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REVIEW

Self-administered C1 esterase inhibitor concentrates for the management of hereditary angioedema: usability and patient acceptance

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Abstract: Hereditary angioedema (HAE) is a rare genetic disease characterized by episodic subcutaneous or submucosal swelling. The primary cause for the most common form of HAE is a deficiency in functional C1 esterase inhibitor (C1-INH). The swelling caused by HAE can be painful, disfiguring, and life-threatening. It reduces daily function and compromises the quality of life of affected individuals and their caregivers. Among different treatment strategies, replacement with C1-INH concentrates is employed for on-demand treatment of acute attacks and long-term prophylaxis. Three human plasma-derived C1-INH preparations are approved for HAE treatment in the US, the European Union, or both regions: Cinryze®, Berinert®, and Cetor®; however, only Cinryze is approved for long-term prophylaxis. Postmarketing studies have shown that home therapy (self-administered or administered by a caregiver) is a convenient and safe option preferred by many HAE patients. In this review, we summarize the role of self-administered plasma-derived C1-INH concentrate therapy with Cinryze at home in the prophylaxis of HAE.

Keywords: C1-INH concentrate, hereditary angioedema, disease management, first line, prophylaxis, self-administration

Introduction

Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency is a rare autosomal dominant disorder characterized by episodic swelling typically involving the skin, abdomen, and larynx.[1,2] Studies suggest that HAE affects up to one in 50,000 people worldwide, regardless of race or ethnicity.[3–5] The majority of HAE cases are due to the deficiency of functional C1-INH. HAE due to C1-INH deficiency is further divided into HAE types I and II, and the presentations of these subtypes are clinically indistinguishable. There are ~300 identified mutations of the C1-INH gene (*SERPING1*) located at 11q12–q13.1 related to HAE.[6]

HAE type I accounts for 85% of cases. Patients with this form of HAE have low-level production of antigenic C1-INH. These patients have normal antigenic levels but abnormal C1-INH function.[7,8] Under physiological conditions, C1-INH regulates the activities of four interlinked proteolytic enzyme cascades, namely, the complement, contact (kallikrein–kinin), fibrinolytic, and coagulation pathways (Figure 1). In particular, C1-INH is the primary inhibitor of the kallikrein–kinin system via inactivation of activated factor XII (factor XIIa) and kallikrein. The excessive production of bradykinin via an overactive kallikrein–kinin system accounts for episodic swelling in patients with HAE.[4,9,10]

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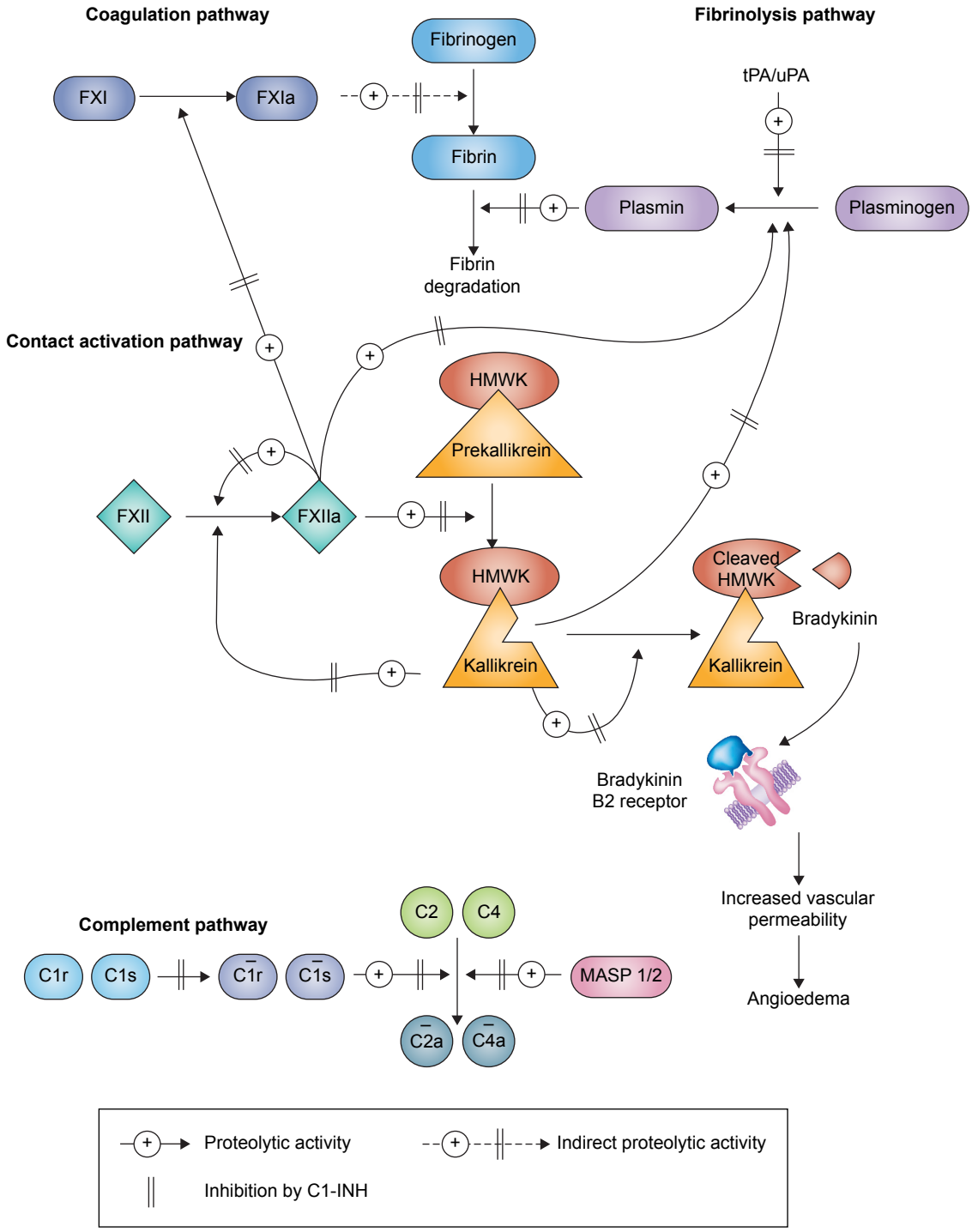

Figure 1 Pathways inhibited by C1-INH.
Notes: Horizontal bars over the complement names indicate activation. Copyright © 2014. Future Medicine Ltd. Reproduced from Bork K. Pasteurized and nanofiltered, plasma-derived C1 esterase inhibitor concentrate for the treatment of hereditary angioedema. *Immunotherapy*. 2014;6(5):533–551.[11]
Abbreviations: C1-INH, C1 esterase inhibitor; FXI, factor XI; FXIa, activated factor XI; FXII, factor XII; FXIIa, activated factor XII; HMWK, high molecular weight kininogen; MASP, mannose-binding lectin-associated serine protease; tPA/uPA, tissue/urokinase plasminogen activator.

For most patients with HAE, their clinical presentation is often unpredictable. The mean time at which the initial symptoms of HAE appear is ~11 years of age. HAE attacks often become more frequent and severe during adolescence and adulthood.[1,4,12] The pattern of HAE attacks may vary tremendously among patients and throughout a patient's life. Many attacks may involve multiple organ systems. Patients can experience symptoms weekly, while others have attacks less than once a year.[12–15]

Without treatment, most episodes of HAE last for 2–5 days.[16] Laryngeal attacks, which occur in up to 50% of HAE patients, are potentially life-threatening;[12,17–19] without

medical intervention, the mortality rate due to laryngeal edema is up to 40%.[18] HAE-associated abdominal attacks have a high symptom burden because local mucosal swelling gives rise to severe abdominal pain, nausea, and vomiting, often necessitating hospitalization. Furthermore, unnecessary exploratory surgery is sometimes performed in undiagnosed patients.[20]

The triggers for a particular attack in a patient with HAE are not always clear, but several factors have been linked to the onset of HAE attacks. The common triggers may include trauma, surgical and dental procedures, stress, infection, hormonal changes, and treatment with estrogens or angiotensin-converting enzyme inhibitors.[21–23] Due to the unpredictable nature of the disease, many patients with HAE are constantly living in fear of another severe attack, disfigured face, impaired functions of hands and feet, agonizing abdominal pain, and possible airway compromise. In addition, they worry about their children inheriting the disease.[15,24] Consequently, HAE exerts a profound humanistic burden, with effects including physical and emotional trauma, educational or professional underachievement, financial hardship, and poor quality of life.[15,24–28]

HAE treatments have been developed for short-term or long-term prophylaxis and for treating acute attacks.[29–31] There are a few human plasma-derived C1-INH concentrates that are currently approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for HAE treatment (Table 1). In line with the current recommendations, all HAE attacks should be treated.[29–31] Moreover, long-term prophylaxis should be considered when the patient has severe and frequent attacks that cannot be adequately controlled by on-demand therapies or when rapid access to treatment of an attack is unavailable.[29–31]

Prophylactic treatment with C1-INH concentrates

To minimize the effect of the disease on patients, effective prophylaxis against HAE attacks is most desirable. The effectiveness of androgens such as danazol is limited by adverse events (AEs). Oral antifibrinolytics such as tranexamic acid have relatively poor efficacy for this rare indication.[29–31] Prophylactic administration of C1-INH concentrates replenishes plasma C1-INH activity and thus addresses the fundamental cause of HAE attacks. There are three highly purified human plasma-derived C1-INH concentrate preparations that are commercially available for HAE treatment (Table 1), but only Cinryze® (Shire ViroPharma Incorporated, Lexington, MA, USA), a nanofiltered human C1-INH concentrate,

Table 1 Approval status of intravenously delivered human plasma-derived C1-INH concentrates for treatment of or prophylaxis against acute HAE attacks

Trade name (company)	Approval status	Dosage	Storage and plasma half-life in adults	Administration
Berinert® (CSL Behring)	EU: approved in April 2013 for short-term prophylaxis only[32] FDA: approved in October 2009 for acute facial and abdominal attacks only[33]	20 IU/kg	Lyophilized and stored at 2°C–25°C; 32–47 hours	For >12 years and <65 years of age; can be self-administered or administered at home
Cinryze® (Shire ViroPharma Incorporated)	EU: approved in June 2011 for acute attacks, short-term, and long-term prophylaxis[34] FDA: approved in October 2008 for long-term prophylaxis[35]	1,000 U every 3–4 days; infusion rate 1 mL/min	Lyophilized and stored at 2°C–25°C; 48±10 hours	In adults and adolescents only (>12 years of age); can be self-administered or administered at home
Cetor® (Sanquin)	EU: approved in 1997 in the Netherlands, Belgium, Finland, France, and Luxembourg only for acute attacks[36] FDA: not approved	1,000 U	Lyophilized and stored at 2°C–8°C; 48±10 hours	In adults and adolescents only (>12 years of age); can be self-administered or administered at home

Notes: Short-term prophylaxis refers to prophylaxis before surgical or dental procedures. Long-term prophylaxis refers to routine prevention. "For acute attacks" means on-demand treatment.
Abbreviations: C1-INH, C1 esterase inhibitor; EU, European Union; FDA, US Food and Drug Administration; HAE, hereditary angioedema.

is recommended as a first-line therapy for routine long-term prophylaxis (in adolescent and adult patients). Berinert® (CSL Behring, King of Prussia, PA, USA) is approved for the short-term prevention (in the EU), and Cetor® (Sanquin, Amsterdam, the Netherlands) has no approval for prophylactic use, although it has the same qualitative and quantitative composition in terms of the active substance as Cinryze.[37] Cinryze is also the only approved C1-INH concentrate for the treatment, preprocedure prevention, and long-term prevention of HAE attacks (in adolescents and adults) albeit only in the EU; in the US, its approved indication is limited to long-term prophylaxis.[38]

Ruconest® (Pharming Group NV, Leiden, the Netherlands),[39,40] which is a recombinant C1-INH produced in transgenic rabbits, ecallantide (Kalbitor®; Dyax Corporation, Burlington, MA, USA),[41] a kallikrein inhibitor, and icatibant (Firazyr®; Shire, Lexington, MA, USA),[42,43] a bradykinin B2 receptor antagonist, are approved treatments for acute HAE attacks in the US, the EU, or both. Because they are not plasma-derived C1-INH concentrates, these drugs are not discussed any further in this review.

The objective of this review is to summarize the role of self-administered plasma-derived C1-INH concentrate therapy at home for the prevention of HAE.

Clinical studies

Plasma-derived C1-INH concentrates have performed well as preventative measures against HAE attacks in controlled studies, as well as in observational and descriptive studies.[44,45]

Cinryze

The preprocedural administration of Cinryze before dental, surgical, or interventional diagnostic procedures was found to prevent edematous episodes; in a retrospective analysis of data from two acute treatment trials, 89 of 91 procedures did not trigger a subsequent HAE attack.[46]

The long-term protective efficacy of Cinryze (open label) was evaluated in a placebo-controlled crossover study of patients with a history of at least two attacks per month. These patients were randomly assigned 1,000 units of open-label nanofiltered C1-INH concentrate for the prevention of acute HAE attacks or a placebo, administered twice weekly.[45] Cinryze had a significant benefit over placebo treatment, as evidenced by a reduction in the number of attacks per 12-week period (6.26 with C1-INH concentrate vs 12.73 with placebo; $P<0.001$). The severity and duration of attacks, the need for open-label rescue therapy, and the total number of days with symptoms of swelling were also reduced.[45] This study also revealed that patients with HAE had significantly better health-related quality of life following 12 weeks of routine prophylaxis with Cinryze. This preventative treatment was compared with acute treatment of attacks without long-term prevention (patients receiving a placebo).[47] In an open-label multicenter extension phase of this study, treatment with Cinryze for up to 2.6 years also exerted durable prophylaxis in most patients with HAE, with a 93.7% reduction in the median number of attacks per month (3.00–0.19).[48]

A further study found that escalating the dose of Cinryze up to 2,500 U every 3 or 4 days is well tolerated and may be required in patients who are not responsive to the approved dose of 1,000 U administered at the same frequency.[49]

Berinert

In a retrospective study based on clinical record review, preprocedural Berinert administration was associated with a lower incidence of facial swelling or laryngeal edema after tooth extraction, compared with patients who did not receive prophylaxis. In a large-scale observational study with long-term follow-up, short-term prophylaxis with Berinert for various dental and nondental surgical procedures reduced the number of patients who experienced postprocedural attacks significantly more than tranexamic acid and danazol.[50]

The data regarding the use of Berinert as a long-term prophylactic measure are limited. However, non-placebo-controlled studies showed that this preparation reduced the severity and number of HAE attacks.[51–53]

Real-world and home use

Administration of plasma-derived C1-INH in a health care facility may be hindered by accessibility and convenience factors, and this is particularly challenging for those who require treatment twice per week. This may affect the patient's time needed to receive treatment and patients' adherence to the regimen. Home infusion provides an easy and convenient modality of C1-INH delivery and use, and a significant proportion of patients prefer self-administered plasma-derived C1-INH at home (Table 2).

Home administration with plasma-derived C1-INH concentrates results in reduced frequency of attacks compared with previous treatment such as danazol or tranexamic acid, fewer days spent in a hospital, and fewer days missed from school or work.[51,54,55] Overall, self-administration of intravenous C1-INH concentrate is associated with enhancing the quality of life of patients with HAE.[51,56]

Table 2 Summary of real-world observational data for home-based HAE therapy with human plasma-derived C1-INH

Drug name	Prior preventative medicine	Number of patients in study	Observational study findings of home therapy	References
Berinert®	Danazol	22 with severe symptoms and incompatibility or lack of response to danazol	Median number of attacks/year decreased ($P<0.001$) 24 laryngeal episodes/year ceased No viral transmission	Kreuz et al[51]
Berinert	Physician-administered Berinert	15 pediatric (on-demand treatment) and five pediatric (prophylaxis)	Significant increase in dosing frequency All attacks including laryngeal edema treated Mean days hospitalized reduced from 3.8 to 0.11/year No side effects or injection site reactions Median time between attack onset and administration reduced from 67.5 to 15 minutes TOSR reduced from 60 to 40 minutes	Kreuz et al[55]
Berinert	Danazol and/or tranexamic acid	Seven with severe or frequent symptoms	After 3–48 months, improved quality of life, DLQI score reduced from 12.6 to 2.7 ($P<0.001$), improved SF-36 scores	Bygum et al[56]
Cetor®	Danazol and/or tranexamic acid	31 on-demand treatment (28 with HAE, three with AAE-C1-INH) and 12 prophylaxis (ten with HAE, two with AAE-C1-INH)	No serious complications at 27–72 months, follow-up All patients capable of intravenous self-administration Technical failure rate <2% Significantly shorter TOSR (2.2 hours) In prophylaxis group, attack rate decreased from 4 to 0.3 per month	Levi et al[54]

Abbreviations: AAE-C1-INH, acquired angioedema due to C1 esterase inhibitor deficiency; C1-INH, C1 esterase inhibitor; DLQI, Dermatology Life Quality Index; HAE, hereditary angioedema; SF-36, 36-Item Short-Form Health Survey; TOSR, time to onset of symptom relief.

Safety and tolerability

Long-term prophylaxis with Cinryze was well tolerated in a placebo-controlled crossover study and its open-label extension phase.[45,48] The most common AEs observed were headache, nausea, rash, and vomiting. A recent systematic review of the literature concluded that Berinert also has a comparable side effect profile.[44]

Hypersensitivity reactions and serious arterial and venous thromboembolic events have been reported at the recommended dose of Berinert[32] and the prescribed dose of Cinryze.[38]

The transmission of blood-borne diseases (viruses or prions) is an inherent risk for all human plasma-derived products, including Cinryze and Berinert (Table 3). In a report of ~260 patients who received Cinryze in clinical studies, a total of ~14,000 doses were administered; none of these patients became positive for parvovirus B19, hepatitis B, hepatitis C, or HIV.[38] A review of the literature for Berinert also ascertained that it was not associated with transmission of viruses.[44]

Overall, numerous studies have demonstrated that home administration of HAE medications is safe, with a low occurrence rate of AEs.[51,54,56–59]

The role of home self-infusion in HAE management

Current clinical guidelines recommend home-based treatment where feasible and that all patients have access to medication supply at all times.[30,60–63] Therefore, a large proportion of patients on long-term prophylaxis using Cinryze choose the home therapy option. The result is significantly reduced HAE-related hospitalizations, androgen-derivative usage, and greater patient satisfaction.[57,64]

Cinryze, initially approved by the FDA in 2008, was approved for self-administration (in patients who receive sufficient training) by the FDA in June 2009[65,66] and by the EMA in June 2011.[67] In June 2010, in a study performed in the US, 243 of 516 patients (47%, 5–84 years of age) administered Cinryze at home, with the remainder of patients receiving treatment in the physician's office or at an infusion center. The proportion of patients receiving treatment in a home setting (ie, 20% of the total study population) who self-administered the drug was 42%, and 16% and 23% of patients were administered the drug by a family member or a home health care worker, respectively.[68] In 2012, following the implementation of an infusion training program in December 2010, the proportion of patients receiving Cinryze at home (rather than at a physician's office or infusion center) increased to 76% and the percentage who self-administered increased from 20% to 44%.[69] In 2010, 30- to 64-year-olds were the largest

Table 3 Treatment-related AEs associated with commercially available human plasma-derived C1-INH concentrates for HAE treatment

AEs	Berinert®	Cinryze®	Cetor®
Allergic or hypersensitivity reactions	Includes hives, generalized urticaria, chest tightness, wheezing, hypotension, and anaphylaxis	Allergic reactions that may occur include wheezing, difficulty breathing, chest tightness, cyanosis (lips and gums), tachycardia, facial swelling, faintness, rash, hives (use is not recommended if the patient has experienced a life-threatening immediate hypersensitivity reaction to the product, including anaphylaxis)	Tachycardia, hyper- or hypotension, flushing, hives, dyspnea, headache, dizziness, nausea, anaphylaxis
Serious events	Arterial and venous thromboembolic events	Arterial and venous thromboembolic events, cerebrovascular accidents	Hypersensitivity or anaphylactic shock
Plasma-derived risks	Risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt–Jakob disease agent	Risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt–Jakob disease agent	Risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt–Jakob disease agent (only one viral removal step in purification process) Physician may recommend hepatitis A or B vaccination if this product is administered frequently
Most serious	Increase in the severity of HAE-associated pain		Reaction at injection site, rise in temperature (classified as rare)
Most common	Dysgeusia (>4% of patients and more frequently than in the placebo group)	Headache, nausea, rash, and vomiting	All considered mild and rare
Additional risks	Has not been evaluated in pregnant women or nursing mothers, and safety and efficacy have not been established in children (0–12 years of age) or in the geriatric population	Has not been evaluated in pregnant women or nursing mothers Risk associated if taking contraceptive pills or androgens Safety and efficacy not established in children (0–11 years of age)	Has not been evaluated in pregnant women or nursing mothers No studies on the ability to drive or operate machines post administration Safety and efficacy not established in children (0–11 years of age)
References	Berinert safety information[70]	Cinryze safety information[71] Cinryze prescribing information[38]	Cetor summary of product characteristics[72] Cetor package leaflet[73]

Abbreviations: AE, adverse event; CI-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

age group in which 50% self-administered, but the patient group who were reported to be self-administering Cinryze excluded children (0–12 years of age) or patients >65 years of age.[68,69] In 2012, only one child and ten older patients were found to be self-administering.[69] The percentage of patients who received C1-INH at home in 2012 was found to be similar across all age groups (≤12 to ≥65 years of age). A total of 57.9% of patients receiving home infusions of Cinryze did so by self-administration.[69]

A European multicenter study of patients with HAE using Cinryze showed that the majority of doses (87%) used for routine or preprocedural prophylaxis were given at home and 67% were self-administered.[74]

For Berinert, as of May 2013, a multicenter registry across the US and the EU found that >90% of intravenous infusions for prophylaxis were given by the patient or a caregiver at home,[75] compared with the 49% uptake rate reported by a German center 3 years earlier.[57]

Relatively fewer pediatric patients with HAE are given long-term C1-INH prophylactic treatment.[76] In a UK survey of 111 children with HAE, one-third were receiving routine preventative medications, of whom only four were receiving C1-INH concentrate. Ten of 16 centers were able to offer training to administer C1-INH concentrate to children at home, but only two patients were participating in this process.[76]

The model for delivering plasma-derived C1-INH concentrates in a home setting is based on other successful home therapy programs, such as those for managing immunodeficiency, hemophilia, and other chronic conditions.[57,77–79] The most notable benefit of C1-INH concentrate self-administration is flexibility and convenience, thus avoiding regular time-consuming visits to the clinic. The process empowers patients to take control of their disease to the extent that they can resume a normal, less restricted life, without the need to visit a doctor's office for treatment. Although the concept of self-administration can be intimidating for both the patient and the physician, the provision of appropriate education and training, possibly with a few hours of counseling by their health care provider, enables most patients to feel comfortable with home therapy.[80,81]

However, it should be noted that, despite the fact that all patients with HAE requiring long-term prophylaxis using C1-INH concentrate are recommended to be considered for home therapy,[61,62,68] the eligibility of patients for this treatment is determined by several factors (Table 4). Patients may experience several challenges, such as acquiring the skill of infusion administration, and other potential barriers include managing nursing resources for patient training and the patient's mental capacity.[83]

For self-administration with C1-INH concentrate, venipuncture using a small (eg, 28G) butterfly needle infusion

Table 4 Patient eligibility criteria for home-based HAE treatment

Factor	Patient criteria for home therapy	References
Nature of HAE	CI-INH deficiency	Gompels et al[16]
Severity and frequency of attacks	Severe or frequent symptoms	Kreuz et al;[51] Bygum et al[56]
Efficacy or tolerability of current prophylactic therapies	Incompatibility or lack of response to danazol or tranexamic acid	Kreuz et al;[51] Levi et al[54]
Current effect of HAE on quality of life	Serious and affected by delay in visiting emergency departments in the event of an attack	Bygum et al[56]
Expectations	Managed via education, training, and support	Longhurst et al[58]
Mental or physical capacity	Essential for self-administration	
Compliance or reliability	Should be optimal	Gompels et al[16]
Maintaining infusion skill set	Infusion required at least once every 3 months	Gompels et al[16]
Consent	Should be obtained in written format	Gompels et al[16]
Awareness of risk	Informed of risk of transmissible infection from a plasma-derived product	Gompels et al[16]
Partner or caregiver	Available at the time of treatment (particularly important if age or disability is a factor)	Gompels et al[16] Gower et al[84]
Local family practice support	Written confirmation of support from general practitioner, including preplanned emergency care if required	Gompels et al[16]
Communication access	Close proximity of a telephone when administering treatment	Gompels et al[16]
Venous access	Good venous access (current approved treatments are intravenous)	Gompels et al[16]
Plan of action if administration is difficult	Agreement by patient to call the emergency service if self-cannulation is unsuccessful at the time of the HAE attack	Gompels et al[16]
Physician's risk–benefit judgement	Do the benefits of home therapy outweigh the risks and possible side effects for the patient?	Cicardi et al[61]

Abbreviations: CI-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

set is recommended;[82] however, safety concerns related to this self-administration procedure exist. Findings from an observational study of the use of Berinert indicated that all AEs (mild cases of redness at the injection site and vertigo) occurring after self-administration were due to either intravenous administration that was too rapid or administration at a suboptimum temperature (ie, <25°C).[51] Furthermore, indwelling venous ports are associated with complications such as infection and occlusion that can increase the frequency of attacks, and hence, they should be avoided whenever possible and only be considered where timely venous access is difficult.[82] In general, however, cannulation failure is uncommon with self-administration after sufficient training, and self-administration may support vein preservation more than that possible in a hospital setting.[54]

Summary and future development

Intravenous administration of C1-INH concentrate is a safe and effective strategy for short-term (preprocedural) and long-term prophylaxis against HAE attacks. The majority of patients who receive Cinryze as a long-term prophylaxis measure can safely administer this product at home. Most notably, 50% of 30- to 64-year-old patients can perform self-infusion. The positive outcomes associated with Cinryze in the home setting may be even better with subcutaneous formulations of plasma-derived C1-INH concentrate, which are currently under clinical evaluation. Clinical trials are underway to establish whether subcutaneous delivery of plasma-derived C1-INH will provide a comparable efficacy benefit. A Phase III randomized, double-blind study for HAE types I and II was recently initiated (ClinicalTrials.gov identifier NCT02584959) to test a low-volume subcutaneous formulation of Cinryze,[85] following a Phase II trial with a different subcutaneous formulation (ClinicalTrials.gov identifier NCT01756157).[37] An open-label, dose-ranging, crossover Phase II trial (COMPACT) indicated that subcutaneous administration of plasma-derived C1-INH concentrate (CSL830; CSL Behring) was well tolerated, and there was a dose-dependent increase in physiologically relevant, functional C1-INH plasma levels.[86] A Phase III randomized, crossover, double-blind study to evaluate subcutaneously administered Berinert for the prophylactic treatment of HAE was recently conducted (ClinicalTrials.gov identifier NCT01912456).[87]

Conclusion

Prophylactic treatment of HAE with EMA-approved and FDA-approved C1-INH concentrate can successfully control and prevent HAE attacks. The treatment can be given at home in the absence of a health care provider. Most patients can be trained for self-administration, which allows for more convenient dosing. The postmarketing safety and efficacy data indicate that self-infusion of Cinryze in a home setting is a safe and well-tolerated HAE treatment with few reported side effects. Further studies with subcutaneous administration of C1-INH (including current clinical trials for Cinryze and Berinert) may further increase the tolerability and acceptance of this important aspect of HAE treatment.

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