NHS England

Evidence Review:
Plasma-derived C1-esterase inhibitor for Prophylactic treatment of hereditary angioedema (HAE) types I and II

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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).

Intravenous administration of reconstituted plasma-derived C1-inhibitor (human) replaces the C1-inhibitor regulatory protein. In normal individuals, this protein controls enzyme cascade reactions so that uncontrolled swelling of the subcutaneous and submucosal tissues do not normally occur. In HAE, the absence of a functional control protein leads to episodes of uncontrolled swelling.

Swellings can be disabling, cause severe pain and can be fatal if occurring in the airways. Most patients require C1-inhibitor, or icatibant, as emergency treatment for acute clinically significant attacks and C1-inhibitor for short term (generally single dose) prophylaxis prior to known triggers which include, for example, dental work or surgery. For the majority of people with HAE, attacks are either infrequent or can be controlled adequately using oral prophylactic medications together with a plan to treat acute attacks as above.

A minority of people who experience two or more clinically significant attacks of swelling per week, for whom oral prophylaxis is not tolerated or is ineffective, may benefit from prophylactic C1-inhibitor injections on a regular basis to reduce the frequency of attacks and the need for emergency treatment.

There are several C1-inhibitors which are licensed for the treatment of acute attacks of HAE. However, Cinryze® is the only C1-inhibitor licensed for long-term prophylaxis.

2. Summary of results

The clinical evidence review sought to provide a response to two key questions:

Question 1. Is prophylactic C1-esterase inhibitor clinically effective in reducing the severity and frequency of HAE attacks for patients who are not responding, or are intolerant to oral prophylaxis (androgens or fibrinolytics) as evidenced by 2 or more clinically significant attacks per week?

Question 2: Is prophylactic C1-esterase inhibitor cost-effective as a prophylaxis to reduce the severity and frequency of HAE attacks for patients who are not responding (or are intolerant) to oral prophylaxis as evidenced by 2 or more clinically significant attacks per week?

A summary of the findings are set out below.

Question 1. Is prophylactic C1-esterase inhibitor clinically effective in reducing the severity and frequency of HAE attacks for patients who are not responding, or are intolerant to oral prophylaxis (androgens or fibrinolytics) as evidenced by 2 or more clinically significant attacks per week?

A review of the literature base on long-term prophylaxis with C1INH for HAE was undertaken. There was no RCT or case-control study specifically evaluating C1INH prophylaxis in patients failing oral prophylaxis with 2 or more acute attacks per week. There was one small cohort study that investigated C1INH prophylaxis in patients failing or intolerant of oral prophylaxis. Several studies investigated the efficacy of C1INH use in a wider HAE population and lend data supporting the general use of long-term prophylaxis for disease control.

In the small cohort study (Levi et al, 2006) evaluating the effectiveness of C1INH for prophylaxis of angioedema in HAE and AAE patients who had failed or were intolerant to oral prophylaxis, the C1INH dosing was a self-administered 1000 U of IV plasma-derived C1-inhibitor concentrate every 5-7 days (actual mean reported was 6.8 +/- 1 days). 12 patients with HAE or acquired angioedema were included. Patients were eligible for the study if their baseline attack rate despite oral prophylaxis or without prophylaxis due to intolerance was >1 attack per 10 days. The baseline attack rate in the study population was reported as 1 attack per 7.9 (+/- 2.0) days. Of the study participants, 5 were on prophylactic treatment with danazol and tranexamic acid at baseline, 6 were intolerant of danazol, and 1 had a contraindication to danazol use.

The mean age of the subjects reported was 38 +/- 12 years. Study subjects were followed-up for a mean of 3.5 years (range 1.6 - 4.3 years). Results showed a statically significant reduction in the number of angioedema attacks after the start of prophylaxis ($p<0.001$ for both HAE and acquired angioedema (AAE) patients, analysed separately). In the combined (HAE and AAE) prophylaxis group, the angioedema attack rate decreased from 4.0 to 0.3 attacks per month (no p-value reported). No serious adverse events were reported, and all adverse events were self-limited without the need for medical assistance. Limitations to the study include the small study size limiting the potential power of the study, the lack of reporting on methods for obtaining baseline attack rates (therefore, possibly retrospective patient self-reported which would create concern for potential recall bias), and the methods for obtaining attack rates during the treatment period through patient self-reporting (and therefore increasing the possibility for error and bias in this study).

It should be noted that many of the limitations are inherent to the disease and therefore expected: recruiting large populations for study in rare diseases is unlikely, and a lack of standard, objective criteria for evaluation of attacks lends to better acceptance of self-reported events (especially with consistency in evaluating / reporting of attacks before and after study intervention). Therefore, the results of this study are supportive of prophylactic treatment, but given the quality concerns of the study, this is considered only weak evidence. The authors were based in the Netherlands and reported no conflicts of interest.

In another study (Zuraw et al, 2012), a relatively large (given the rarity of HAE) nonrandomised open-label cohort study, 146 patients were evaluated for response to long-term nano filtered C1INH prophylaxis. Subjects were given long-term prophylaxis with C1INH every 3-7 days for up to 2.6 years. At baseline, almost a third of patients were taking prophylactic androgens. During the study, over half of those patients discontinued the androgen prophylactic therapy. A subgroup analysis of the patients who were able to discontinue androgen use entirely (23 subjects), revealed a reduction in attacks from a median rate of 3.00/month (interquartile range: 1.25-11.00) on androgens to 0.00 (interquartile range: 0.00-0.31) on prophylactic C1INH. Overall results of the entire study population demonstrated a decrease in the mean frequency of attacks from 4.7 +/- 5.2 to 0.47 +/- 0.83 per month ($p<0.001$). The study therefore concluded that C1INH use is efficacious in long-term prophylaxis of HAE attacks at a dose of 1000 units twice per week. Notably, once a week dosing also showed a positive, though weaker, benefit. Limitations of this study include the nonrandomised and open-label study design, the pre-treatment attack rate being estimated based on the patient's reported history (potential recall bias), and the allowance for variance in administration of the prophylactic doses (protocoled as every 3-7 days). Overall, this is a well conducted prospective cohort study with results that support the policy under review.

In a 2013 systematic review, Bork et al, 2013 noted 2 prospective cohort trials, 1 retrospective survey study, and 5 case reports examining long-term prophylaxis with C1INH. Two of the case studies reported successful long-term prophylactic therapy with C1INH in patients who had failed or had side effects to oral prophylaxis previously. However, it is unclear from these reports how many attacks per week they had before C1INH use or what level of control they had been able to obtain with the previous oral prophylaxis. The retrospective survey reported on two pregnant patients, for which androgen use is contraindicated. One of the prospective cohort studies reported good control of HAE attacks with C1INH use, however it is unclear if they were on an oral prophylactic regimen prior to C1INH use or not. The second prospective cohort study of 19 patients (Bork et al, 2011) contained a subgroup of 10 people who had previously been treated with danazol. However, acute attack severity with danazol use was not reported, nor was this subgroup analysed separately. Additionally, results were reported for the overall study population, which included patients who had crossed over from on-demand therapy only into the prophylactic group as well as patients who had begun the study in the prophylactic group. This heterogeneity makes interpretation of results difficult, but overall patients reported a decrease in the percentage of severe attacks from 93.3% to 3.8% by the end of the study with C1INH use (which was an average of 9 years). Additionally, 8 of the 14 patients in the prophylactic subgroup, reported a lower number of attacks per month in the final year of the study as compared to the time before C1INH prophylactic use.

In an open-label study (Reshef et al., 2013), the response of a 25 person cohort of HAE patients to long-term prophylaxis with C1INH over 8 weeks was evaluated. The study found that weekly administrations of 50 U/kg C1INH reduced the frequency of HAE attacks in study participants. The baseline attack rate of 0.9 attacks/week decreased to 0.4 attacks per week while on long-term prophylaxis with C1INH, with a 95% CI ranging from 0.28 to 0.56. Unfortunately, prior prophylactic drug use in this cohort of patients was not reported. The drug was also found to be safe and well tolerated. The key limitations of this study were the open-label design and the method of data collection on attack rate prior to study entry (patients' recollection), which create concern for the introduction of bias into the study.

In a 24-week cross over study (Zuraw et al., 2010), C1INH for prophylaxis, given as twice-weekly injections of 1000 units, significantly reduced the frequency of acute attacks (6.26 per 12-week period), as compared with placebo (12.73 per 12-week period). There were 3 patients on baseline androgen therapy in this study, and subjects were not required to discontinue their androgen therapy during the trial. This multi-centre, double-blind, randomised study was designed for 90% power. The primary endpoint results were statistically significant with a $p < 0.001$ reported. Secondary endpoints showed the subjects who received the C1-inhibitor concentrate also had significant reductions in both the severity and the duration of attacks, in the need for open-label rescue therapy, and in the total number of days with swelling. There were only 3 AEs and no SAEs considered possibly related to C1INH. This was a well designed study with low concern for bias, demonstrating the efficacy and safety of prophylactic use of C1INH over a 12 week period. Unfortunately, prior androgen or antifibrinolytics therapy and characterisation of disease severity on oral prophylaxis was not reported.

In addition to the above studies, two studies of HAE patient subgroups were noted on pregnant and paediatric patients. A small retrospective review (Baker et al, 2013) of outcomes experienced in pregnant women with HAE using C1INH was conducted as androgen therapy is contraindicated in pregnancy. Difference sources of data were used (3 studies and 1 compassionate-use program), and some patients only had acute treatment, while others had long-term prophylaxis with acute treatment as needed, and some patients began in an acute treatment only protocol but later transferred into a long-term prophylaxis protocol programme. There was no analysis done across the study patients, no statistical analysis of the results. However, given that androgens are generally contraindicated in pregnancy and concern for safety of antifibrinolytics during pregnancy, the reported safety outcomes in this study are encouraging. As well, efficacy outcomes were generally supportive of long-term prophylaxis with C1INH in pregnancy. Unfortunately, the strength of this evidence is low due to the weaknesses in study design.

In addition, in a post hoc analysis of data on paediatric patients from 4 prospective clinical trials of C1INH (Lumry et al, 2013), 2 trials were relevant to reviewing long-term prophylaxis treatment with C1INH. The placebo-controlled cross-over trial of long-term prophylaxis only contained 4 paediatric patients for inclusion in this article's analysis, while the open-label long-term prophylaxis study included 23 patients. Efficacy and safety results were supportive of long-term prophylaxis use with C1INH. In the cross-over trial, the mean number of attacks per 12 week period was 7.0 while on long-term prophylaxis versus 13.0 while on placebo. Additionally, the number of open-label rescue doses required was less in the long-term prophylaxis group, severity of attacks was unchanged, mean duration of attacks was less while on long-term prophylaxis, and mean duration of swelling was lower while on long-term prophylaxis. In the open-label extension prophylactic study, the median monthly attack rate before enrolment was 3.0 (range, 0.5-28.0) and decreased to 0.39 (range, 0-3.36) with long-term prophylaxis, with 87% reporting 1 or less attacks per month and 22% reporting no attacks during the study period.

The clinical evidence available suggests that the use of C1INH for long-term prophylaxis of acute attacks in hereditary angioedema is effective and safe. There is limited high quality data and a notable lack of comparative data. The evidence base should continue to be reviewed over time, as more data could become available.

Question 2: Is prophylactic C1-esterase inhibitor cost-effective as a prophylaxis to reduce the severity and frequency of HAE attacks for patients who are not responding (or are intolerant) to oral prophylaxis as evidenced by 2 or more clinically significant attacks per week?

The literature search revealed no studies on the cost-effectiveness of this intervention.

3. Research Questions

1. Is prophylactic C1-esterase inhibitor clinically effective in reducing the severity and frequency of HAE attacks for patients who are not responding, or are intolerant to oral prophylaxis (androgens or fibrinolytics) as evidenced by 2 or more clinically significant attacks per week?

2. Is prophylactic C1-esterase inhibitor cost-effective as a prophylaxis to reduce the severity and frequency of HAE attacks for patients who are not responding (or are intolerant) to oral prophylaxis as evidenced by 2 or more clinically significant attacks per week?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the appendix.

Appendix

Level	Design	Size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Endpoint Result	Reference	Complications noted	Benefits noted	Comments
2++	Systematic	N/A	Medline (1950 to December 31, 2011; In-Process other Non-Indexed Citations), EMBASE (1980 to December 31, 2011), Biosis Previews (1985 to December 31, 2011), CINAHL (1982 to December 31, 2011), and the Cochrane Library using Ovid. Grey literature and hand literature searches also. To be considered for inclusion, studies had to evaluate C1-INH (Berinert) in paediatric or adult patients with HAE–C1-INH. Data were extracted systematically by two independent reviewers according to the study design, participant characteristics, interventions, and outcomes. The data were examined and found to be inappropriate for meta-analysis; thus, a qualitative data synthesis was performed.	Clinical effectiveness of the intervention	Systematic review of the literature on the efficacy of Berinert (C1-INH) for acute attacks, ST prophylaxis, and LT prophylaxis of angioedema attacks in HAE-C1-INH	In the prospective cohort study by Bork and Hardt, 14 patients received long-term prophylaxis with C1-INH for an average of 9 years. The most important benefit of this treatment was a reduction in symptom intensity; all patients reported that all or most of their attacks were considerably less severe than beforehand (% of severe attacks, 93.3% without prophylaxis and 3.8% with prophylaxis). In the prospective cohort study by Martinez-Saguer et al., 30 patients were treated with C1-INH two to three times per week, and significant reductions in the number of attacks were observed, compared with pre-treatment control data; 15 of the 30 patients who had one or two attacks per week before treatment had no attacks with long-term C1-INH therapy. In the retrospective survey study, two patients with severe HAE–C1-INH received C1-INH once per week during the first trimester of pregnancy and no attacks occurred during treatment. The efficacy of long-term prophylaxis with C1-INH was also evaluated in five case studies. One patient was treated with danazol and subsequently with E-aminocaproic-acid over many years. He had to be taken off the medication because of side effects and lack of effect and then received routine prophylactic therapy with C1-INH for HAE symptom control. His attacks ceased almost completely after 1 year of treatment with 500 U of C1-INH every 4–5 days. In a 2nd patient, who had danazol-related focal nodular hyperplasia of the liver, disease control was obtained with 1000 U of C1-INH every 4 days. In a 3rd patient, a significant reduction in attack frequency was only observed when long-term prophylaxis with C1-INH (500 U/wk) was combined with 100 mg/day of danazol (0.7 attacks per month compared with 2.2 attacks per month during the prestudy year). A 4th patient became asymptomatic when C1-INH was administered at 1000 U every 2 weeks during pregnancy. Finally, a 5th patient became asymptomatic when C1-INH (1000–1500 U) was administered three times a week via a portacath and has been asymptomatic for almost 5 yrs while on this regimen.	Safety was reviewed in the studies included	AEs: In the RCT, there were no SAEs or AEs that lead to discontinuation within 4 hours after treatment. 46 patients (19.6%) in the C1-INH arm and 41 patients (43.9%) in the control arm experienced AEs within 4 hours of study treatment. The article notes that most AEs were reflective of the underlying disease and type of attack. - In the open-label follow-up to the RCT, there were no drug related SAEs and only nine attacks were associated with AEs possibly related to treatment. - In two of the cohort studies, anaphylaxis related to treatment was reported in one patient receiving C1-INH and acute urticaria with hypotension (within 30 minutes of C1-INH administration, recurred with C1-INH rechallenge) was reported in a second patient. - None of the remaining studies included in the review reported any SAEs related to treatment with C1-INH. Viral transmission: - One cross-sectional study of 14 patients revealed no evidence of infection with hepatitis C, HIV, hepatitis core antigen, hepatitis B surface antigen, or Hepatitis A IgM Antibodies. - Transmission was evaluated by examining for seroconversion. No evidence of transmission was found in the following studies: 1) An RCT and its open-label extension study (Negative for HIV, hepatitis, or B19); 2) Case-crossover study of 22 patients over 20 years (Negative for HIV, hepatitis, B19); 3) two cohort studies, one prospective/retrospective survey study, three retrospective survey studies, one case series and 2 case reports (192 patients in total, negative for HIV or hepatitis transmission). C1 Inh Antibodies: - One prospective cohort study found that C1-INH autoantibodies are present with highly elevated frequency in patients with HAE–C1-INH irrespective of prior treatment with C1-INH. - A second prospective cohort study also found no relationship between prior treatment with C1-INH and presence of autoantibodies. In addition, this study found no relationship between the mean dose of C1-INH and positive titers. - One retrospective survey study found patients with HAE–C1-INH treated with C1-INH over a 4-year period showed no significant increase in the titers of C1-INH autoantibodies (IgG, IgA, and IgM). - One case report found that no C1-INH autoantibodies were detected in a patient 2 years after having received 1 year of prophylactic therapy with C1-INH - In the open-label section of the RCT, non of the C1 INH antibodies were thought to be inhibitory.	-	Bork, Konrad; Steffensen, Isabella; Machnig, Thomas. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: a systematic literature review. Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies 2013;34(4):312-327.	In a few patients on long-term prophylaxis with C1-INH (14 patients studied for an average length of 9 years), an increased amount of C1-INH was required to control the disease. (A gradual increase in frequency of attacks versus pre-treatment frequency was also noted in 3 out of 27 patients who received individual replacement therapy / on demand treatment with C1-INH in one retrospective cohort study over 18–27 years)	No evidence for viral transmission in the studies examined. Autoantibodies against C1-INH appear to be found at higher rates in HAE-C1-INH patients than healthy controls; but there has not been a relationship found between prior use of C1-INH and the presence of autoantibodies in HAE-C1-INH patients.	The data didn't allow for a MA. However, this article is a good quality qualitative SR of the literature up to Dec 31, 2011 on acute, ST prophylactic and LT prophylactic C1-INH treatment in HAE-C1-INH patients. Unfortunately, there was only 1 RCT that met inclusion criteria for this review, and this was not a study on LTP. In evaluating the LTP treatment, there were only 2 prospective cohort trials, 1 retrospective survey study, and 5 case reports that met inclusion criteria (study designs as classified by the authors of this review). The evidence from these studies concludes that LTP with C1-INH significantly decreases the frequency and severity of attacks in HAE-C1-INH patients with baseline disease severity indicating a need for prophylactic treatment. C1-INH was generally safe and well tolerated. Treatment with C1-INH was not found to be associated with transmission of viruses, including HIV and hepatitis, in any of the included studies. In a few patients on long-term prophylaxis with C1-INH (14 patients studied for an average length of 9 years), an increased amount of C1-INH was required to control the disease. (A gradual increase in frequency of attacks versus pre-treatment frequency was also noted in 3 out of 27 patients who received individual replacement therapy / on demand treatment with C1-INH in one retrospective cohort study over 18–27 years) The authors conclude that "treatment with C1-INH did not appear to be associated with the development of neutralizing antibodies to C1-INH." Limitations include: 1) exclusion of studies of other C1-INH products (e.g. nanofiltered C1-INH); 2) potential for bias in the studies included (especially with only 1 RCT study design across the entire review; the authors note this generally in their discussion but do not report on levels of concern for bias by individual study); 3) the "lack of objective, measurable parameters or validated outcome measures to evaluate the onset of an attack, the severity of the episodes, and the resolution of symptoms;" and 4) the lack of prospective, parallel, direct comparison studies of C1-INH versus other treatments (there were, however, studies comparing outcomes before and after use of LTP C1-INH where the effect of other treatments were represented in the "before" status); and 5) the limitations on analysis imposed by the data (many case reports, many small studies, and the general variation in the study protocols/reporting) which prevented a MA from being conducted and resulted instead in a qualitative review. This review does not re-evaluate and analyse the quality or validity of the findings from the included studies, rather the findings of the various studies are presented here in a consolidated report. Therefore, it is difficult to comment on the strength of the evidence reported in this review beyond the level of study design.

2+	Crossover design	Sixteen of the 22 randomized patients who crossed over completed SF-36 questionnaires at baseline, in between treatment periods, and at the end of the second treatment period	Patients received intravenous injections of 1000 U of C1 INH-nf or placebo every 3 to 4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. Patients could receive open-label C1 INH-nf (1000 U) for the acute treatment of angioedema attacks in either arm of the study. All infusions were administered at the study site. SF-36 Version 1.0 questionnaires12,13 were administered at the beginning and end of each of the two 12-week treatment periods.	Other	QoL results from SF-36 questionnaire	Baseline mean PCSs and MCSs were 36.41 +/- 10.23 and 49.90 +/- 9.96, respectively. PCS scores were 43.92 +/-12.84 after C1INH 12-week period and 37.06 +/- 11.60 afar placebo 12-week period. MCS score were 54.00 +/- 7.82 and 44.98 +/- 16.07, respectively. SDs of mean scores while patients received placebo (ranging from 10.41 to 16.19) were generally greater than those observed while patients received C1 INH-nf (ranging from 7.63 to 14.69; Fig. 2), indicating greater variability in SF-36 scores while patients were receiving placebo.	-	-	-	Lumry, William R.; Miller, Dave P.; Newcomer, Scott; Fitts, David; Dayno, Jeffrey. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies 2014;35(5):371-376.	-	-	Patients received intravenous injections of 1000 U of C1 INH-nf or placebo every 3 to 4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. Patients could receive open-label C1 INH-nf (1000 U) for the acute treatment of angioedema attacks in either arm of the study. All infusions were administered at the study site. SF-36 Version 1.0 questionnaires 12,13 were administered at the beginning and end of each of the two 12-week treatment periods. The authors concluded, "In a clinical trial setting, patients with HAE had significantly better HRQoL after 12 weeks of treatment with C1 INH-nf for routine prevention compared with acute treatment of individual angioedema attacks in the absence of routine prevention while on placebo. Two of the domains with the greatest deficit for patients at baseline versus the general population (bodily pain and social functioning) showed the greatest benefit after routine prevention with C1 INH-nf." This is a study embedded within a study, and the limitations of the initial study should be noted (reviewed elsewhere on this CER). It should also be noted that the SF-36 and not a HAE-specific QoL questionnaire was used. Overall, this study provides some evidence of the improvement in QoL with C1INH-nf prophylactic use.

2-	Cohort	25	50 U/kg body weight rhC1INH was administered by slow IV injection over 4–5 min, once a week during an 8-week period	Clinical effectiveness of the intervention	Occurrence of HAE attacks under prophylactic administration of rhC1INH (50 U/kg/week).	Over the 8 week treatment period the mean breakthrough attack rate was 0.4 attacks per week (95% CI 0.28–0.56) and the median 0.25 attacks per week	Pharmacokinetic/pharmacodynamic (PK/PD) parameters, immunogenicity and safety of repeated administration of rhC1INH	Overall, there was a consistency in levels of antigenic C1INH, functional C1INH and C4 levels between the 1st and 8th treatments	-	Reshef A, Moldovan D, Obtulowicz K, et al. . Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study.. Allergy 2013; 68(1):118–124..	A total of 30 treatment-emergent AEs were observed during the study in 13 patients (52%). Two were serious AEs: acute appendicitis and laryngeal edema. The former was resolved 3 days after onset with an appendectomy. The latter was a 50 year old female patient who experienced laryngeal edema and fatally suffocated 25 days after the last administration of the study drug. Two events were of severe intensity, eight events were of moderate intensity and 20 events were of mild intensity. 4 events were considered possibly drug-related by the investigator. All these events were of mild intensity. These events were dry mouth, dizziness, hypotension (5 days after dosing), and anxiety. There were no events that led to study drug discontinuation or study interruption. 2 patients developed C1-INH antibodies during the study; one's levels subsequently decreased. None of these antibody responses were accompanied by clinical symptoms of hypersensitivity, or other clinically significant abnormalities in routine haematology and biochemistry evaluations. Neutralizing antibodies were not detected in any patient.	Weekly administrations of 50 U/kg rhC1INH appeared to reduce the frequency of HAE attacks and were generally safe and well tolerated	Patients had a history of frequent HAE attacks occurring at least every 2 weeks (prior 2 year mean attack rate of 0.9 attacks per week (range 0.4–4.5)). The study concluded that "weekly administrations of 50 U/kg rhC1INH appeared to reduce the frequency of HAE attacks and were generally safe and well tolerated." The baseline attack rate mean reported was 0.9 attacks per week. The mean attack rate reported while on the study drug was 0.4 attacks per week, with a 95% CI ranging from 0.28 to 0.56 that defines the statistical significance of this reduction. In terms of safety, only four AEs were considered possibly drug-related by the investigator, and all four AEs were mild in intensity. The key limitations of this study are the open-label design and the method of data collection on attack rate prior to study entry (patients' recollection), which create concern for the introduction of bias into the study. It is also important to note that the severity of disease in this study population may vary from that intended to be addressed with the policy.

1+	Randomised trials (one RCT; one a cross-over trial) Note: double-blind, placebo-controlled trials	22	A crossover trial involving 22 subjects with hereditary angioedema that compared prophylactic twice-weekly injections of nanofiltered C1 inhibitor concentrate (1000 units) with placebo during two 12-week periods. Subjects were not allowed to change their prophylactic androgen or antifibrinolytic medications during or for 30 days before the prophylaxis study. Subjects were asked to keep a daily diary of symptoms throughout both study periods. All subjects with acute attacks of angioedema were eligible for rescue treatment with open-label C1 inhibitor.	Clinical effectiveness of the intervention	The primary end point was the number of attacks of angioedema per period (normalized for the number of days the subject participated during that period), with each subject acting as his or her own control.	The number of attacks per 12-week period was 6.26 with C1 inhibitor concentrate given as prophylaxis, as compared with 12.73 with placebo (P<0.001)	For each period: the average severity of attacks, average duration of attacks, number of open-label injections of C1 inhibitor, and total number of days of swelling.	The subjects who received the C1 inhibitor concentrate also had significant reductions in both the severity and the duration of attacks, in the need for open-label rescue therapy, and in the total number of days with swelling (The mean (±SD) score for the severity of attacks (on a 3-point scale, with 1 indicating mild, 2 moderate, and 3 severe) was significantly lower with C1 inhibitor prophylaxis than with placebo (1.3±0.85 vs. 1.9±0.36, P<0.001). Likewise, the total duration of attacks was significantly shorter with C1 inhibitor prophylaxis than with placebo (2.1±1.13 vs. 3.4±1.39 days, P = 0.002). A total of 11 subjects receiving C1 inhibitor prophylaxis required open-label rescue therapy, as compared with 22 subjects receiving placebo. C1 inhibitor prophylaxis was associated with fewer open-label injections (4.7±8.66 vs. 15.4±8.41, P<0.001) and fewer days of swelling (10.1±10.73 vs. 29.6±16.9, P<0.001))	-	Zuraw BL, Busse PJ, White M, et al. . Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. . N Engl J Med. 2010;363(6):513–522..	In the prophylaxis trial, 21 of 24 subjects (88%) had one or more adverse events. Three adverse events (pruritus and rash, light-headedness, and fever) were classified as possibly related to the study drug. There were 5 serious adverse events (SAE) in the prophylactic study that resulted in hospitalization of the subjects (4 occurred during the study and 1 occurred after enrolment but before randomization). Three of the 4 consisted of HAE attacks and 1 was for placement of a port for venous access. None of the SAEs were judged related to C1INH-nf.	When used for prophylaxis, C1 inhibitor significantly reduced the frequency of acute attacks, as compared with placebo	Participants had a history of at least two attacks per month. Nanofiltered C1 inhibitor concentrate for prophylaxis, at a dose of 1000 units in twice-weekly injections, significantly reduced the frequency of acute attacks (6.26 per 12-week period), as compared with placebo (12.73 per 12-week period) in this 24-week cross over study. This multi-centre, double-blind, randomised study was designed for 90% power and funded by Lev Pharmaceuticals. The primary endpoint results were statistically significant with a p < 0.001 reported. Secondary endpoints showed the subjects who received the C1 inhibitor concentrate also had significant reductions in both the severity and the duration of attacks, in the need for open-label rescue therapy, and in the total number of days with swelling. There were only 3 AEs and no SAEs considered possibly related to nfC1INH. This is a well designed study with low concern for bias (Randomised, cross-over, medication not self-administered and therefore attacks requiring treatment were not self-reported), demonstrating the efficacy and safety of prophylactic use of nfC1INH over a 12 week period. However, despite a significant reduction, attacks were not completely eliminated. Consideration of further investigation into the dosing schedule in order to determine optimal response is noted. Finally, the study period is relatively short, given the nature of this disease and likely need for many years of treatment.

2-	Dose-escalation study	Of the 24 patients who were screened for this study, 20 were enrolled and received 1500 U in the first dosage step, 13 of these patients escalated to 2000 U, and 12 of these patients escalated to 2500 U. Overall, 4 patients discontinued the study; 2 patients withdrew consent and 2 patients discontinued at investigator and/or sponsor discretion	A treatment algorithm was used to escalate doses of C1 INHnf at 500-U intervals (1500, 2000, and 2500 U) for successive 12-week treatment periods. At the end of each treatment period, the patients were evaluated for tolerability and attack frequency. Attacks of any severity and location were counted. The patients who tolerated their current dose and had an average of 1 attack/month continued to receive their current dose for a 3-month follow-up period and then completed the study. Patients with an average of >1 attack/month received dose escalation to the next dose level and received infusions every 3 or 4 days for 12 weeks.	Safety of the intervention	This open-label, multicentre, phase 4 study was conducted to assess the safety, tolerability, immunogenicity, and clinical effect of escalating doses of C1 INH-nf doses as prophylactic therapy for angioedema attacks in patients who were not adequately controlled while receiving 1000 U every 3 or 4 days. The primary end point was safety, which was evaluated by monitoring adverse events, vital signs, and clinical laboratory test results.	Overall, C1 INH-nf was well tolerated at all dose levels. The majority of adverse events were considered by the investigator to be unrelated to the study drug (86/91 [95%]) and were mild to moderate in intensity (77/91 [85%]). Eighteen patients (90%) experienced 1 adverse event. The most frequently reported adverse events were upper respiratory tract infection (5 [25%]) and nasopharyngitis (3 [15%]) (Table II). No patients discontinued study medication because of an adverse event. Two patients (10%) reported adverse events that were considered by the investigator to be related to the study drug. One patient developed a medical device complication (verbatim: blood clot in port) during the first dosage step; the clot resolved completely with streptokinase. Based on a review of medical history and adverse event information, 3 other patients reported the presence of catheter ports without having any complications. A second patient experienced muscle spasms during the second dosage step. Two patients experienced serious adverse events. One patient was diagnosed with a cerebral cystic hygroma during the third dosage step. A second patient experienced a laryngeal angioedema attack during the first dosage step, and anaemia and choledocholithiasis during the second dosage step that required hospitalization. No serious adverse events were determined by the investigator to be related to the study drug. No systemic thrombotic events occurred. Antibodies to C1 INH were detected in 2 patients. One patient had antibodies before the first dose that were detectable through each dose escalation step, and 1 patient first had borderline detectable antibodies at the end of the third dosage step (2500 U). Both were diagnosed with AAE.	The secondary objective of this study was to evaluate the effect of escalating doses of C1 INH-nf on the monthly rate of angioedema attacks.	Four patients were per-protocol successes while receiving 1500 U for 12 weeks, and 1 patient was an investigator determined success. Four of these 5 patients continued to receive 1500 U during the 3-month follow-up period: 1 of these discontinued treatment during the follow-up period. Of the remaining 15 patients, 2 discontinued treatment before proceeding to dose escalation at step 2. One of these patients had a reduction in attack rate of >1.0 attack/month during the 1500-U treatment period and discontinued at the end of the treatment period because he was traveling out of the country. Another patient withdrew consent during the 1500-U treatment period and was considered to have had a treatment failure. The remaining 13 patients were escalated to 2000 U. One of these patients discontinued treatment during step 2 (moved out of state) and was considered to have had a treatment failure. Aside from the patient who discontinued during step 2, no patients who entered step 2 met the criteria for treatment success at the end of the step 2 treatment period. Therefore, in accordance with the protocol, they received a dose escalation to 2500 U. After 12 weeks of treatment at 2500 U, 5 patients had per protocol successes, and 1 patient had an investigator-determined success. All 6 of these patients continued to receive 2500 U during the 3-month follow-up period. Of the patients who did not enter the follow-up period, 2 had a reduction of >1.0 attack/month during the 2500-U treatment period, and 4 were considered to have had treatment failures during this period.	-	Bernstein JA, Manning ME, Li H, et al. . Escalating doses of C1 esterase inhibitor (Cinryze) for prophylaxis in patients with hereditary angioedema.. J Allergy Clin Immunol Pract. 2014;2(1):77–84.	-	Dose escalation of nanofiltered C1 inhibitor (human) up to 2500 U was well tolerated and reduced attack frequency in the majority of patients. Overall, 9 patients (45%) met criteria for per-protocol treatment success, 2 (10%) were investigator-determined successes, and 3 additional patients (15%) experienced a reduction of >1.0 attack/month. Overall, the majority of patients (14 [70%]) experienced notably reduced rates (per protocol, investigator determined, and reduction >1.0) of angioedema attacks in comparison with the historic attack rate while receiving escalated doses of C1 INH-nf. Patients who proceeded to the 3-month follow-up period (11 [55%]) at their final dose continued to experience similarly low attack rates. Six patients (30%) were categorized as having treatment failures. One of these patients experienced a reduction of 1.4 attacks/month by the end of the 2500-U dosing step. However, this patient was considered to have had a treatment failure because the majority of attacks were severe, including some with laryngeal involvement. Two of the patients considered as having treatment failures were those described above who had antibodies to C1 INH at one or more time points during the study. Neither patient reported a family history of HAE, and both patients were diagnosed late in life (<2 years since diagnosis).	This was a dose-escalation study primarily intended to assess the safety of dose escalation up to 2500U of C1INH-nf in LTP. Secondary endpoints were efficacy of the treatment. The study is limited by the non-randomised study design, the short follow-up period (maximum 48 weeks versus the much longer treatment period likely to be given in practice), and the small number of patients (albeit, consistent with a rare disease study). There was no statistical analysis. 95% of AEs were not related to the drug and 85% of AEs were mild in intensity. No patients discontinued the study medication because of an adverse event. Two patients (10%) had AEs thought related to the study drug (blood clot in port and muscle spasms). No SAEs were thought related to the study drug. There were no systemic thrombotic events noted. 70% of patients experienced "notably reduced rates" (per protocol, investigator determined, and reduction >1.0) of acute attacks versus previous rates during the dose escalation study. This study provides some evidence of safety and efficacy for dose escalation of C1INH-nf up to 2500units in LTP in up to 48 weeks of therapy. Limitations are noted and further studies would be needed to create a generally accepted dose escalation protocols/regimen.

2-	Cohort	19	Dose and schedule varied; no systematic assignment was discussed in the publication. The mean weekly doses were 1,253 U (SD 641 U, range 500–2,300 U) at the onset of treatment and 2,564 U (SD 1,835, range 500–7,000 U) at the end.	Clinical effectiveness of the intervention	The study reviewed regular recordings by the patients of the severity and number of attacks at the beginning and the end of the study.	Patients reported that either all or most of their attacks became considerably less severe than before WLTC. Before treatment, the percentage of severe attacks was 93.3%; at the end of the study, it was 3.8%. In 8 of the 14 patients in the LRT group, the number of attacks per month was lower during the last 12 months of the study compared with the time before LRT.	-	-	-	Bork K, Hardt J. . Hereditary angioedema: long term treatment with one or more injections of C1 inhibitor concentrate per week.. Int Arch Allergy Immunol 2011;154;82-8. .	-	LT replacement seems to decrease severity and number of attacks based on these case reports.	This is a weak cohort study reviewing the patient recordings of severity and number of attacks over a range of time (mean of 9 years). Some patients began the study with prophylactic C1 inhibitor, others began with C1 inhibitor on demand for attacks and then switched into the prophylactic group. There is much room for bias, including the patient self-reported data. The dosing and methods of determining dosing for C1 inhibitor are not discussed. The outcomes are not statistically analysed for significance. Overall, this provides some, albeit very weak, evidence.

2-	Cohort	16 patients received nfC1INH for HAE treatment or prophylaxis during pregnancy: 2 subjects from the acute treatment study (LEVP 2006-1), 11 subjects from the routine prophylaxis study (LEVP 2006-4), and 2 subjects who were enrolled in both open-label extensions. One additional subject received C1 INH-nf in a compassionate-use program.	Retrospective analysis of C1 INH-nf use during pregnancy using data from open-label extension studies of two randomized, double-blind, placebo-controlled trials and from a compassionate-use program. The first open-label extension studied C1 INH-nf as acute treatment for HAE attacks with optional preprocedural prophylaxis; the other studied C1 INH-nf as routine prophylaxis for prevention of HAE attacks with optional acute treatment if needed. For routine prophylaxis, C1 INH-nf at 1000 U was given every 3–7 days. In the compassionate-use program, patients received C1 INH-nf at 1000 U twice weekly for prophylaxis.	Clinical effectiveness of the intervention	Efficacy assessments in this analysis of C1 INH-nf use in pregnancy included dosing data, total number of attacks during pregnancy versus historical attack rates, and frequency of attacks during prophylactic treatment.	Prophylaxis study: Most of the patients experienced a lower attack rate on C1 INH-nf therapy. Three subjects experienced attacks while pregnant but had fewer attacks on C1 INH-nf therapy versus their historical rates. One subject experienced 1 attack during 122 days, another experienced 4 attacks during 253 days, and the third subject experienced 11 attacks during 267 days of prophylactic treatment. Six subjects experienced no attacks while receiving routine prophylaxis. Outcomes for two subjects were unknown. Compassionate-use program: The subject was 25 years old and received an estimated 12 doses of C1 INH-nf (based on the compassionate-use dosing regimen and available exposure data) during the last 5 weeks of her third trimester. Her historical attack rate was 6–10 attacks per month. Although this subject's attack rate while on C1 INH therapy was not documented, it is noteworthy that she delivered a healthy male infant. Both studies (acute and prophylaxis): One subject was 33 years old and received 25 doses of C1 INH-nf (3 for prophylaxis and 22 as acute treatment) during the first two trimesters of her pregnancy. Her historical attack rate was 3 to 4 attacks per month. The subject experienced 19 unique attacks; 16 occurred while enrolled in the acute treatment study and 3 occurred in the 3 weeks during which she was also enrolled in the prophylaxis study. Difficult to interpret as there was overlap in study periods and relative lack of data. She delivered a healthy female infant. The other subject was 23 years old and received 26 doses of C1 INH-nf (20 for prophylaxis and 6 as acute treatment) during her pregnancy. Before enrolment, her historical attack rate was 0.33 attacks per month and increased during pregnancy to 1.3 attacks per month; she received acute treatment for each attack. She then received routine prophylaxis for the remainder of her pregnancy and experienced no additional attacks. She delivered a full-term healthy female infant.	Safety assessments included pregnancy outcomes, viral safety testing (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and parvovirus), and testing for antibodies to C1 INH. Treatment-emergent AEs were summarized and relation of AEs to study drug was recorded.	In the subjects from the two open-label trial extensions, the most commonly reported treatment-emergent AEs were infection (e.g., upper respiratory infections, nasopharyngitis, urinary tract infection, sinusitis, and candidiasis), gastrointestinal disorders (e.g., nausea, vomiting, constipation, abdominal pain, and diarrhoea), headache, and rash. No serious AEs were considered drug related by the investigators and no clinically relevant antibodies to C1 INH were detected. There was no evidence of viral transmission related to C1 INH-nf exposure. No AEs were reported in the compassionate-use program. From the 11 prophylaxis study patients: 8 subjects delivered nine healthy neonates (one set of twins). There was one spontaneous abortion which was considered unrelated to C1 INH-nf by the investigator. One subject delivered a stillborn infant with multiple congenital anomalies detected at week 23 of the pregnancy and considered unrelated to C1 INH-nf by the investigator because the anomalies would have predated C1 INH-nf use. One subject was lost to follow-up, and the infant outcome is unknown.	-	Baker, James W.; Craig, Timothy J.; Riedl, Marc A.; Banerji, Aleena; Fitts, David; Kalfus, Ira N.; Uknis, Marc E.. Nanofiltered C1 esterase inhibitor (human) for hereditary angioedema attacks in pregnant women. Allergy Asthma Proc 2013;34(2):162-169.	-	The authors conclude that this retrospective analysis establishes the favourable risk– benefit profile of C1 INH-nf for HAE management during pregnancy. C1 INH is noted by authors as the safest prophylactic agent to use during pregnancy relative to attenuated androgens, which are generally contraindicated, and antifibrinolytics, which are only administered with caution during pregnancy.	This is a small retrospective review of outcomes experienced in pregnant women with HAE using C1-INH-nf. Difference sources of data were used (3 studies and 1 compassionate-use program), and some patients only had acute treatment. The original studies were designed to evaluate the effects of C1INH-nf, not to specifically evaluate pregnancy outcomes; however, ethical considerations would prevent that study. Limited information is given about the original study designs from which patient data was collected for this report. Changes in HAE disease activity in pregnancy have not always been controlled for / reported (one patient was noted to have increased attacks in pregnancy before starting LTP with C1INH-nf, but similar data was not available for all patients nor was there mention of a generally accepted level of disease severity change in pregnancy). There was no analysis done across the study patients, no statistical analysis of the results, and no consideration of potential confounders affecting results. However, given that androgens are generally contraindicated in pregnancy and concern for safety of antifibrinolytics during pregnancy, the reported safety outcomes in this study are encouraging. As well, efficacy outcomes were generally supportive of LTP with C1-INH-nf in pregnancy. Unfortunately, the strength of this evidence is low due to the weaknesses in study design previously noted.

2+	Cohort	Forty-six children and adolescents ranging in age from 2 to 17 years received a total of 2237 C1 INH-nf infusions in the 4 studies. Four children (aged 9-17 years) enrolled in and completed the pivotal prophylaxis trial. Twenty-three children received open-labelC1 INH-nf prophylaxis.	Data from 2 randomized, placebo-controlled studies and their open-label extensions were used in this analysis. One of the studies evaluated the use of C1 INH-nf in acute attacks, and the other study evaluated its use as prophylaxis. The placebo-controlled prophylaxis trial consisted of 2 consecutive 12-week treatment periods during which patients received study medication to prevent HAE attacks. Patients were randomly assigned to receive intravenous infusions of C1 INH-nf 1000 U or placebo every 3-4 days. After the first 12-week treatment period, patients crossed over to the alternate treatment arm for the second 12-week treatment period; thus, each individual served as his or her own control. Patients were eligible to receive rescue treatment with open label C1 INH-nf for acute attacks. Patients (or their parents/ guardians) were asked to keep a diary of daily symptoms during both study periods. In the open-label prophylaxis extension study, intravenous infusions of C1 INH-nf 1000 U were administered every 3-7 days. Patients were also eligible for treatment of acute attacks with the dosing regimen described for the open-label, acute attack treatment study.	Clinical effectiveness of the intervention	In the prophylaxis trials, patients kept a daily diary of symptoms. The number, duration, and severity of attacks during the treatment periods were assessed. Attack severity was scored on a 3-point scale, with 1 indicating mild, 2 moderate, and 3 severe.	In the prophylactic trial, the children had a nearly 2-fold reduction in number of HAE attacks while receiving C1 INH-nf prophylaxis compared with the time period during which they received placebo (mean number of attacks, 7.0 vs 13.0 over 12 weeks). The mean severity score during each arm of the crossover was 1.6. The mean duration of attacks was 2.3 days during C1 INH-nf therapy and 2.6 days during placebo therapy. A mean of 6.8 open-label doses of C1 INH-nf were required for treatment of attacks while patients were receiving active prophylaxis treatment with C1 INH-nf, compared with 15.0 open-label doses while patients were receiving placebo. The mean duration of swelling in the 2 groups was 9.0 days and 20.8 days, respectively. In the prophylaxis open-label extension (n = 23), patient reported median monthly attack rate before enrolment was 3.0 (range, 0.5-28.0) and decreased to 0.39 (range, 0-3.36) during C1 INH-nf prophylaxis. The majority of patients (87%; 20 of 23) experienced 1 or less attacks per month, and 22% (5 of 23) reported no attacks during the study period.	In these studies, safety was evaluated by assessing adverse events, monitoring vital signs, and performing viral safety testing and anti-C1 INH antibody testing.	One patient in the pivotal prophylaxis study experienced pyrexia that was considered possibly related to the study drug. In the open-label prophylaxis extension, 17 of 23 patients (74%) reported adverse events. Two patients reported a total of 3 adverse events that were considered related to C1 INH-nf; 1 patient had headache and nausea, and the other had infusion-site erythema. All 3 of these events were of mild severity. No serious or severe adverse events were considered by the investigator to be related to C1 INH-nf, and no adverse events led to discontinuation of treatment. There was no evidence of HIV or viral hepatitis transmission or development of clinically relevant anti–C1 INH antibodies in these studies	-	Lumry, William; Manning, Michael E.; Hurewitz, David S.; Davis-Lorton, Mark; Fitts, David; Kalfus, Ira N.; Uknis, Marc E.. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J. Pediatr. 2013;162(5):1017-1022.e1-2.	-	In children, C1 INH-nf was well tolerated and reduced the rate of attacks. Most attacks (71%) were adequately treated with the initial dose of C1 INH-nf, which was also consistent with the overall rate for the open-label acute treatment study (69%).	Patients included in this study were those aged 6 years or older with a confirmed diagnosis of HAE, including a low C4 level, a normal C1q level, and a low antigenic or functional C1 inhibitor level or a mutation in the C1 inhibitor gene known to cause HAE, were eligible for the randomized, placebo-controlled studies. Patients with a low C1q level, a history of B-cell cancer, presence of antibodies to C1 inhibitor, or a history of allergic reaction to blood or blood plasma products were excluded. Those patients who were randomized in the acute treatment trial (or met the entry criteria after the close of enrolment) and had a history of 2 or more attacks per month were eligible for the placebo-controlled prophylaxis study. Patients were eligible for the open-label extension studies if they had completed participation in the previous randomized, placebo-controlled studies. In addition, patients aged over 1 year who were excluded from the placebo-controlled studies for pregnancy or lactation, age <6 years, narcotic addiction, or presence of antibodies to C1 INH were allowed in the open-label studies. Patients who otherwise would have met the entry criteria for the placebo-controlled studies but did not participate in those studies, or who had a diagnosis of HAE based on a family history of HAE as determined by the principal investigator, were also eligible for the open label studies. To participate in the open-label extension of the prophylaxis study, patients must have had a history 1 or more HAE attacks per month or a history of laryngeal oedema. In this post hoc analysis of data on paediatric patients from 4 prospective clinical trials of C1-INHnf, 2 trials were relevant to this policy evidence review on LT prophylactic treatment with C1-INH. The placebo-controlled cross-over trial of LTP only contained 4 paediatric patients for inclusion in this article's analysis, while the open-label LTP study included 23 patients. Efficacy and safety results were supportive of LTP use with C1-INHnf. In the cross-over trial the mean number of attacks per 12 week period was 7.0 while on LTP versus 13.0 while on placebo. Additionally, the number of open-label rescue doses required was less in the LTP group, severity of attacks was unchanged, mean duration or attacks was less while on LTP, and mean duration of swelling was lower while on LTP. In the open-label extension prophylactic study, the median monthly attack rate before enrolment was 3.0 (range, 0.5-28.0) and decreased to 0.39 (range, 0-3.36) with LTP, with 87% reporting 1 or less attacks per month and 22% reporting no attacks during the study period. Limitations to the study are the post-hoc analysis, the evaluation of a subgroup of patients that the original study was not powered to assess in isolation, the small numbers of study patients in line with the rarity of the disease, the potential bias introduced with self-reported outcomes, the open-label recruitment of the larger study, and the lack of statistical analysis of findings.

2++	Cohort	146 patients	Subjects received prophylactic injections of C1INH-nf (1000 units) at the study site. The suggested dose of C1INH-nf was 1000 units every 3 to 7 days. Subjects had laboratory studies performed every 3 months while in the study. Subjects were asked to keep a daily diary of symptoms. Study personnel collected data about breakthrough attacks or adverse events at each visit. All angioedema attacks were eligible for treatment with open-label C1INH-nf (1000 units, with a second dose 60 minutes later if needed).	Clinical effectiveness of the intervention	The primary efficacy variable recorded for each subject was the number of angioedema attacks.	The median (IQR) historical attack rate was 3 (2-4) attacks per month, with a range of 0.08 to 28. 5 subjects (3.4%) had a historical attack frequency of <1 attack per month. The frequency of HAE attacks was significantly decreased during treatment with prophylactic C1INH-nf compared with the historical rate at screening (P .001). The median frequency of hereditary angioedema attacks during the study was 0.19 attacks per month (IQR, 0.00-0.64), a 93.7% reduction from the baseline median frequency of 3 (IQR, 2-4). The mean frequency of hereditary angioedema attacks during the study was 0.47 0.83, a 90.0% reduction from the historical mean frequency of 4.7 5.2 attacks per month. The median frequency of attacks during the study in the 67 subjects who did not complete the study was 0.12 (IQR, 0.00-0.74) attacks per month. Substantial differences in efficacy were seen within the study population. 51 subjects (34.9%) reported no attacks during the study, and 128 subjects (87.7%) reported 1 attack or less per month during the study. In contrast, 18 subjects (12.3%) reported more than 1 attack per month during the study. Although 18 subjects had an overall attack rate of more than 1 per month on C1INH-nf, only 4 subjects (2.7%) failed to achieve an attack rate of 1 or less per month when treated with C1INH-nf at the recommended twice per week schedule. At enrolment, 42 subjects (28.8%) were taking regular prophylactic androgens. During the study, 23 subjects (54.8%) discontinued androgens, 6 subjects (14.3%) discontinued regular use and switched to as-needed use, 5 subjects (11.9%) reduced the androgen dose, and 8 subjects (19.0%) remained on the same dose. The median monthly attack rate in the 23 subjects who discontinued androgens went from 3.00 (IQR, 1.25-11.00) on androgens to 0.00 (IQR, 0.00-0.31) on prophylactic C1INH-nf. 9 subjects not taking androgens at entry were prescribed androgens during their participation in the study. Twice weekly dosing with C1INH-nf resulted in a favourable response rate that varied from 95.7% at 30 days (88/92) to 70.7% at 120 days (41/58). Once-weekly dosing resulted in a favourable response rate that varied from 69.3% at 30 days (79/114) to 45.7% at 120 days (37/81).	Safety was evaluated by the number and severity of adverse events, and changes in clinical laboratory values (viral serology performed every 3 months) and vital signs	No subjects discontinued the study drug because of an adverse event. 86% of treatment-emergent adverse events were of mild or moderate intensity. Two deaths (not study drug related) were reported. One subject died of pulmonary arterial embolization of foreign material from intravenous injection of an oral medication, and 1 subject died of worsening of pre-existing hepatocellular carcinoma. A total of 99 of 101 serious adverse events reported were considered not related to C1INH-nf, and 2 serious adverse events (musculoskeletal chest pain and major depression) were of unknown relationship. Five subjects (all with underlying risk factors for thrombotic events) experienced serious adverse events of a thromboembolic nature (myocardial infarction, deep vein thrombosis, cerebrovascular accidents [x2] and pulmonary embolism), but none were considered study drug related. no evidence of transmission of hepatitis B or C, HIV, or B19	Sixty-seven subjects (45.9%) did not complete the study—40 transitioned to commercial C1INH-nf, 3 transferred to another ViroPharma Inc C1INH-nf study, 2 withdrew because of logistic difficulties, 1 transferred to another C1INH drug, 8 withdrew consent, 10 were lost to follow-up, 1 was withdrawn by an investigator, and 2 died.	Zuraw, Bruce L.; Kalfus, Ira. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. Am. J. Med. 2012;125(9):938.e1-7.	Hereditary angioedema was not well controlled even at twice-weekly dosing in a relatively small fraction of the subjects; whether these subjects would benefit from a higher dose per injection was not addressed in this study. Individual patients may benefit from further dose optimization based on response to therapy and individual preference.	This open-label study demonstrates that prophylactic C1INH-nf therapy at the recommended dose of 1000 units twice per week was highly effective, durable, and safe in the majority of patients with hereditary angioedema. We found that hereditary angioedema seemed to be well controlled in many subjects with once-weekly dosing.	This is a relatively large (given the rarity of HAE), nonrandomised, open-label cohort study of 146 patients who were given LTP with C1INH-nf every 3-7 days for up to 2.6 years. Subjects had a known diagnosis of hereditary angioedema who had a history of at least 1 angioedema attack per month or of any laryngeal angioedema. At enrolment, 42 subjects (28.8%) were taking regular prophylactic androgens. During the study, 23 subjects (54.8%) discontinued androgens, 6 subjects (14.3%) discontinued regular use and switched to as-needed use, 5 subjects (11.9%) reduced the androgen dose, and 8 subjects (19.0%) remained on the same dose. The median monthly attack rate in the 23 subjects who discontinued androgens went from 3.00 (IQR, 1.25-11.00) on androgens to 0.00 (IQR, 0.00-0.31) on prophylactic C1INH-nf. Nine subjects not taking androgens at entry were prescribed androgens during their participation in the study. Of these, 5 subjects were prescribed androgens for short-term prophylaxis and 4 subjects were started on regular androgens. Results demonstrated a statically significant decrease in acute attacks, thus demonstrating efficacy, with C1IN-nf use for LTP (1000units twice per week); once a week dosing also showed a positive but weaker benefit. There was a high drop out rate, but no subjects discontinued the study drug secondary to an adverse event and the majority of drop outs were transitioned to commercial C1INH-nf. Most treatment-emergent adverse events were mild - moderate. Five thrombotic events were not thought due to the study drug. All but two of the SAEs were deemed not related to the C1INH-nf use, with the other 2 (musculoskeletal chest pain and major depression) being of unknown relationship. Limitations include the nonrandomised and open-label study design, the pre-treatment attack rate being estimated based on the patient's reported history, and the allowance for variance in administration of the prophylactic doses (protocoled as every 3-7 days). Overall, this is a well conducted prospective cohort study.

2-	Crossover design	Three phase II/III pre-authorization studies were performed in 4 centres in the Netherlands from September 2005 until April 2007: a pharmacokinetic (PK) analysis in nonsymptomatic HAE patients, an on-demand study in HAE patients with an angioedema attack, and a prophylactic study in HAE patients. Five HAE type I patients and one AAE patient were treated in the prophylactic study (4 females, 2 males). One HAE patient discontinued the study after withdrawal of consent because of personal reasons.	Patients were treated prophylactically with intravenous C1-INH-NF to prevent attacks of angioedema for a period of 16 weeks (hospital treatment, self-treatment or home treatment, as the patient was used to). Patients had to stop their current C1-inhibitor concentrate treatment and received C1-INH-NF instead. Treatment was once every 5–7 days dependent on the usage before the study. Standard therapy was 1000 U C1-INH-NF, but could be adjusted as deemed necessary by the treating physician. The use of C1-INH-NF, prophylactically and in case of an attack (including the course and severity), were recorded in a diary by the patient. Patients visited the investigator at day 0, weeks 1, 4, 9 and 16. Historical data on attack frequency and duration with and without prophylaxis were obtained	Clinical effectiveness of the intervention compared to existing interventions	The primary efficacy parameters were the number, type, duration (time-to-relieve/time-to-resolve) and severity of attacks. The number of extra doses of C1-INH-NF required was assessed.	The six patients experienced in total 31 breakthrough attacks during in total 748 observation days. Peripheral attacks were most frequent (n=16), followed by abdominal attacks (n=6). The majority of the attacks were of moderate severity (n=16), ten were severe, 3 mild and in two cases severity was unknown. Extrapolated to a period of 1 year, the number of attacks was 86. Based on the historical data of the five patients using C1-INH as prophylactic treatment before participating in the study, 138 attacks were expected to occur in 1 year	Safety was monitored by recording signs and symptoms possibly related to (serious) adverse events in patients repeatedly measuring vital signs and routine haematological and chemical tests.	In the prophylactic study over a median study period of 140 days (range 65–143) per patient, 141.000 units of C1- INH-NF were used. Three of the 6 patients experienced in total 9 adverse events, from which one was serious (erysipelas, already present before start of study, requiring hospitalization). One of the adverse events (increased ALAT) was first considered as possibly related to treatment. However, this patient appeared to have cholelithiasis and after cholecystectomy, the liver values normalized. All other laboratory data and vital signs in all three studies did not reveal clinically significant abnormal values and no C1-inhibitor antibodies were induced.	-	Hofstra, J. J.; Kleine Budde, I.; van Twuyver, E.; Choi, G.; Levi, M.; Leebeek, F. W. G.; de Monchy, J. G. R.; Ypma, P. F.; Keizer, R. J.; Huitema, A. D. R.; Strengers, P. F. W.. Treatment of hereditary angioedema with nanofiltered C1-esterase inhibitor concentrate (Cetor®): multi-center phase II and III studies to assess pharmacokinetics, clinical efficacy and safety. Clin. Immunol. 2012;142(3):280-290.	-	Overall, it is concluded that the efficacy of C1-INH-NF in prophylactic treatment of HAE and AAE patients is effective and comparable to C1-INH. The results presented in the current paper demonstrate that the addition of the nanofiltration in the production process of C1-inhibitor concentrate did not affect the pharmacokinetics and efficacy of symptomatic and prophylactic treatment of angioedema patients. C1-INH-NF (marketed as Cetor®) was shown to be effective and safe.	This is a very small, 6 patient, cohort study comparing the use of C1INH with C1INH-nf in LT prophylaxis for HAE and AAE patients. All patients were on prophylactic treatment with C1-INH before the study started (Table 4). Two patients also used other prophylactic medication for their angioedema, which was stopped at the start of the study. With the prophylactic treatment before the study, the number of attacks per patient per year varied from 5 to 50. Prior history was the control / C1INH and this was compared with prophylaxis on C1INH-nf. However, patient's prior prophylactic regimens varied and therefore there are limitations to the direct comparison that can be made. The small number of patients also limited the analysis that could be done. Results from the 16 week trial were extrapolated out for a year and used for comparison with prior history. Results showed a lower rate of breakthrough attack than had been predicted based on the prior data, and the conclusion drawn was that the C1INH-nf product was effective. Overall, this study provides weak, but supportive evidence of the efficacy of C1INH-nf use for LT prophylaxis in HAE and AAE.

2++	Systematic	A total of 434 citations were identified in the literature search. Following screening of titles and abstracts, 408 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 18 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report.	A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), and ECRI databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 24, 2015.	Clinical effectiveness of the intervention	-	-	-	-	-	Canadian Agency for Drugs and Technologies in Health. C1 Esterase Inhibitor for Prophylaxis against Hereditary Angioedema Attacks: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2015;0(0):0.	Major limitations to this report include the lack of cost-effectiveness data regarding the prophylactic use of C1-INH. High quality systematic reviews and randomized controlled trials were also lacking. More high quality evidence is needed regarding prophylactic use of C1-INH for the prevention of HAE attacks. Due to the rare nature of the disease, large scale clinical trials were not possible, and the included RCT9 had a small number of patients participate. The systematic review8 included only a descriptive summary of the identified studies, as meta-analysis was not feasible or appropriate, and was limited in the scope of study drug (restricted to Berinert). Findings from the review may not be applicable to other C1-INH products. Lack of control or comparator groups is also a limitation of the studies included in this report. The majority of the studies did not have any comparators or controls groups.8,10-14,17,18 While some conclusions can be drawn regarding the clinical effectiveness of C1-INH in general, there is limited information on how C1-INH compares to placebo, or other HAE management and prevention treatment therapies. This limits the knowledge about the place of C1-INH in therapy. The studies that did include comparator data, either placebo9,15 or other treatment therapies,16 were marked by their own set of limitations, including uncertain blinding and patient allocation,9,15 small number of patients,9,15 and lack of randomization.	While evidence was found regarding the clinical effectiveness of prophylactic C1-INH for the prevention of HAE attacks, as already noted, these studies were marked by many limitations and the findings should be interpreted with a degree of caution. According to the identified studies and guideline, the use of C1-INH for the prophylaxis of HAE attacks is clinically effective and relatively safe. This includes its use as a short-term prophylactic before surgical or invasive procedures, or as a long-term prophylaxis agent. This was found for patients of all ages, including vulnerable patient populations such as pregnant women. However, due to the lack of high quality data, and lack of comparator or control data, there are many limitations and the findings should be interpreted with caution. The prophylactic use of C1-INH in clinical practice may depend on a patient's disease history, including responses to other therapies, attack severity, attack frequency, and exposure to known HAE attack triggers (i.e., surgical procedures). Lack of cost-effectiveness data additionally limits the application of these findings, as C1-INH has an unclear place in therapy for the general HAE population. More high quality trials, and cost-effectiveness data, are needed in regards to the prophylactic use of C1-INH in the prevention of HAE attacks.	All of the studies included in this systematic review that referred to LT prophylactic treatment were included individually in the literature search results for this policy evidence review. They were individually assess and included in the policy review where appropriate. This is a systematic review of the evidence which concludes that use of C1INH for the LT prophylaxis of HAE attacks is clinically effective and relatively safe. Major limitations to this report include the lack of cost-effectiveness data regarding the prophylactic use of C1-INH. High quality systematic reviews and randomized controlled trials were also lacking. More high quality evidence is needed regarding prophylactic use of C1-INH for the prevention of HAE attacks. Due to the rare nature of the disease, large scale clinical trials were not possible, and the included RCT9 had a small number of patients participate. The systematic review8 included only a descriptive summary of the identified studies, as meta-analysis was not feasible or appropriate, and was limited in the scope of study drug (restricted to Berinert). Findings from the review may not be applicable to other C1-INH products. Lack of control or comparator groups is also a limitation of the studies included in this report. The majority of the studies did not have any comparators or controls groups.8,10-14,17,18 While some conclusions can be drawn regarding the clinical effectiveness of C1-INH in general, there is limited information on how C1-INH compares to placebo, or other HAE management and prevention treatment therapies. This limits the knowledge about the place of C1-INH in therapy. The conclusions note the caveat that findings are limited by the lack of high quality data and the lack of comparator data, among others, and therefore findings should be interpreted with caution.

2-	Cohort	The prophylaxis group included 10 patients with hereditary C1-inhibitor deficiency and 2 patients with acquired C1-inhibitor deficiency (total of 12 patients).	administration of C1-inhibitor concentrate every 5 to 7 days (intravenous administration of 1000 U of plasma-derived C1-inhibitor concentrate (Cetor; Sanquin, Amsterdam, The Netherlands).	Clinical effectiveness of the intervention	A severe attack of angioedema was defined as an attack of angioedema in the orofacial region or in the upper airway or a serious abdominal attack (severe abdominal pain with nausea and vomiting). Other attacks, such as swelling of the extremities or angioedema in the genitourinary region, were recorded as less severe angioedema attacks.	In the prophylaxis group the number of angioedema attacks was dramatically reduced after the start of prophylaxis, both in patients with hereditary C1-inhibitor deficiency and in patients with acquired C1-inhibitor deficiency (p<0.001 for both groups). In the overall prophylaxis group, self-administration of C1-inhibitor concentrate decreased the angioedema attack rate from 4.0 to 0.3 attacks per month. The mean interval between 2 prophylactic injections was 6.8 +/- 1 days. Seven (58%) of 12 patients were completely free of angioedema attacks after the start of prophylaxis, whereas 5 patients had occasional angioedema attacks despite prophylaxis but not more frequently than once per 6 months (3 patients [25%]) or once per 3 months (2 patients [17%]). In case of a severe angioedema attack during the prophylaxis period, patients used additional C1-inhibitor concentrate, which was successful in all instances.	-	-	-	Levi M, Choi G, Picavet C, Hack C. . Self administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency.. J Allergy Clin Immunol 2006;117(4):904-8.	No serious adverse events occurred with self-administration of C1-inhibitor during the follow-up period. Recorded adverse events included skin irritation at the site of injection (2.1% of injections), minor hematomas at the puncture site (1.6% of injections), dizziness at the time of injection (0.3% of injections), mild pain in the extremities after the injection (0.3% of injections), and a subfebrile increase in temperature (0.1% of injections). All adverse events were self-limiting and did not result in the need to seek medical assistance.	Conclusion: Intravenous self-administration of C1-inhibitor concentrate is a feasible and safe option and results in prevention of severe angioedema attacks in patients with C1-inhibitor deficiency. Clinical implications: Self-administration of C1-inhibitor concentrate could be a valuable and convenient treatment modality to prevent or treat angioedema attacks in patients with C1-inhibitor deficiency.	This is a small cohort study evaluating the effectiveness of self-administered intravenous administration of 1000 U of plasma-derived C1-inhibitor concentrate every 5-7 days (actual mean reported was 6.861 days) for prophylaxis of angioedema in HAE and AAE patients. The study included patients with HAE or acquired angioedema were included. Patients who, despite preventive medication or without preventive medication because of intolerance, had very frequent attacks of angioedema (>1 per 10 days) and who were therefore eligible for prophylactic administration of C1-inhibitor concentrate (prophylactic treatment) for an observation period of longer than 1 year. Overall baseline: 1 attack per 7.9 (+/- 2.0) days. Five of the 12 patients in the prophylaxis group had very frequent (>1 per 10 days) angioedema attacks despite full treatment with danazol and tranexamic acid and were therefore considered for C1-inhibitor concentrate prophylaxis. The other 7 patients did not receive danazol because of intolerable virilisation effects in women (n 5), severe dyslipidaemia in a patient with a history of cardiovascular disease (n 5), and nonspecific side effects (n 5). In these patients prophylaxis was started because all of them had very frequent (>1 per 10 days) angioedema attacks. Results showed a statically significant reduction in the number of angioedema attacks after the start of prophylaxis (p<0.001 for both HAE and AAE patients, analysed separately). In the combined (HAE and AAE) prophylaxis group, the angioedema attack rate decreased from 4.0 to 0.3 attacks per month (no p-value reported). No serious adverse events were reported. Limitations to the study include: small patient size, no reporting of the power of the study, no reporting of statistical methods used, no reporting of methods for obtaining baseline attack rates (therefore, possibly patient self-reported and concerning for potential recall bias), and methods for obtaining attack rates during the treatment period were through patient self-reporting (and therefore increase the possibility for error and bias in this study). Therefore, the results of this study are supportive of prophylactic treatment, but given the quality concerns of the study, this is considered only weak evidence.

Appendix

Literature search terms

Level	
Original search terms:	n/a
Updated search terms - Population	Hereditary Angioedema Hereditary Angioedemas Hereditary Angioneurotic Edema HAE "C1 Inhibitor deficiency" "C1 Esterase Inhibitor deficiency"
Updated search terms - Intervention	Cinryze C1 Esterase Inhibitor C1-Esterase Inhibitor Plasma-derived C1-esterase inhibitor Plasma-derived C1 Esterase inhibitor Plasma derived C1-esterase inhibitor Plasma derived C1 Esterase inhibitor C1 INH-nf C1INH-nf C1 Inhibitor Complement C1 Inactivator Proteins Prevent* Prophyla*

Updated search terms - Comparator	Androgens Fibrinolytic* Antifibrinolytic agents Epsilon aminocaproic acid EACA Danazol Danol Stanazolol Winstrol Tranexamic Acid EACA Berinert Ruconest Conestat alfa
Updated search terms - Outcome	None
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systemic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reached 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reached 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reached 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	The following studies were also included and are documented in Appendix 1: Levi M, Choi G, Picavet C, Hack C. . Self administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency.. J Allergy Clin Immunol 2006;117(4):904-8. Canadian Agency for Drugs and Technologies in Health. C1 Esterase Inhibitor for Prophylaxis against Hereditary Angioedema Attacks: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2015

Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
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