Treatment of hereditary angioedema with plasma-derived C1 inhibitor

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Background: Plasma-derived C1 inhibitor (C1-INH) concentrate is a treatment option for acute hereditary angioedema (HAE) attacks and is considered the standard-of-care in many countries, although it is not yet available in the United States. Studies are still being conducted to establish its safety and efficacy as required by the FDA.

Objective: To review the medical literature to determine if C1-INH concentrate is a safe and effective treatment for acute HAE attacks.

Methods: The following keywords were searched in PubMed and OVID: *C1 esterase inhibitor, C1-inhibitor*, *C1 inhibitor*, and *hereditary angioedema treatment*. English-language articles were searched from 1966 to the present to look for studies demonstrating the efficacy and the safety of C1-INH concentrate.

Results: The English-language literature search revealed several studies showing significantly improved relief of HAE symptoms with the administration of C1-INH concentrate – many studies demonstrated some improvement of symptoms within 30 minutes. Side effects have been similar to placebo, and no proven cases of viral transmission have occurred in over 20 years.

Conclusion: C1-INH concentrate appears to be a very safe and effective treatment option for HAE.

Keywords: hereditary angioedema, c1 inhibitor, c1 esterase inhibitor, hereditary angioedema treatment

Introduction

Hereditary angioedema (HAE) is an autosomal dominant inherited condition caused by a quantitative or qualitative deficiency of C1-esterase inhibitor (C1-INH). C1-INH is the main regulator of the early steps of the classic complement pathway. Without C1-INH, uncontrolled activation of the classic pathway of the complement system can occur, along with the activation of other inflammatory mediators. In addition to the suppressive effect on the complement pathway, C1-INH also inhibits the kallikrein-kinin system, bradykinin activation, lectin pathway, plasmin, and factors 11a and 12a of the coagulation pathway. Presently, the unregulated activation of bradykinin is thought to cause the changes we call angioedema (Schneider et al 2007). Angioedema can either occur spontaneously or after a traumatic or stressful event, which leads to edema formation. The condition is characterized by acute attacks of sudden edema formation in the skin or in the walls of the upper respiratory tract or gastrointestinal tract. Cases of laryngeal edema can rapidly become life threatening. Cases of gastrointestinal attacks have been misdiagnosed and have lead to unnecessary surgeries (Ohela et al 1973). The clinical course, triggers, and frequency of attacks can be difficult to predict. The approach to treatment has two main goals: one is to prevent acute attacks of hereditary angioedema from developing, and the other is to rapidly terminate acute angioedema attacks if they do occur.

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The prevention of HAE attacks should begin with practical measures, which include avoidance of trauma and other interventions. Some medications can predispose an HAE patient to increased episodes of angioedema – these include estrogens and ACE inhibitors, which both should be avoided in patients with HAE. Patients are also likely to do better if conditions like gastritis and Helicobacter pylori infections are treated (Rais et al 1999; Visy et al 2007). Long-term prophylaxis for patients with HAE has been achieved in some cases with antifibrinolytics, C1-INH and attenuated androgens.

Epsilon-aminocaproic acid (EACA) is an antifibrinolytic agent used to treat HAE, and doses of 8–10 g per day have been shown to reduce frequency and severity of HAE attacks. Side effects of this medication include muscle discomfort, postural hypotension, sedative properties, and menstrual discomfort that is caused by the clotting of menstrual blood. In addition to these side effects is the theoretical risk of thrombophilia (Frank et al 1976). A contraindication to the use of EACA is a history of thrombosis and epilepsy. In countries outside the US, tranexamic acid has also been used as prophylaxis, but is not approved for use in the US.

Attenuated androgens have also been used as prophylaxis for acute attacks of HAE. Danazol is the attenuated androgen most often prescribed to treat HAE, and is used in adults at doses of 50–200 mg 1 to 3 times daily and in some cases every other day therapy is effective. Once it has been initiated, its dose can often be titrated down slowly as tolerated in order to minimize its side effects. Some of these side effects include masculinization, acne, voice deepening, hirsutism, weight gain, and anxiety. This medication can also affect the liver, so liver function tests must be monitored. Additionally, danazol can slow growth in children and is contraindicated during pregnancy due to the possibility of masculinization of a female fetus. While attenuated androgens have been shown to be an effective agent, they do have significant dose-related side effects that can limit their use (Hosea et al 1980).

In many countries C1-INH is used for the treatment of acute HAE attacks; however, C1-INH is not yet approved in some countries, including the US. Thus, there are limited treatment options for acute HAE attacks in these areas, but several other products are being studied in clinical trials that may soon be available (Table 1). One such product is a recombinant human C1-INH (rhC1-INH) (Rhucin®; Pharming, Leiden, The Netherlands). This product is made by the introduction of a human C1-INH gene into rabbits. Specifically, the C1-inhibitor gene construct is under the milk-specific casein promoter for expression in rabbit milk. This recombinant C1-INH is then secreted into rabbit milk and is purified. Initial studies show that infusion of 100 units per kg body weight (U/kg) of this product is effective in terminating acute attacks of HAE with initiation of improvement recorded at a median time of 0.5 hours after infusion. However, the half-life of this product is 3 hours, which is shorter than the reported half-life of C1-INH concentrate, which is 36–48 hours. The shorter half-life of recombinant C1-INH is due to differences in glycosylation of this product. The possible benefits of recombinant C1-INH include its theoretical reduced risk of viral transmission and that its production is not dependent on plasma donations. One drawback includes the potential for allergic reactions to rabbit proteins. Also, the short half-life raises concern for relapses of acute HAE attacks, although no relapses were reported in recent studies (van Doorn et al 2005; Choi et al 2007).

Ecallantide® (Dyax Corp., Cambridge, MA, USA) is another product currently being studied for the treatment of acute HAE attacks. Decreased levels of C1-INH are believed to allow increased activation of the kallikrein cascade leading to an increase in bradykinin as a mechanism of angioedema. Ecallantide is a recombinant protein produced by the *Pichia pastoris* strain of yeast. It acts as a direct kallikrein inhibitor, blocking its action and preventing the downstream formation of bradykinin. It can be administered intravenously or subcutaneously. A recent randomized, double-blind, placebo-controlled clinical trial was conducted which demonstrated that the median time from infusion to the beginning of effect was 30.5 minutes. Patients in the study received a dose ranging

Table 1 A comparison of developing treatments for acute hereditary angioedema attacks in the US

	Method of production	Mechanism of action	Half-life	Infusion method	FDA status
Berinert P®	Plasma concentrate	C1-inhibitor	36–48 h	iv	Pending FDA approval
Cinryze®	Plasma concentrate	C1-inhibitor	20–92 h	iv	Pending FDA approval
Rhucin®	Recombinant protein	C1-inhibitor	3 h	iv	Was not FDA approved
Ecallantide®	Recombinant protein	Kallikrein inhibitor	1–4 h	Subcutaneous	Pending resubmission to the FDA
Icatibant®	Synthetic peptide	Bradykinin-2 receptor antagonist	1–4 h	Subcutaneous	Was not approved by the FDA

Abbreviation: h, hours; iv, intravenous.

Table 2 Suggested follow-up of patients treated with plasma-derived C1 inhibitor (C1-INH)

Baseline assessment prior to starting C1-INH	Test	Frequency
	LFTs	Baseline
	HIV serology	Baseline
	HepB-surface ag	Baseline
	HCV-Ab	Baseline
	Give hepatitis B vaccine	Baseline (series of 3 injections)
Twelve-month intervals	LFTs	Every 12 months

Note: Presently no guidelines exist for serial assessment of patients on C1-INH in the US and the table includes information that is expected to be included in future guidelines.
Abbreviation: LFTs, liver function tests.

from 5 to 40 mg/m^2 intravenously, and 29 of 40 (72.5%) patients reported significant improvement within 4 hours, which was statistically significant compared with 2 of 8 (25%) in placebo. This is a promising study which demonstrates that Ecallantide® may be another potent therapy for acute HAE attacks in the near future (Schneider et al 2007).

Icatibant (Jerini, Berlin, Germany) is yet another product being studied for the treatment of acute HAE attacks. Icatibant is a synthetic agent that can be administered intravenously or subcutaneously. It is similar in structure to bradykinin and acts as a selective bradykinin-2 receptor antagonist. One uncontrolled study examined Icatibant at 3 different intravenous doses and 2 different subcutaneous doses (Bork et al 2007). The median time to onset of symptom relief was reduced from the historical data of 42 hours without treatment to 1.16 hours with Icatibant. While this study was not a controlled trial, it demonstrated good evidence of potential benefits of this therapy.

Where C1-INH concentrate is unavailable, fresh frozen plasma (FFP) has also been used with success to treat acute attacks of angioedema (Pickering et al 1969). However, because FFP also contains other substrates, including kininogens, there is a potential to worsen some acute attacks of HAE (Rosen and Austen 1969). Despite this potential risk, several groups still treat acute attacks of HAE with FFP when C1-INH concentrate is unavailable (Prematta et al 2007) with the knowledge that the benefit and adverse effect profile of C1-INH is superior to that of FFP.

As mentioned above, C1-INH concentrate has been available for greater than 20 years in parts of Europe for the treatment of acute HAE attacks, and it is currently considered the standard of care in many countries (Gompels et al 2005). However, C1-INH concentrate is unavailable in many countries including the US. Currently, two different companies are involved in clinical trials to introduce C1-INH to the US. CSL Behring (Marburg, Germany) is investigating Berinert P®, while Lev Pharmaceuticals (New York, NY, USA) is investigating Cinryze® for approval in the US. The purpose of this paper is to review the current literature on C1-INH concentrate and evaluate its safety and efficacy in the treatment of HAE.

Methods

The literature was searched to review the data demonstrating the efficacy and safety of C1-INH for the treatment of acute HAE attacks. The following search terms were used in PubMed and OVID: *C1 esterase inhibitor*, *C1-inhibitor*, *C1 inhibitor*, and *hereditary angioedema treatment.* English-language articles were searched from 1966 to the present to look for studies demonstrating the efficacy and the safety of C1-INH concentrate.

Results

In 1980, Gadek et al (1980) published a manuscript on the treatment of HAE with C1-INH protein that was removed from pooled plasma via chromatography. They referred to 1 unit (U) of C1-INH as being the amount of C1-INH found in 1 mL of plasma, which is still the terminology used. The group demonstrated the effect of purified C1-INH in vivo in patients with HAE when given between 410 and 1000 U of C1 inhibitor to 8 patients with HAE. 3 patients were given the product during asymptomatic periods and 5 patients were given the inhibitor during acute HAE attacks. All of the symptomatic patients experienced improvement of symptoms with C1-INH infusion. Their symptoms began to improve within 30 minutes and were completely resolved within 5–7 hours. C1-INH and C4 levels were measured after plasma infusion. Gadek et al demonstrated that C1-INH levels peaked rapidly and dropped quickly; however, C4 levels peaked approximately 6 hours after the C1-INH levels, and the C4 levels remained elevated for a much longer period of time. None of the patients demonstrated any adverse reactions related to C1-INH concentrate treatment.

Waytes et al (1996) published the first randomized, double-blind, placebo-controlled trial on C1-INH concentrate. This product was purified from plasma and vapor-heated to inactivate viruses. The group tested C1-INH concentrate used as both a prophylactic agent and as an agent to treat acute attacks of HAE. The infusion dose of C1-INH was 25 U/kg body weight in both groups. The prophylactic group was investigated as a cross-over study in which 6 patients were

randomly assigned to receive C1-INH or placebo infusion every 3 days in two different 17-day treatment periods to evaluate for a difference in the frequency of acute attacks. Disease activity was reduced 60% during the C1-INH treatment period compared with the placebo treatment period. Also from that publication was a study on acute HAE attacks in which patients were randomly assigned to receive C1-INH concentrate versus placebo for acute treatment. Patients treated with C1-INH showed a significantly shorter mean time from infusion to the initial signs of improvement of symptoms (55 minutes versus 563 minutes). Moreover, 38 of 55 attacks (69%) treated with C1-INH concentrate had some improvement within 30 minutes of infusion compared with 1 of 49 (2%) attacks in the placebo group. Patients had no serious short-term side effects from receiving C1-INH and were monitored for up to 4 years without anyone developing HIV, hepatitis B, or hepatitis C.

Another randomized, double-blind, placebo-controlled trial was conducted by Kunschak et al (1998). They compared 11 patients treated for acute HAE attacks with 25 U/kg body weight of C1 INH (60 total treatments) with 11 patients treated with placebo for acute HAE attacks (57 total treatments). The mean time from infusion to the earliest sign of symptom relief was significantly shorter in patients given C1-INH concentrate compared with placebo. The mean time from infusion to complete resolution of symptoms was also significantly shorter in the treatment group: 23.98 hours in the treatment group compared with 34.98 hours in the placebo group. However, because the placebo data included 49 of the 57 treatments that required open-label C1-INH as rescue therapy, the difference between these two groups is probably underestimated. Kunschak et al also studied the half-life of C1-INH by investigating both functional and antigenic C1-INH levels. They found that the mean functional C1-INH half-life was 38.87 ± 19.75 hours, and the mean antigenetic C1-INH half-life was 24.01 ± 9.70 hours. They also noted that serum C4 concentrations remained elevated much longer than C1-INH levels – staying at peak levels at least 24 hours post C1-INH infusion. They also reviewed the viral safety of C1-INH concentrate and found that of the 22 patients receiving a total of 157 C1-INH concentrate infusions, there was no evidence of viral infections. Only minor adverse reactions related to C1-INH were reported and included 1 patient with nausea and bad aftertaste, 1 patient with shortness of breath, and 1 patient with dizziness and headache.

As stated previously, C1-INH concentrate has been available for HAE treatment for many years in parts of Europe and several groups have published their personal results for the treatment of acute HAE attacks with C1-INH. Bork and Barnstedt (2001) compiled data from HAE patients in Germany who received C1-INH concentrate for laryngeal edema and compared the length of attacks with patients who had laryngeal edema in the past, but did not receive C1-INH concentrate. The study was not double-blinded or placebo-controlled as everyone was treated with C1-INH concentrate when it was available. The group treated 18 patients for a total of 193 episodes of laryngeal edema with 500–1000 U of C1-INH. Most of the patients treated with C1-INH had some improvement of symptoms within 1 hour with a mean time of 42.2 minutes. The group found that the patients treated with C1-INH concentrate for symptoms of laryngeal edema had an average duration of symptoms of 15.3 ± 9.3 hours which was significantly shorter than patients who did not receive C1-INH concentrate and had a mean duration of symptoms of 100.8 ± 26.2 hours.

Bork et al (2005) retrospectively examined acute abdominal attacks of HAE and compared 75 patients with 17,444 untreated acute abdominal attacks to 4,834 acute abdominal attacks treated with C1-INH concentrate (Bork et al 2005). The usual dose of C1-INH concentrate was 500 U; however, higher doses were given if a clinical response was not achieved, or if the patient's weight was over 80 kg, then they were treated with 1000 U of C1-INH concentrate. The mean duration of an acute abdominal attack was significantly shorter at 30.3 ± 23.2 hours when treated with C1-INH concentrate compared with 93.8 ± 42.7 hours when patients were not treated for their attacks. However, the group also noted that C1-INH concentrate seemed to have a more dramatic effect on an acute attack if given early in the course of the attack. Patients often needed a larger amount of C1-INH if they were treated later for their acute attack. Bork et al noted that the mean time from injection to initial improvement of symptoms varied depending on the timing of infusion; 53.5 minutes if C1-INH concentrate was given within 2 hours of the onset of an attack compared with 114 minutes if C1-INH was given greater than 2 hours after the onset of symptoms. This group also examined the safety of C1-INH concentrate in these patients. They reported no HIV, hepatitis B, or hepatitis C transmission after C1-INH concentrate administration. The only adverse effects were faintness, vertigo, headaches, reddened face, feeling of warmth or coldness, paresthesias, coldness, fevers, and chills in a small group of patients. All of the patients who had some side effects were reportedly able to receive subsequent infusions and had fewer side effects with additional treatments.

Farkas et al (2007) reviewed a group of patients treated for HAE with C1-INH from 1996 to 2006. The patients,

22 children and 39 adults, were treated for a total of 468 acute attacks, which included 230 abdominal attacks and 133 cases of laryngeal edema. C1-INH successfully treated the symptoms in all of the patients; for most, 500 U were required; however, 9 patients required an additional 500 U to achieve symptom control. Eight of these 9 were due to laryngeal edema triggered by an airway infection. The group also examined a subset of the patients to determine average time between receiving C1-INH and the first signs of clinical improvement. On average, laryngeal edema symptoms started to improve within 15 minutes of receiving C1-INH, while abdominal symptoms started to improve within 30 minutes. The improvement in subcutaneous edema usually took longer than 30 minutes. Patients were also followed for adverse reactions or hepatitis B, hepatitis C, or HIV transmission, and none of the 61 patients had any severe adverse effects or viral transmission after C1-INH therapy.

A poster presentation from the 2007 ACAAI meeting presented a randomized, double-blind, placebo-controlled trial with 68 subjects receiving nanofiltered C1-INH versus placebo for the treatment of acute HAE attacks involving the abdomen, face, or genitourinary area. They demonstrated significantly shorter time from treatment infusion to "beginning of unequivocal relief" in the C1-INH treatment group ($n = 35$; median time = 2 hours) versus placebo group ($n = 33$; median time >4 hours) (Zuraw et al 2007).

At the 2008 AAAAI Meeting, 3 abstract presentations reported some of the most recent trials with C1-INH concentrate. The IMPACT 1 (International Multicenter Prospective Angioedema C1-INH Trials) involved 125 HAE patients randomly assigned to receive 1 of 3 different treatments for acute HAE attacks (Bernstein et al 2008): placebo; 10 U/kg of C1-INH; 20 U/kg of C1-INH. The time from the treatment infusion to the beginning of improvement was significantly shorter in the group treated with 20 U/kg of C1-INH (median time 30 minutes) versus placebo (median time 90 minutes). However, the group treated with the 10 U/kg C1-INH infusion was not significantly shorter (median time 70 minutes). There was no reported viral seroconversion after C1-INH administration. Only minor side effects were reported which were actually more common in the placebo group.

The IMPACT 2 is an open-label North American study in which 39 subjects were treated for 355 episodes of HAE acute attacks with 20 U/kg of C1-INH (Craig et al 2008). Median time to the beginning of symptom relief after administration of the C1-INH was 30 minutes – the same as that in the IMPACT 1 Trial. The time from infusion to the beginning of relief of symptoms was similar in all types of HAE attacks: for laryngeal attacks median time was 25 minutes; for abdominal attacks the median time was 26 minutes; for both peripheral and facial attacks median time was 32 minutes. There were no confirmed viral seroconversions during this study.

Another poster presentation, from the 2008 AAAAI meeting, demonstrated the use of C1-INH as a prophylactic treatment. Twenty-two patients were involved in a 24-week cross-over study receiving C1-INH 1000 U twice weekly for 12 weeks and placebo (normal saline) treatment for 12 weeks. The subjects had fewer attacks during the C1-INH treatment period than the placebo period (mean 6.1 versus 12.7, $p < 0.0001$) (Zuraw et al 2008).

Because some patients with HAE are subject to frequent attacks, several groups have examined C1-INH concentrate infusions at home so patients do not have to obtain urgent care each time they have an attack (Levi et al 2006; Longhurst et al 2007). This includes Levi et al who assessed the option of self-administration of C1-inhibitor concentrate in patients with HAE as well as patients with acquired angioedema. In their study, patients were taught to establish intravenous access and infuse C1-INH at home. They enrolled only patients with frequent attacks for two different studies: one group of 12 patients received C1-INH regularly to prevent acute attacks, and the other group of 31 patients had C1-INH available at home "on demand" for the treatment of acute attacks. In the "on demand" group, when the patient administered the C1-INH at home, the time from symptom onset to treatment was reduced compared with those who had to travel to a hospital (1.4 ± 1.0 hours compared to 3.4 ± 2.1 hours). More importantly, the time to complete resolution of symptoms was even more reduced (5.9 ± 2.2 hours versus 13.8 ± 2.9 hours), which is a reflection that earlier treatment may be more effective and lead to a more rapid resolution, as seen in other studies (Bork et al 2005). The second study group received C1-INH as a prophylactic treatment at home. At the time of enrollment, patients had exacerbations at least once every 10 days and an average of 4 attacks per month. These patients were then treated with a prophylactic dose of 1000 U of C1-INH approximately every 5–7 days (mean 6.8 days). The patients had a significant reduction in the number of attacks – 7 of 12 had no angioedema attacks after prophylaxis, 3 of 12 had fewer than 1 attack every 6 months, and 2 of 12 had fewer than 1 attack in 3 months. The overall angioedema attack rate decreased from a mean of 4 attacks per month to 0.3 attacks per month. Patients had no serious reactions. These studies demonstrated that home administration of C1-INH has the

potential to be quite beneficial. Patients receive treatment much earlier than they otherwise might, which reduces the duration of symptoms. In addition, the prophylactic portion demonstrated that weekly to biweekly injections could reduce and at times eliminate attacks.

Discussion

C1-INH concentrate has been available in parts of Europe for over 20 years with many studies showing strong evidence that it significantly shortens an acute HAE attack. However, many of the studies are based on retrospective data because until recently, only a limited number of randomized, placebo-controlled, double-blind clinical trials to establish its efficacy were available. Ethically, it is difficult to withhold C1-INH concentrate to a patient with an acute attack because some attacks can be very serious or fatal; therefore, most studies have used open-label C1-INH concentrate for urgent conditions in patients receiving the placebo. Multiple groups have presented their data for C1-INH concentrate with apparent success, but given the fact that an acute attack can have an unpredictable course with sudden worsening or improvement, it is difficult to prove efficacy without assessing varied doses in a placebo-controlled and double-blinded clinical trial.

Several recent articles have demonstrated the efficacy of C1-INH concentrate for the treatment of acute HAE attacks. The doses given in these studies have ranged from 400 to 1000 U and in other studies have ranged from 10 to 25 U/kg body weight. The most recent studies used 20 U/kg body weight as the dose for treatment. Several groups have demonstrated that the time from infusion to the beginning of relief of symptoms is faster than 1 hour and some have shown that the time to first symptom improvement is within 30 minutes. One study even showed that 95% of patients have some response within 60 minutes of receiving C1-INH (Craig et al 2008). Laryngeal edema attacks seem to respond most rapidly to treatment followed by abdominal, then facial and peripheral attacks. Shorter times from the onset of symptoms to the infusion of C1-INH (especially within 2 hours) seem to be associated with faster and more effective improvement of symptoms.

One of the drawbacks of comparing these studies is that the criteria to determine which types of attacks to treat were not consistent from study to study. It seems reasonable to treat any attack causing a patient distress. Since HAE is a complex disease, predicting when a patient's symptoms may become worse can be very difficult.

Several groups also demonstrated that C1-INH concentrate infusions given regularly can prevent acute attacks. The intervals at which C1-INH concentrate is given for prophylaxis can vary considerably, with one study demonstrating a reduction in acute attacks with infusion every 3 days (Waytes et al 1996), and another study demonstrating a reduction in attacks with infusions every 5–7 days (Levi et al 2006). It is interesting that the half-life of C1-INH has been reported to be from 36 to 48 hours (Bernstein 2008), so one might think that infusions given every 5–7 days would not be adequate. However, the study by Levi et al (2006) does indeed demonstrate improvement in symptoms with this interval, suggesting that even increasing C1-INH levels slightly can result in significant reduction of HAE attacks. This is consistent with the observations that C4 levels peak several hours after C1-INH levels and remain elevated for a longer period of time, demonstrating a biochemical effect that exceeds the serum half-life of C1-INH levels. However, the actual frequency of C1-INH infusions should probably be tailored on an individual basis, attempting to eliminate acute attacks with the lowest necessary frequency of C1-INH treatment. The data from these studies support the use of C1-INH concentrate for long-term prophylaxis for either patients that continue to have attacks despite prophylactic therapy with agents like attenuated androgens, or for patients with unwanted side effects related to androgen treatment.

Several authors have demonstrated home therapy as a potential option for patients with HAE. Levi et al (2006), as mentioned previously, demonstrated a significant reduction in attack frequency in patients with scheduled C1-INH concentrate self-infusions at home. They also demonstrated faster treatment and improvement of acute attacks when patients were able to treat themselves at home. Patients in their study were successful in self-administering an intravenous catheter and infusion at home in 98% of cases. Initiating home therapy would require a significant amount of patient education on safely administering infusions. Patients should also be educated on symptoms that would require immediate medical attention. Certainly, in a case of laryngeal edema, a patient should first call their emergency number before attempting a home infusion. In cases of abdominal attacks, patients should call their physician or report to the hospital if their symptoms are at all different from typical attacks or if they are not resolving with therapy. Patients with HAE can certainly develop other abdominal conditions that may present similarly. These studies demonstrate that if done in the appropriate environment with adequate education and patient understanding, home C1-INH concentrate infusion for prophylaxis or acute treatment is a promising therapy leading to significant improvement of quality of life, faster

and more effective treatment of attacks, reduced frequency of acute HAE attacks, and fewer hospitalizations.

While C1-INH concentrate appears very effective from clinical trials, its safety is also very important. Since C1-INH concentrate is purified from human plasma, there is a theoretical risk of transmission of infectious agents such as hepatitis B, hepatitis C, HIV, and other viruses. The safety of C1-INH concentrate is ensured through multiple steps. The initial step is plasma donor selection. Individual donors are screened for risk factors for viral diseases along with elevated ALT. In 1986, the donor screening for HIV began and was added to hepatitis B serology screening. Serologic testing for hepatitis C began in 1993, and has since advanced to include screening for other viruses. In 1985, the safety of C1-INH concentrate improved after the introduction of a step in which the concentrate was heated for 10 hours at 60 °C to inactivate viruses (Cicardi et al 1995). Also, one company now uses a nanofiltration step in which a 15 nm filter is used to remove viruses and even prions (Terpstra et al 2007). None of the studies using either Lev's or CSL Behring's products have found any evidence of viral seroconversion with C1-INH concentrate infusions; however, earlier studies before viral inactivation procedures demonstrated HCV transmission secondary to C1-INH from Immuno produced C1-INH (Cicardi et al 1995). One of the main C1-INH products is Berinert P®, and the company that produces it claims that over 100 million units of Berinert P® have been administered with no proven cases of viral transmission (Juers and Groner 2004). Thus, it appears to be a very safe treatment with few reported side effects compared with placebo and no proven viral infections in association with infusion since the introduction of the heat step. Similarly, Cinryze® has been used in Europe both in trials and clinical use and has no evidence of viral transmission (Lev, pers comm).

Based on over 20 years of data, including recently completed double-blind, placebo-controlled trials, C1-INH concentrate appears to be very effective in the treatment of acute HAE attacks. The only other currently available treatment for acute attacks is FFP, which is a controversial treatment. C1-INH concentrate does not have the other substrates that FFP carries that give FFP the theoretical risk of worsening an attack. C1-INH also has the added benefit of increased viral safety compared with FFP due to the purification and pasteurization steps performed. No studies have compared C1-INH concentrate with any of the new emerging therapies. These alternative therapies may prove to be as effective for acute attacks, but will unlikely be utilized for prophylaxis secondary to their short half-lives.

Conclusion

C1-INH concentrate is considered standard of care in many countries for the treatment of HAE, and will likely soon be available in the US. Studies have shown it to be a very effective treatment with improvement of symptoms within 30 minutes to one hour. It appears very safe with no proven viral transmission since the introduction of the heat step. The side effect profile in a recent study was very similar to placebo. In addition to treating acute HAE attacks, it may also be beneficial as a chronic prophylactic agent, and may one day be approved for home infusion in properly selected patients with appropriate training. The present data on C1-INH concentrate appear very promising, and the availability of C1-INH concentrate in more countries will improve quality of life and productivity, as well as reduce anxiety and disability for patients with HAE.

Disclosures

Dr. Timothy Craig has been involved in research for Jerini, Dyax Corp., CSL Behring, Pharming, and Lev Pharmaceuticals. He is also on the advisory board for Jerini, CSL Behring, Pharming, and Lev Pharmaceuticals.

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