



Cinryze™ (C1-inhibitor) for the treatment of hereditary angioedema

Expert Rev. Clin. Immunol. 7(5), 569–573 (2011)

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Cinryze™ is a pasteurized, nanofiltered plasma derived concentrate of C1-inhibitor (pdC1-INH) licensed for the prophylactic treatment of hereditary angioedema. In a double-blind placebo-controlled crossover trial to evaluate Cinryze as prophylaxis, the frequency of attacks was halved (6.26 per 12 weeks on Cinryze versus 12.73 per 12 weeks on placebo). Furthermore, attacks were generally milder and of shorter duration. For treatment of acute attacks in patients receiving Cinryze, 1000 units, within 4 h of the start of an attack, the estimated time to the onset of unequivocal relief was reduced to 2 h, compared with more than 4 h in those treated with placebo. Cinryze and other similar products are going to change the future management of hereditary angioedema and have potential in other areas of medicine.

KEYWORDS: C1-inhibitor • Cinryze™ • hereditary angioedema • prophylaxis

Hereditary angioedema (HAE) is a rare autosomal dominant disorder affecting around 1 in 50000 persons in the USA, caused by a deficiency of the complement regulatory protein C1-inhibitor (C1-INH). It is C1-INH's additional role in the inhibition of bradykinin production that is responsible for the swelling association with HAE. HAE may present as one of two subtypes. In Type 1, 85% of HAE, there is a deficiency of C1-INH protein production. In contrast, in Type 2, 15% of HAE, C1-INH is produced and detectable in serum in normal concentration but has poor function [1]. In both Type 1 and Type 2 almost all are heterozygotes (only 2 cases of homozygous C1-INH deficiency have been described thus far [2,3]), so normal C1-INH is also found, but at reduced concentration, often less than 30% of normal [4]. Both are characterized by random and, at times, frequent attacks. The pathology is subcutaneous and submucosal swelling at the time of an acute attack. Abdominal and urogenital attacks causing acute and sub-acute obstruction can be very painful. In areas where tissue swelling is restricted by normal anatomy, attacks again may be painful. Laryngeal involvement may be life threatening.

More rarely, C1-INH deficiency may be found as a secondary disorder (acquired angioedema). Whilst these rare cases may respond to

C1-INH replacement therapy there are currently no data on the use of pdC1-INH (Cinryze™; ViroPharma) in this context and we will not consider it further here.

A third estrogen-dependent form of HAE has been described, in which C1-inhibitor levels and function appear entirely normal [5]. In this form, different studies report contradictory responses to C1-INH replacement therapy [5,6]. Patients with this condition were excluded from the Cinryze trials and will not be considered further here.

The C1-inhibitor is a serine protease inhibitor that has several functions (Box 1). Deficiency of C1-INH therefore results in dysregulation of several pathways, resulting in increased vascular permeability and local edema. The subsequent unopposed production of bradykinin appears to be pivotal in disease expression. It is responsible for the relaxation of epithelial control of intravascular fluid, thereby generating the angioedema [7]. A more detailed review of the pathways involved has recently been published [8].

Purified human C1-inhibitor has been available for many years in Europe (Berinert P™, CSL Behring) and has now been shown to be an effective treatment, particularly in acute attacks [9] or as short-term prophylaxis [10]. The use (unlicensed in the USA

Box 1. A brief listing of the functions of C1-inhibitor, emphasizing the pivotal role played in the complement classical pathway, the kallikrein-kinin (contact) pathway, coagulation and fibrinolysis.

- Main regulator of the early activation steps of the classical pathway of complement (C1s, C1r, MASP1, MASP2)
- Regulates conversion of prekallikrein to kallikrein and therefore bradykinin production
- Blocks the cleavage from high molecular weight kininogen to bradykinin
- Inhibitor of factor XIIa (Hagemann factor)
- Inhibitor of factor XII fragment (XII_f)
- Inhibitor of factor XIa
- Inhibitor of plasmin

prior to 2009; licensed in Europe for over 20 years) of C1-INH concentrate has been supported by both the UK [11] and Canadian–Hungarian [12,13] consensus documents. The UK consensus document further recommended that all patients should have access for emergency treatment [11]. Berinert has an excellent safety record [14] and is now approved in the USA for acute attacks and facial swelling [101]. That said, all plasma-derived products have a theoretical possibility of transmission of infectious agents, and the clinician must remain vigilant to this possibility. In order to further reduce the possible risk of viral transmission, Cinryze and Ceter (Sanguin) has an additional nanofiltration step after pasteurization. Cinryze is manufactured from plasma from US donors. Recently, data from two randomized trials to evaluate the efficacy of Cinryze have been published [15].

Pharmacology

pdC1-INH replaces absent or nonfunctional C1-INH. In treating attacks, the most important action is on the contact pathway of the coagulation cascade, preventing inappropriate activation and thus abrogating the production of bradykinin. C1-INH regulates the conversion of prekallikrein to kallikrein. Deficiency in C1-INH leads to an increase in kallikrein and hence the production of bradykinin. Bradykinin is a potent vasodilator involved in pathways which generate the mediators nitric oxide, endothelium-derived hyperpolarizing factor and prostacyclin (PGI₂). Restoring C1-INH inhibits further production of bradykinin. Existing bradykinin rapidly decays and so this corrects the increased vascular permeability and thus reduces the edema and associated symptoms.

Pharmacokinetics

A randomized, parallel-group study was conducted in subjects with HAE (who were not experiencing an attack at the time) [102]. Patients received either a single dose (1000 units) of pdC1-INH (Cinryze) or a double dose (1000 units followed by a further 1000 units 1 h later). In the first group, the mean half-life for functional C1-INH was 56 h (range 11–106 h) and in the second 62 h (range 16–152 h). Mean functional C1-INH increased from 0.31 to 0.68 U/ml in the first group and from 0.33 to 0.85 U/ml in the second. In both groups, an increase in complement C4 was also demonstrated. It should be noted that the

pharmacokinetics of C1-INH may vary according to the provenance of the product (plasma-derived or recombinant) and the rate of consumption during an attack. Of particular note, recombinant C1-INH has a half-life in asymptomatic HAE patients of only 2.9 ± 0.6 h, when administered at 100 U/kg [16].

Acute attacks of HAE clinical presentation

Acute attacks are characterized by subcutaneous and submucosal swellings, which

may be in any part of the skin, the respiratory tract or the gastrointestinal tract. The consequences of this may vary from painless angioedema of the skin, to severe abdominal pain to life-threatening angioedema involving the larynx [17]. Attacks are episodic and patients vary considerably in their presentation from occasional and mild-to-frequent (up to several times a month) and severe.

Prophylaxis of attacks of HAE

Attacks are frequently disabling, either due to their appearance or obstruction of an organ causing pain and loss of function. For this reason treatment is actively sought.

Prophylaxis may either be short term or long term. Short-term prophylaxis might be appropriate in anticipation of times of physiological or psychological stress, for example to prepare a patient for elective dental surgery [10]. Long-term prophylaxis should be considered in patients with a history of frequent or severe attacks. Until recently, long-term prophylaxis was by either attenuated androgens (danazol, stanozolol) or antifibrinolytics (tranexamic acid, ϵ -aminocaproic acid) [11]. pdC1-INH has now been added to this list.

In a double-blind placebo-controlled crossover trial to evaluate Cinryze as prophylaxis in HAE, Zuraw *et al.* noted the frequency of attacks was halved (6.26 per 12 weeks on Cinryze vs 12.73 per 12 weeks on placebo, $p < 0.0001$) [15]. Dosage of C1-INH was 1000 units twice weekly. Furthermore, the attacks were generally milder and of shorter duration. However, it is worth noting that benefit was seen in 19 of the 22 patients enrolled. Two patients had an increased attack rate whilst on replacement therapy and one showed no change.

This study shows that Cinryze has good efficacy in the prophylaxis of C1-INH deficiency over a 12-week period.

During this trial 21 out of 24 subjects had one or more adverse events. Of those classified as possibly related to the study drug (six events), three occurred during the placebo period in a single individual (chest discomfort, cough, erythema) and three occurred during the C1-INH period (three subjects; one pruritis and rash, one light headedness, one fever).

Treatment of acute attacks of HAE

A trial of treatment in acute attacks was carried out alongside the prophylaxis trial. Patients were randomized to receive either placebo or 1000 units of pdC1-INH (Cinryze) within 4 h of the

start of an attack. The estimated time to the onset of unequivocal relief was reduced to 2 h in the Cinryze group, compared with more than 4 h in those treated with placebo [15].

During this trial, six out of 36 subjects assigned to C1-INH and seven out of 35 assigned to placebo had adverse effects. Of these, only three were possibly attributed to the study drug, two were in the placebo arm (one carpal tunnel spasm, one contact dermatitis) and one in the C1-INH arm (rash at injection site) [15].

Current guidelines

The use of C1-INH for the treatment of HAE is advocated in international guidelines [11–13,18]. Until recently, C1-inhibitor was not approved for use in the USA. Cinryze was approved by the US FDA in 2008 for prophylactic use in HAE. In this context, it has been clearly shown to reduce the frequency of attacks [14]. Cinryze is not yet licensed for use in acute attacks in the USA.

Alternative products

In many ways experience with Cinryze has mirrored that of Berinert. The International Multicenter Prospective Angioedema C1-inhibitor Trial 1 (IMPACT1) was completed in 2007 [9]. This too showed good efficacy for treating C1-INH deficiency. The median time of onset of symptom relief was 90 min for those treated with placebo versus 30 min for those treated with 20U/kg C1-INH. The difference was even more marked in those with severe symptoms, where median time to onset of relief of symptoms was 810 min in the placebo group. The side-effect profile was similar with adverse events reported in 18 out of 41 patients in the placebo group compared with nine out of 46 in the patients treated with C1-INH. None were considered serious. There were no injection-site reactions and no anaphylactic reactions. In contrast to Cinryze, Berinert is licensed for acute HAE attacks, but not licensed for long-term prophylactic use in the USA.

In addition to the purified human C1-INH products (Cinryze, Berinert P) a recombinant human C1-INH (rhC1-INH) has been developed (Rhucin™; Pharming [marketed as Ruconest in Europe]). This is expressed in rabbits and extracted from their milk. This product has a shorter half-life in serum [16] although this does not seem to reduce its efficacy. No direct comparisons have been performed with any product. Some rabbit proteins may remain after purification and these are potentially allergenic. For this reason it is recommended that patients be tested for rabbit allergy prior to administration (in Europe). Patients allergic to rabbit should not receive rhC1-INH. rhC1-INH is administered at a much higher dose than the purified products (50 U/kg or 100 U/kg). The higher dose is rapidly effective with a short median time to onset of relief of symptoms; 66 min for 100 U/kg, 122 min for 50U/kg and 495 min for placebo. As with the purified products, there were few adverse reactions to treatment, these being more common in the placebo group. No postexposure antibodies against recombinant C1-INH or host-related impurities were found [19].

It would appear that in terms of efficacy (in so far as a comparison is possible with different end point scoring criteria), that the plasma-derived products could be used interchangeably. However,

each is licensed differently in the USA; Cinryze for prophylaxis and Berinert for acute attacks. rhC1-INH is not yet licensed in the USA.

There are two other important therapies that have recently come to the market that act on the kinin system, icatibant (Jerini; a selective bradykinin B2-receptor antagonist) and ecallantide (Dyax; a recombinant kallikrein inhibitor). Trial data on both of these has recently been published [20,21] and both have efficacy for treatment of acute attacks of HAE. Ecallantide is licensed in the USA but not Europe and icatibant is licensed in Europe and not the USA.

Expert commentary

Remarkably, we now have two plasma-derived products, one recombinant product and two novel products to inhibit bradykinin production or effect. As there are no direct comparative studies and where the therapy of choice is replacement of C1-inhibitor then it is reasonable to assume, on the present data, that the efficacy of the two plasma-derived products (Berinert and Cinryze/Cetor) is similar.

Consider prophylactic treatment. Previous prophylactic treatment has been focused on the use of the anti-fibrinolytics (tranexamic and ϵ -aminocaproic acid), and on attenuated androgens. The former are felt to be less efficacious than the current treatments and the latter have a high rate of side effects resulting in their discontinuation. This then necessitates the use of pdC1-INH. Cinryze is well placed for this in the USA. Other pdC1-INH has been used in this way, off-license.

We remain uncertain as to whether purchasers of healthcare will commit to life-long prophylaxis with C1-inhibitor on the basis of only 12-week data and the inherent individual variability of an individual's frequency of attacks. The role of rhC1-INH in prophylaxis is yet to be established due to its shorter plasma half-life.

Regarding acute treatments, there is more competition, with the use of bradykinin B2-receptor antagonist (icatibant), a specific inhibitor of plasma kallikrein (ecallantide) and rhC1-INH, as well as established purified plasma products (Berinert, Cinryze/Cetor) and attenuated androgens.

Currently, for an acute attack necessitating treatment, the choice would be between of an infusion of pdC1-INH (Cinryze or Berinert P), rhC1-INH or a dose of ecallantide (in the USA) or icatibant (in Europe). The exact choice would be down to individual circumstances and clinician.

There is a large group of patients requiring acute treatment in whom inhibition of the kinin system by means other than C1-INH may not be appropriate. This group includes patients who are pregnant, for prophylaxis or where the use is outside of the licensed conditions. We therefore feel that there is room for all but ultimately, safety, license, ease of use and price will determine use as all appear efficacious.

Five-year view

Since the UK consensus guidelines were written in 2005 [11] there has been a very welcome array of licensed treatments. For acute attacks, we have inhibitors of bradykinin, at different points in

the pathway, icatibant and ecallantide. We also now have available pdC1-INH for treatment of HAE, and perhaps in the near future rhC1-INH. Efficacy is difficult to directly compare due to different measurement mechanisms. The challenge is to learn how best to incorporate these into our model of care.

The model of care is very much going to progress to immediate patient access to the treatment. This will involve much more self administration, either via the intravenous or subcutaneous route [18].

Additionally, C1-INH has been used in a number of scenarios outside HAE. C1-INH attenuates renal impairment in patients with severe sepsis [22]. Its use has also been advocated in vascular leak syndrome and in myocardial infarction, although the evidence remains relatively inconclusive [23]. It is not yet clear how much of a role it will have but it is certainly an area of interest for both recombinant and plasma-derived products.

Looking at acute attacks of HAE first, we would predict that, as earlier treatment results in a shorter duration of symptoms, whichever treatment allowed the earliest intervention would be most adopted. Self administration would be the ideal choice and subcutaneous delivery might be the most rapid and convenient modality, although there are no comparative data yet.

This would also be likely to be a product that is suitable for out of hospital use. We know that icatibant can be administered subcutaneously, and (in Europe) has a license for self administration. It will not be suitable for all patients and for these C1-INH will be used.

Patients can be trained to self-administer C1-INH intravenously and this is currently an option for some patients [18]. We are awaiting data from a multicenter, open-label, multi-dose Phase II of subcutaneously administered C1-INH, which may then become an alternative [103].

Prophylactic treatment is likely to move away from the older therapies of androgens and tranexamic acid, in view of the side effects [24], to use of C1-INH products. The most chosen product will be that that can be self administered with the longest time period between doses. Again, there is great interest in the pharmacodynamics of subcutaneously administered C1-INH, but at present Cinryze, administered intravenously, has the clinical data to support its efficacy [15]. Other C1-INH products have been used in this role but are not licensed in the USA.

Conclusion

For those patients who have frequent attacks, or for whom avoidance of an attack is essential, there now exists a new option for prophylaxis, Cinryze. There are further development needs. We do not know what the impact will be of the long-term use over the whole lifetime of a patient. Is prophylaxis needed for every patient for every day of their life, or will it be possible to return to symptomatic control after significant periods of prophylaxis? Now that we have the necessary tools to treat patients' symptoms we need to work out the best way to use them. Never have patients with HAE had such a good choice. This is an excellent situation in which to be!

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Hereditary angioedema is a rare autosomal dominant disorder resulting from deficiency of C1-inhibitor.
- Attacks are frequently disabling, either due to their appearance or obstruction of an organ causing pain and loss of function.
- Cinryze™ is a pasteurized, nanofiltered plasma-derived concentrate of C1-inhibitor (pdC1-INH).
- Cinryze is licensed in the USA for the prophylactic treatment of hereditary angioedema. Patients require treatment every 3–4 days.
- As prophylaxis, Cinryze reduces both frequency and severity of attacks in the majority of patients; a minority did not respond or got worse.
- Although not yet licensed in the USA, Cinryze also appears to be effective in the treatment of acute attacks.

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