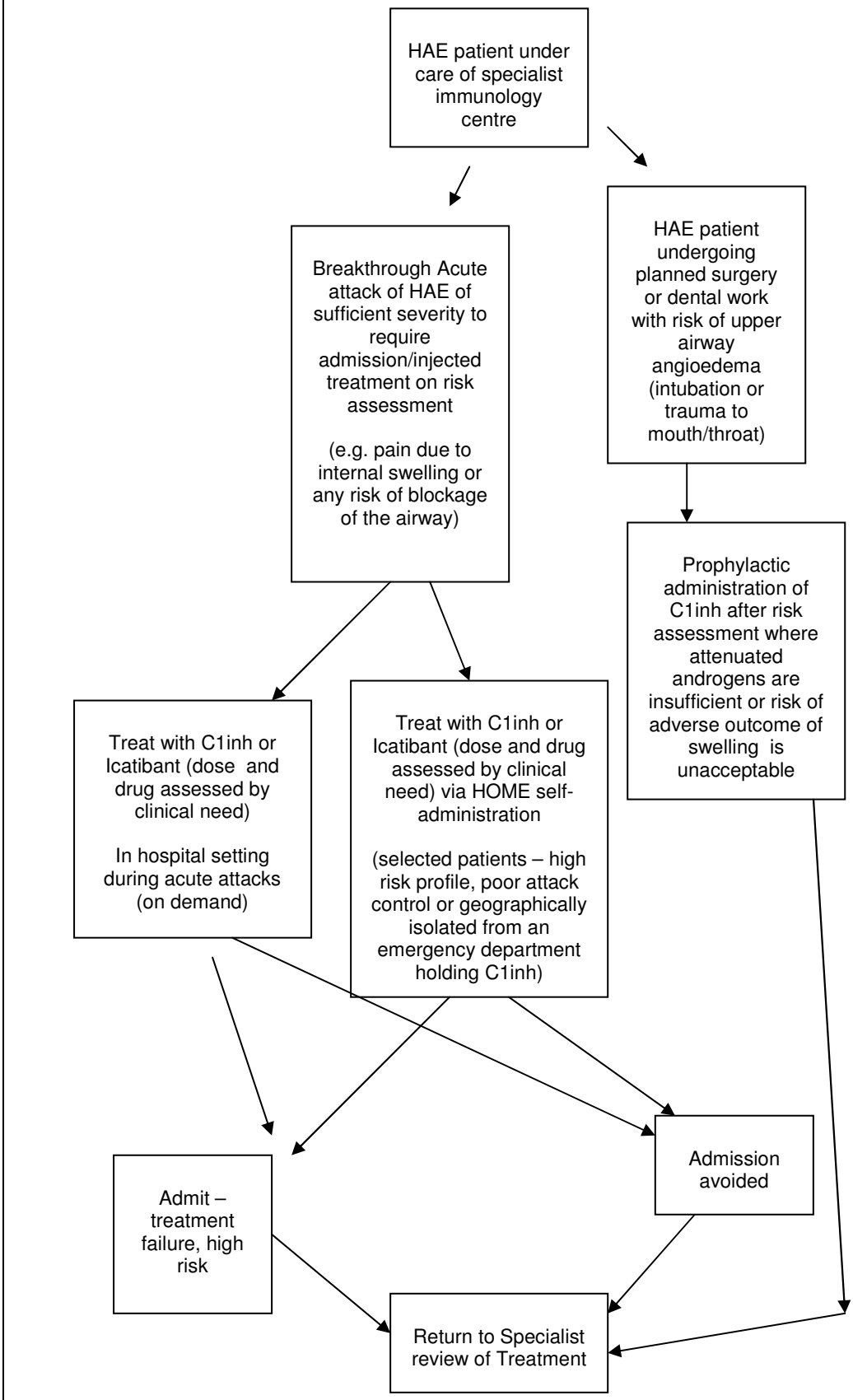
Treatment of mild/moderate attacks vary, but increasing attenuated androgens, adding in Tranexamic acid and/or non-steroidal painkillers are often used to attempt to ameliorate the symptoms until natural resolution occurs although there is evidence that they have little effect in acute treatment [14], although they do have a weak effect in prophylaxis.

Patients attend Accident and Emergency departments (preferably of specialist units, but in reality the nearest accessible unit) for injected therapy when attacks of sufficient severity to cause debilitating pain or risk to the upper airway occur, or if trained and in possession of C1inhibitor or Icatibant at home, they will administer treatment at home. However not all emergency units carry C1inh readily available in the hospital and delays in obtaining appropriate treatment are common.

It is well recognised that delay in treatment is associated with adverse outcomes (not uncommon in A&E) and early treatment with better outcomes.

Trauma is often associated with acute attacks of angioedema, and fatal outcomes from Dental work are well-recognised. Therefore single dose prophylaxis is commonly used where the patient has uncontrolled attacks or an increased risk of airway obstruction due to the nature of the intervention.

Regular prophylaxis in patients who fail maximal oral prophylactic therapy and who are judged to have sufficiently severe or frequent attacks to potentially justify time-limited regular injected prophylaxis are not included in this policy, and an IFR request specific to the patients circumstances would need to be made for each instance. These very severe cases are thankfully relatively rare, but there is an increasing body of evidence to suggest that prophylaxis is clinically effective and cost-effective in some patients with repeated use of rescue medication for frequent attacks and this evidence will need to be reviewed for future iterations of this policy


HAE patient under care of specialist immunology centre
Breakthrough Acute attack of HAE of sufficient severity to require admission/injected treatment on risk assessment
(e.g. pain due to internal swelling or any risk of blockage of the airway)
HAE patient undergoing planned surgery or dental work with risk of upper airway angioedema (intubation or trauma to mouth/throat)
Prophylactic administration of C1inh after risk assessment where attenuated androgens are insufficient or risk of adverse outcome of swelling is unacceptable
Treat with C1inh or Icatibant (dose and drug assessed by clinical need)
In hospital setting during acute attacks (on demand)
Treat with C1inh or Icatibant (dose and drug assessed by clinical need) via HOME self-administration
(selected patients – high risk profile, poor attack control or geographically isolated from an emergency department holding C1inh)
Admission avoided
Admit – treatment failure, high risk
Return to Specialist review of Treatment

6. Governance arrangements

Treatment should be directed by Specialist physicians who are experienced in the diagnosis and management of patients with hereditary angioedema and who are working centres that have sufficient caseload to maintain expertise and deliver the elements of the Immunology Specialised Services commissioning specification.

7. Epidemiology and needs assessment

HAE affects around 1 in 50,000 to 100,000 people of any ethnic group and of either gender. Although the deficiency is life-long, attacks rarely occur before two years of age and are less frequent before adolescence. Mean age at onset is between eight and twelve years.

Incidence of swellings varies from more than one per week to less than one per year. In a random sample of 103 patients with HAE, with or without long term prophylaxis, the mean frequency of angioedema was once every 45 days [4].

Death due to asphyxiation is a serious risk in patients with previously undiagnosed HAE and in patients who do not receive treatment for a laryngeal attack. Estimates of the frequency of serious adverse events vary widely. A review of HAE published in the 1960s estimated that 25% of HAE patients died from asphyxiation [5]. A later study by Bork et al in 1999, involving a retrospective survey of 58 patients in Germany over the previous 50 years, reported that 28 patients (40%) had died from asphyxiation at an average age of 39 years [6].The study also found that the risk of asphyxiation had no relationship to the number of frequency of previous episodes of laryngeal oedema.

A DH Horizon scanning review [15] determined that the average attack frequency was 12 per year and that 5 patients had died in the UK from angioedema in 2008. Approximately a quarter of swellings are sufficiently severe to require rescue medication like C1inhibitor or Icatibant [14].

Factors which may play a part in determining the frequency and severity of swellings include variations in mutations of the C1-inhibitor gene, environmental factors such as emotional stress, inflammatory stimuli, exposure to infections, low level trauma and variations in concentrations of sex hormones. Attacks can also be precipitated by angiotensin-converting-enzyme inhibitors, surgery and dental work.

8. Evidence Base

In the modern NHS cost savings are demanded that require difficult decisions to be made. A treatment that is supported by high quality evidence such as meta-analyses of randomised controlled trials is likely to be favoured over treatments with less evidence behind them. It is much more difficult to generate the same statistical evidence of efficacy in rare diseases compared to common diseases because there are insufficient patients available to power the clinical trials. In the case of HAE/AAE this problem is further compounded by the fact that the frequency, severity and duration of angioedema attacks are inherently variable and there are often few objective, measurable signs of disease activity. For these reasons, drugs are sometimes prescribed "off license" and patients with C1INH deficiency lose out in the fight for limited funds compared to patients with more common, more easily defined diseases. There is no equity in this approach and there remains a risk that evidence based treatments for acute attacks are not available to all sufferers in all commissioning areas. The social and financial costs of these patients being intermittently unable to perform their role activities has not been well defined, but the risk of avoidable death remains

Consensus international and UK guidelines that pertain to the diagnosis and management of HAE have been produced and there are also consensus guidelines that cover home therapy and the gynaecologic and obstetric management of female patients with HAE. The international consensus guidelines have recently been revised to include evidence-based recommendations and this process is likely to continue as the results of on-going clinical trials are published [16-20].

C1 esterase inhibitor

There have been three randomised placebo-controlled trials of different preparations of C1-inhibitor licensed in the UK for the treatment of HAE: one RCT (IMPACT1) of Berinert [7], one RCT of Cinryze [8] and one RCT of conestat alfa [9].

A fourth trial reported in 2 papers Waytes et al 1996, Kunschak et al 1998 showed benefit of a vapour-treated C1 inhibitor vs. placebo in acute treatment (and for prophylaxis)

IMPACT 1 compared two doses of Berinert with each other and with placebo [7].It indicated that Berinert at a dose of 20 U/kg begins to relieve symptoms more quickly than placebo and resolves them fully sooner. Compared with placebo, the higher dose brought the beginning of symptom remission forward by about an hour on average. The results for the lower dose of 10 U/kg are less clear, with a smaller effect on onset of symptoms, and a longer time before symptoms resolved completely than with placebo.

Zuraw et al conducted a trial of Cinryze [8] similar in design to IMPACT-1, comparing speed of recovery from an acute attack with the drug and with placebo. The onset of symptomatic relief was about two hours earlier with Cinryze than with placebo.

Zuraw was also the first author of a trial with two linked components examining the effect of recombinant human C1-inhibitor, conestat alfa, in acute attacks of HAE [9]. The trials were in Europe and North America and appear to be identical except for a difference in the lower age limit, and the addition of a lower dose arm of conestat alfa in the North American element. They compared recombinant C1-inhibitor at doses of 50 U/kg and 100 U/kg with placebo and reported earlier remission of symptoms with

the higher dose than with the lower dose, both being more effective than placebo.

Icatibant

There have been two systematic reviews of the treatment of HAE with icatibant [10] [11]. The search dates are not stated but were in late 2011. Both reviews included the same three randomised trials and we found no randomised trials not included in these reviews. All the trials were well-designed, analysed and reported, and all used an intention-to-treat analysis.

The reviews included three trials of icatibant for the treatment of an acute attack of HAE: FAST-1 [12], FAST-2 [12] and FAST-3 [13]. In all these trials, icatibant was administered by a healthcare professional in a hospital or clinic, not by the patient at home.

As in the trials of C1-inhibitor in the treatment of acute attacks, participants' eligibility was assessed initially, then they were asked to return to the hospital within six hours of the onset of an attack of HAE of at least moderate severity. They were then randomised and treated with icatibant or the control treatment. Rescue therapy with C1-inhibitor concentrate, anti-emetic agents or opiates was permitted, but withheld as long as possible, ideally for at least eight hours after administration of the study drug.

FAST-1 was a placebo-controlled trial. The primary outcome measure was the median time to the onset of relief of the index symptom. On this measure, the trial gave a non-significant result ($P = 0.14$), though there were significant differences in favour of icatibant on other measures (median time to regression of symptoms according to patient 0.8 h v 16.9 h, $P < 0.001$, and median time to overall patient improvement according to doctor 1.0 h v 5.7 h, $P < 0.001$). Rescue medication was used more often in the first twelve hours after taking placebo than after taking icatibant. Post-hoc analysis indicated that 50% relief of all symptoms was attained significantly earlier with icatibant than with placebo, and that this difference was larger if those participants who took rescue medication were excluded from analysis.

The authors argued that the confounding effect of rescue medication, coupled with possible lack of statistical power, explained the lack of statistical significance of their result, rather than icatibant's lack of efficacy.

FAST-2 was a comparison of icatibant with tranexamic acid, at an appropriate dose. Tranexamic acid is a fibrinolytic agent administered orally and licensed for use in HAE FAST-2 reported that relief of symptoms occurred sooner after icatibant than after tranexamic acid (median time to onset of symptom relief 2.0 hours v 12.0 hours, $P < 0.001$), and that the use of rescue medications was similar in the two arms of the trial.

The FAST-3 trial had the same entry criteria and randomised interventions as FAST-1, but a different primary endpoint: median time to 50% relief of cutaneous or abdominal, or laryngeal symptoms, rather than time to onset of relief of the index symptom. This trial reported earlier achievement of the endpoint with icatibant than with placebo (median time to 50% relief of cutaneous or abdominal symptoms 2.0 hours v 19.8 hours, $P < 0.001$).

Recombinant human C1-inhibitor has a half-life after injection of about three hours, compared with at least twenty hours for the plasma-derived product. This has potential implications for dosing and treatment intervals, because an attack of HAE can last several days. However, none of the patients in the Zuraw et al trial of the recombinant product reported a relapse after treatment.

None of the trials of the treatment of acute attacks of HAE reported any incidence of complications of HAE such as asphyxia, brain damage from cerebral hypoxia or death.

No serious side effects have been associated with C-1 inhibitor; in the randomised trials, it was associated with fewer adverse reactions than placebo. There was no significant development of antibodies either to rabbit proteins or to C-1 inhibitor in people exposed to the recombinant product. There is a theoretical risk of infection with blood-borne viruses with Berinert and Cinryze, but no evidence that the extensive steps taken to decontaminate the product are not wholly effective.

The main reported side effects of icatibant are recurrent or worsening angioedema and injection-site reactions. The latter are common but not serious, and resolve within a few hours. They may have compromised blinding in the FAST trials.

Cost effectiveness

There have been two health economic analyses of icatibant. There have been no analyses of the use of other drugs.

The first was a cost minimisation analysis carried out by the manufacturer of icatibant for the Scottish Medicines Consortium [11]. It compared the self-administration of icatibant at home with the administration of Berinert in an accident and emergency department. Based on an unpublished indirect comparison, the model assumed equivalent effectiveness for icatibant and Berinert. It relied on a commercial-in-confidence patient access scheme in order to lower the cost of icatibant, and there were other relevant data which were also not disclosed at the request of the manufacturer of icatibant.

Based on this undisclosed price, icatibant was estimated to lead to a saving of £813 per attack, mainly due to differences in drug acquisition, monitoring, administration training and adverse event costs. This led the Scottish Medicines Consortium to accept icatibant for use in NHS Scotland.

The model itself is unpublished, as are the inputs, including most relevantly the discount on the list price of icatibant. This makes it impossible to assess the reliability of the analysis, and its relevance to the NHS in England, where locally negotiated procurement discounts may not be available, and vary where they exist.

The All Wales Medicines Strategy Group has also published a review of icatibant, with a health economic analysis which appears to be the same as the one used in Scotland [10]. However, the Welsh review contains more information on the cost-minimisation analysis, though it is still reliant on an unpublished discount to the list price. The manufacturer's model presented no clinical data about the need for attendance at A&E following self-administration of icatibant (for example if the symptoms do not improve, or involve the larynx) and need for admission for overnight

stay following A&E attendance. The sources of the probabilities of these events are not discussed in the company submission and they appear not to be tested in any sensitivity analyses. The model also apparently ignores costs arising from the licensing requirement that a healthcare professional must inject the first dose of icatibant that a patient receives.

Based on the manufacturer's model, home self-administered treatment with icatibant was almost £600 less expensive than treatment in Berinert in an accident and emergency department. However, this result was sensitive to assumptions about the number of vials of Berinert required. The manufacturer's preferred assumptions were based in the weight distribution of patients in the FAST trials. Expert opinion suggested fewer vials would be needed, reducing the incremental cost of Berinert to about £180; based on an audit of Berinert use in hospitals in Wales, Berinert would cost about £200 *less* than icatibant. The All Wales Medicines Strategy Group also recommended icatibant as an option for the treatment of HAE in NHS Wales.

Cost impact

The list prices of drugs available for the management of acute episodes of HAE are shown in the table below together with the recommended dose and cost for a person weighing 70kg.

Drug	**Price**	**Dose**	**Dose for 70kg person**	**Cost for 70kg person**
Berinert®	500-unit vial £550	20 units/kg	1500 units = 3 vials	£1650 for 3 vials £1100 for 2 vials
Cinryze®	500-unit vial £668	2 to 4 vials depending on response	2 to 4 vials	£1336 to £2672
Conestat alfa	2100-unit vial £1400	100 units/kg (max 4200 units)	4200 units = 2 vials	£2800
Icatibant	3 ml prefilled syringe (10 mg/mL)	30mg/3ml	30mg/3ml	£1395

Source: www.bnf.org, accessed 14 June 2012

These figures indicate that the cost of treating a patient of average weight 70kg at the recommended dose may be lowest with Cinryze. Icatibant is slightly more expensive, followed closely by Berinert, with conestat alfa substantially the most expensive.

However these figures do not reflect the reality that many UK physicians in the UK will use an initial dose of 1000 units of C1inh (2 vials) with good effect where this is clinically appropriate and the cost comparisons may not be wholly valid in clinical practice, nor do they take account of VAT and other savings which can accrue from

home administration for some products. While 1000 units for the average adult is lower than the recommended doses, it is often effective and the number and dose administered to patients is individualised after risk assessment and assessment of response to initial treatment. The evidence is of limited utility to judge the relative efficacy of different treatments as there is little reliable head-to-head comparison of clinical efficacy of the different acute treatment options, and all are compared to tranexamic acid treatment which is not a recommended first line treatment for severe or life-threatening swellings. Furthermore many of the episodes treated in some studies may have had a different severity profile from that used in general UK clinical practice.

The prevalence of HAE is 1 in 50,000 to 100,000 per year, indicating about 500-1000 residents with the diagnosis in England[3]. Attack frequency is not known with certainty, but the Welsh analysis assumed three to six per patient per year. This gives a likely range of about 1500 to 6250 attacks per year in England. Further uncertainty is introduced by the unknown body weights of patients, and the fact that not all attacks will be treated with parenteral drugs. Assuming an average weight of 70kg and that three-quarters of attacks receive parenteral treatment, the annual drug costs without vial-splitting would be approximately:

Berinert®: £1.8m to £7.7m for 3 vials (if reduced to 2 vials to reflect commonly used lower initial dose of 2 vials this would range from 1.2 million to 7.7 million, Vial splitting is obviously impractical)

Cinryze®: £1.5m to £6.3m (for 2 vials)

Conestat alfa: £6.3m to £26.3m

Icatibant: £1.6m to £6.5m

This analysis estimates the cost of treatment of acute episodes only and ignores all non-drug costs. These estimates of usage can be double checked by triangulation utilising the following data:

In 2011/12 £3.7 million was spent on C1inhibitor in England and £608,000 on Icatibant (reference source please Malcolm)

If the average dose of C1inh was 1000 units and the main product Berinert then this equates to a probable total of 3,364 treatment episodes at 1000 units per patient or 2,643 at 1,500 units (assuming all adult patients).

There would be an additional 436 treatment episode with Icatibant.

There were therefore actually between 3,079 to 3,800 acute severe episodes of HAE/AAE recorded in England in 2011/12 which met the current clinical threshold for treatment with injectable C1inh or Icatibant.

There were approximately 1257 admissions in the UK for HAE in 2005/6 and 5 deaths in 2008 (15) suggesting that just under half of acute HAE presentations result in admission if that figure remained constant (each admission usually lasting 3-5 days).

A QIPP has been proposed to ensure that home treatment is offered to those patients who are eligible on the basis of disease severity or geographical isolation from centres with appropriate expertise and to examine cost-efficacy of home vs. hospital treatment and an evidence review is currently underway. Early treatment is likely to be associated with avoidance of admission and reduced severity.

9. Rationale behind the policy statement

Historically, the aim in treating HAE was to minimise the frequency and severity of attacks with prophylactic medication and to provide hospital-based management of acute symptoms when they arose. Patient support groups advocate an approach whereby they can manage their own symptoms proactively such that their personal safety is maintained, with minimal disruption to them living healthy and productive lives -this is the standard of care in haemophilia, an equally rare disease similarly characterised by need for unpredictable emergency treatment. Effective treatments for C1INH deficiency are available to enable this approach. However, it is our experience that the degree to which healthcare commissioners are prepared to fund the relatively expensive treatments is variable. There is evidence that treatment administered very early in an attack is more effective, and for this reason, and because it precludes the need to attend A&E, many patients prefer to self-administer their acute treatments at home. However, not all patients have access to a centre with specialist nurses able to provide and support this service. Hence, the treatment available to a patient with C1INH deficiency depends on where they happen to live [15, 17-20].

All clinical and consensus opinion agree that early treatment with C1inhibitor replacement therapy is the only appropriate treatment for severe HAE attacks. Practice varies in different countries but in the UK such treatment is reserved for severe attacks causing intolerable pain or risk of suffocation from airway obstruction, and in individuals judged to be at high risk of progression to that state because of the severity and/or frequency of their swellings. Less commonly, planned single dose prophylaxis is used to cover risk of fatal angioedema during selected surgical/dental or obstetric procedures judged to be a high risk for airway obstruction.

To fail to give C1inh in such life threatening or preventable circumstances would almost certainly be judged clinically negligent. All such patients should have access to C1inh or Icatibant treatment and a commissioning policy would reduce any variations where automatic access to such treatment in appropriate clinical circumstances is not available. The policy enshrines current practice, eliminates IFR requests, ensures equity of access to gold standard treatment and should have no major effect on total drug usage. An alternative C1inh preparation which is not a blood product will be needed to ensure equity of treatment for individuals unable to receive blood products for religious or clinical reasons.

Home administration of treatment would be facilitated by the policy, opening the possibility of QIPP cost savings, usage monitoring and integrated care. This would also eliminate the clinical risk that the nearest A&E or hospital may not have C1inh or Icatibant available in a timely manner for treatment, and would remove or ameliorate the logistical difficulties of ensuring a geographical network of pharmacies with appropriate stocks of C1inh at all times. This would also provide a major improvement in the management of HAE patients.

The exact place of Icatibant and C1inh relative to each other in the management of HAE/AAE has yet to be established, but there is greater cumulative clinical experience with C1inhibitor treatment in the UK. The evidence shows that Icatibant is effective in treating acute attacks, and the costs of the drug currently appear similar to C1inhibitor. However the half-life, mode of action is different. The fact that the route of administration is subcutaneous rather than intravenous will facilitate self-

treatment in some patients who are unable to inject intravenously and therefore would be denied access to home treatment. Most acute episodes in England are currently treated with C1 inhibitor according to the data above. Price competition or national contracting arrangements similar to that of immunoglobulin may affect future costs and usage as may additional evidence on best management, and this should be kept under regular review.

10. Mechanism for funding

Through the relevant Area Team.

11. Audit Requirements

Trusts will be expected to audit the use of these agents as outlined in the service specification.

Additional evaluation will be provided by the proposed QIPP.

12. Documents which have informed this policy

1. Angostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992; 71: 206-15.

2. Bowen T, Cicardi M, Farkas H et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy, Asthma & Clinical Immunology* 2010; 6: 24.

3. Cicardi M, Bork K, Caballero T et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012; 67: 147-157.

4. Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet* 2012; 379: 474-81.

5. Landerman NS. Hereditary angioneurotic edema. I. Case reports and review of the literature. *J Allergy* 1962; 33: 316-29.

6. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc.* 2000; 75(4): 349-354.

7. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009; 124: 801-8.

8. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010; 363: 513-22.

9. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010; 126: 821-827.

10. All Wales Medicines Strategy Group. AWMSG Secretariat Assessment Report – Advice no. 0512. Icatibant (Firazyr®) 30 mg solution for injection. Cardiff: 2012.

11. Scottish Medicines Consortium. Icatibant acetate, 30mg, solution for injection in pre-filled syringe (Firazyr®), SMC No. (476/08). Glasgow, 2012.

12. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; 363: 532-41.

13. Lumry WR, Li HH, Levy RJ, Potter PC, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011; 107: 529-37.

14. Zanichelli,A, Vacchini R, Badini, M, Penna, V, and Cicardi, M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: A 21-month prospective study in a cohort of 103 patients. Allergy 2010.

15. National Horizon scanning centre: Conestat alfa (Ruconest) for acute hereditary angioedema. June 2010.

16. An Integrated Care Pathway for C1 Inhibitor deficiency (Hereditary Angioedema (HAE) and Acquired Angioedema (AAE). Hereditary Angioedema Integrated Care Pathway Steering Group. *Evidence Base, December 2011. Manson, A, Longhurst, H. Barts and the London NHS Trust (unpublished)*

17. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):24

18. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, Fay AC, Longhurst HJ, Morrison L, Price A, Price M, Watters D. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005 Mar;139(3):379-94. Review. Erratum in: Clin Exp Immunol. 2005 Jul;141(1):189-90

19. Longhurst HJ, Farkas H, Craig T, Aygören-Pürsün E, Bethune C, Bjorkander J, Bork K, Bouillet L, Boysen H, Bygum A, Caballero T, Cicardi M, Dempster J, Gompels M, Gooi J, Grigoriadou S, Huffer U, Kreuz W, Levi MM, Long J, Martinez-Saguer I, Raguet M, Reshef A, Bowen T, Zuraw B. HAE international home therapy consensus document. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):22.

20. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, Björkander J, Bork K, Bygum A, Cicardi M, de Carolis C, Frank M, Gooi JH, Longhurst H, Martínez-Saguer I, Nielsen EW, Obtulowitz K, Perricone R, Prior N. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. J Allergy Clin Immunol. 2011 Dec 24. [Epub ahead of print]

13. Links to other policies

The mechanism operated by the NHSCB for funding requests outside of the clinical criteria in this policy is yet to be finalised

14. Date of Review

April 2014

References

All studies that have informed this policy are cited in the policy and listed in section 12.