

Current Management Options for Hereditary Angioedema

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Abstract The aim of treatment of hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency (HAE-C1-INH) is either treating acute attacks or preventing attacks by using prophylactic treatment. For treating acute attacks, plasma-derived C1 inhibitor (C1-INH) concentrates, a bradykinin B2 receptor antagonist, and a recombinant human C1-INH are available in Europe. In the United States, a plasma-derived C1-INH concentrate, a bradykinin B2 receptor antagonist, and a plasma kallikrein inhibitor have been approved. Fresh frozen plasma is also available for treating acute attacks. Short-term prophylactic treatment focuses on C1-INH and attenuated androgens. Long-term prophylactic treatments include attenuated androgens such as danazol, stanozolol, and oxandrolone, antifibrinolytics, and a plasma-derived C1-INH concentrate. Plasma-derived C1-INH and a bradykinin B2 receptor antagonist are permitted for self-administration and home therapy. The number of management options has increased considerably within the last few years, thus helping to diminish the burden of HAE.

Keywords Angioedema · Hereditary angioedema · Management · C1 esterase inhibitor · Bradykinin · Kallikrein · Androgens · Danazol · Treatment · Prophylaxis · Plasma-derived C1-INH · Recombinant C1-INH · Bradykinin B2 receptor antagonist · Icatibant · Conestat alpha · Ecallantide · Self-administration · Home therapy · Tranexamic acid

Introduction

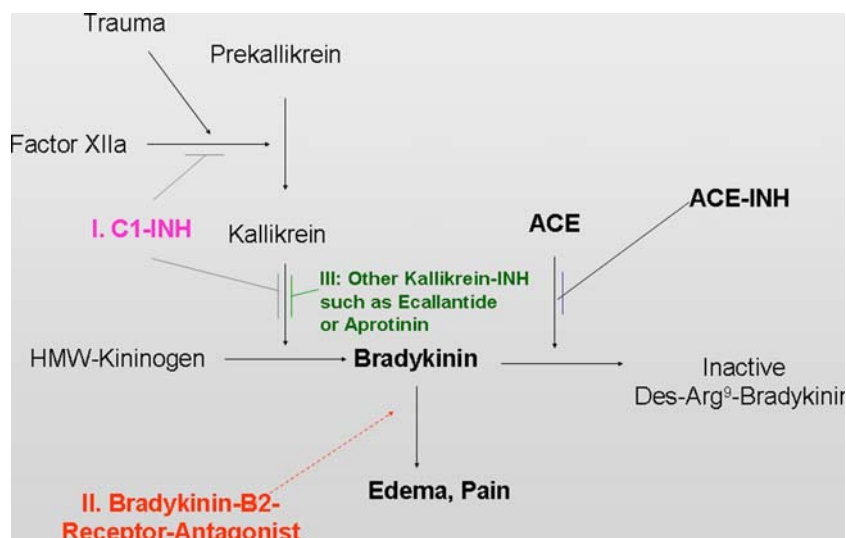
Hereditary angioedema (HAE) constitutes a defined autosomal dominant disease (Mendelian Inheritance in Man #106100), caused by an inherited deficiency of functionally active C1 esterase inhibitor (C1-INH). More than 200 C1-INH gene mutations have been described [1, 2]. Spontaneous new mutations occur often, and are related to about 20 % of HAE cases. The low plasma concentration of functionally active C1-INH permits activation of the kallikrein-kinin system, the classical complement pathway, the fibrinolytic system, and the coagulation system, with release of vasoactive peptides, including bradykinin (BK), which is considered to be the most important mediator [3]. In 2000, a new type of angioedema that was not associated with a C1-INH deficiency and that was dominantly inherited, was described in ten families [4]. This was termed “HAE with normal C1-INH” or “HAE type III.” In six of 20 unrelated families, two missense mutations in exon 9 of coagulation factor XII gene were identified to be associated with the disease [5, 6]. This article focuses on the classical type of HAE caused by a deficiency of C1-INH (HAE-C1-INH).

C1-INH deficiency is estimated to affect 1 in 10,000 to 1 in 50,000 of the worldwide population. Clinically, HAE-C1-INH is characterized by episodic cutaneous swelling, attacks of abdominal pain, and, rarely, episodes of potentially life-threatening upper airway obstruction. HAE-associated mortality is usually caused by suffocation resulting from laryngeal edema [7]. Laryngeal edema and death may follow trauma of the oral cavity, e.g. following dental surgery [8].

In the last few years, a number of new drugs have been developed to improve the treatment of HAE-C1-INH (Fig. 1). This article focuses primarily on reviewing recently published clinical studies of therapeutics developed for

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Fig. 1 Mechanisms of treatment of HAE-C1-INH in the kallikrein-kinin system



HAE-C1-INH. Table 1 shows the medication available for the treatment of HAE-C1-INH.

Treatment of HAE Due to C1-INH Deficiency

Aims of treatment are either treating acute attacks or avoiding attacks by use of a prophylactic treatment.

Treatment of Acute Attacks

C1-INH Concentrate

The first treatment with C1-INH concentrate derived from human plasma was performed in HAE-C1-INH in 1973 [9]. Since then, C1-INH concentrate has been shown to be effective in treating and preventing all kinds of attacks. For the treatment of acute attacks, three licensed C1-INH concentrates are currently available: Berinert® (CSL Behring GmbH, Marburg, Germany), Cinryze® (ViroPharma Inc., Exton, PA, USA), and Ceter® (Sanquin, Amsterdam, the Netherlands).

Berinert. Berinert P was first licensed in Germany in 1979. It then underwent a series of developments to improve tolerability, and the first pasteurized C1-INH concentrate was subsequently licensed in Germany in 1985. Berinert is nanofiltered and currently licensed for the treatment of acute HAE attacks in Europe, the USA, and numerous other countries.

Clinical Efficacy. In a case collection study, treatment of C1-INH-deficient patients suffering from laryngeal edema was compared with a historic control group of C1-INH-deficient patients who had not received C1-INH concentrate [10]. Berinert P was effective in treatment of edema episodes in all patients, with the time to relief of symptoms ranging from ten minutes to four hours (mean $\pm$ SD, 42.2 $\pm$ 19.9 min). In this study, the mean $\pm$ SD duration of laryngeal edema was 15.3 $\pm$ 9.3 h in patients who had received Berinert P, and 100.8 $\pm$ 26.2 h in those who had not received it. The efficacy of Berinert P was further demonstrated in a retrospective study of 75 C1-INH-deficient patients with HAE in whom a total of 4834 abdominal attacks were treated with C1-INH concentrate [11]. Relief of symptoms

Table 1 New treatment options for hereditary angioedema due to C1-INH deficiency

	Mode of action	Available in Germany/ Europe since	Available in the USA since	Mode of application
Plasma-derived C1-INH Berinert®	Replacing the deficient C1-INH	1979 (for treatment of HAE attacks)	2009 (for treatment of HAE attacks)	Intravenous
Cinryze®		2011 (for treatment and prevention of HAE attacks)	2008 (for prevention of HAE attacks)	Intravenous
Icatibant Firazyr®	Bradykinin B2 receptor antagonist	2008	2011	Subcutaneous
Recombinant C1-INH, Conestat alfa, Ruconest®	Replacing the deficient C1-INH	2010	Currently not available	Intravenous
Ecallantide, Kalbitor®	Kallikrein inhibitor	Currently not available	2009	Subcutaneous

started after at least 10 min, and within 30 min to 150 min in most attacks. Furthermore, this study also addressed the need for rapid treatment of acute attacks of HAE. The mean time to relief of symptoms was 53.5 min in patients treated early (within 2 h after abdominal complaints began), compared with 114 min when treatment was delayed. In 2008, a retrospective study on the efficacy of Berinert P in the treatment of skin swellings in patients with HAE-C1-INH was published [12].

In a randomized, double-blind, placebo-controlled study (International, Multi-center, Prospective, Angioedema, C1-INH Trial 1 [I.M.P.A.C.T.1]) of 125 patients with HAE-C1-INH, the efficacy of Berinert given at intravenous doses of 10 or 20 U/kg body weight was compared with placebo [13•]. The efficacy was studied in abdominal attacks and facial swellings. The median time to onset of relief was significantly shorter with 20 U/kg of Berinert than with placebo (0.5 h vs. 1.5 h). With a dose of 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 h vs. 1.5 h), and the difference did not reach statistical significance. The conclusion was that Berinert, given intravenously at a dose of 20 U/kg, is an effective treatment for abdominal and facial attacks in patients with HAE-C1-INH [13•]. In this study, however, the time of only 1.5 h to first symptom of relief after treatment with placebo seemed unexpectedly short and is conspicuous.

Recently, the efficacy of Berinert was assessed in the treatment of 39 laryngeal attacks in 16 patients with HAE-C1-INH in a prospective, uncontrolled, open-label study (I.M.P.A.C.T.2) [14]. The patients received Berinert at a single dose of 20 U/kg for the treatment of each attack. The median time to onset of symptom relief was 15 min. The median time to complete resolution of all symptoms was 8.25 h. These results confirmed a previous report on the efficacy of Berinert P in the treatment of 193 laryngeal attacks [10].

In a further analysis of the I.M.P.A.C.T.2 study, the efficacy of Berinert was investigated at a dose of 20 U/kg for the treatment of 663 abdominal attacks in 50 patients, and for the treatment of 43 facial attacks in 16 patients [15]. The median time to onset of relief was 19.8 min for abdominal attacks and 28.2 min for facial attacks. Only in 0.28 % (2 out of 706) of the attacks treated with Berinert was the time to onset of relief of symptoms > 4 h. In the I.M.P.A.C.T. studies, no relapses of the acute attacks have been observed. These results confirmed a previous report on the efficacy of Berinert P in the treatment of abdominal attacks and facial swellings [11, 12].

In the I.M.P.A.C.T.1 study [13•], the treatment of facial swellings and abdominal attacks with Berinert at a dose of 20 U/kg was significantly more effective than treatment with placebo. Treatment with 10 U/kg was also more effective than with placebo; the difference, however, did not reach statistical

significance. In this respect, the results of this study contrasted with practical experience published to date on the use of C1-INH concentrates to treat thousands of HAE attacks in hundreds of patients, including patients in a randomized, double-blind study from 1996 conducted in the US [16]. According to these studies, in the majority of patients, a dose of 500 U, i.e. 7.1 U/kg in a patient weighing 70 kg, was highly effective. In some patients, 1,000 U (14.2 U/kg) were necessary to successfully control an HAE attack. In an uncontrolled observational study in 61 patients experiencing 468 HAE attacks, Berinert P given at a dose of 500 U was usually effective, and a dose of 1,000 U was needed for the treatment of only nine attacks (2 %) [17]. In further studies, a dose of 500 U was effective in treating 68.6 % of 4,834 abdominal attacks in 75 patients [11], 81 % of 2,104 skin swellings in 47 patients [12], and 24.9 % of 193 laryngeal attacks in 18 patients [10].

A dose of 20 U/kg should be obligatory for the treatment of laryngeal attacks, due to their potentially life-threatening nature. If an attack is not potentially life-threatening (i.e. skin swellings and abdominal attacks, which together comprise approximately 99 % of all HAE attacks), the dose can be adjusted to the patient's individual requirement and administration of 500 or 1,000 U per attack may be sufficient (German guideline "Hereditary Angioedema") [18]. Berinert is licensed for self-administration and home therapy.

Cetor nf. Cetor is a C1-INH concentrate derived from human plasma. It is available in the Netherlands and some other countries. In 2006, a total of 31 patients with hereditary (28 patients) or acquired C1-INH deficiency self-administered Cetor for acute attacks. Times between the onset of the attack and the initiation of relief or complete resolution of symptoms were significantly shortened, compared with times before the start of self-administration [19].

Cinryze. Cinryze is a plasma-derived C1-INH and received marketing authorization in the US in October, 2008 for prevention of HAE attacks, and in Europe in June 2011 for treatment and prevention of HAE attacks. Concerning the treatment of acute attacks, two studies have been performed: One study used a randomized, double-blind, placebo-controlled, parallel group design; 71 subjects with acute HAE attacks were randomized (36 Cinryze, 35 placebo). The study demonstrated that treatment with Cinryze within 4 h after the onset of an HAE attack resulted in a greater than two-fold decrease in the time to beginning of unequivocal relief of the defining symptom of the HAE attack, compared to placebo (median 2 h for Cinryze vs. >4 h for placebo, $p=0.048$) [20].

In an open-label study, 101 subjects were treated for a total of 609 acute HAE attacks (median three attacks per subject; range: 1–57). Within 4 h after Cinryze dosing, 87 %

of attacks achieved unequivocal relief from the defining symptom. For 95 % of attacks, clinical relief was observed and/or subjects were discharged to home within 4 h [20].

Bradykinin B2 Receptor Antagonist

Icatibant. Bradykinin (BK) causes vasodilation via its B2 receptor (Fig. 1) through increases in nitric oxide (NO), epoprostenol (previously known as prostacyclin), and endothelium-derived hyperpolarizing factor. The B2 receptor is constitutively expressed on many cell types, and is considered to be the major mediator of the effects of BK involved in HAE [21, 22].

In July 2008, icatibant (Firazyr®; Jerini AG, Berlin, Germany, and Shire Pharmaceuticals, Basingstoke, UK), a BK B2 receptor antagonist, was granted market authorization by the European Commission for the symptomatic treatment of acute attacks of HAE in adults. It was licensed in the USA in December 2011. Icatibant is a new principle of treatment in HAE due to C1-INH deficiency, antagonizing the BK B2 receptor [23]. Firazyr can be injected subcutaneously. It is also licensed for self-administration.

Icatibant is a competitive and selective B2 receptor antagonist [21, 24]. It is a synthetic decapeptide that has a similar structure to BK, but contains five nonproteinogenic amino acids (D-Arg, L-Hyp, L-Thi, D-Tic, and L-Oic). Its half-life in plasma is one to two hours.

Clinical Efficacy. In an initial open-label Phase II study, 15 patients with 20 HAE attacks were treated with icatibant either intravenously or subcutaneously [25]. Symptom intensity decreased within 4 h after administration of icatibant; the median time to onset of symptom relief was 1.50 h, 1.42 h and 1.13 h in the *i.v.* groups, and 0.58 h and 0.45 h in the *s.c.* groups, respectively. The median difference in the visual analogue scale 4 h after start of treatment was 4.11 cm (95 % CI 1.72 – 6.07). Compared to untreated attacks, icatibant treatment reduced the mean (SD) time to onset of symptom relief by 97 %, from 42 ±14 h to 1.16 ±0.95 h (all groups combined). This was the first report demonstrating the clinical usefulness of antagonizing bradykinin binding to bradykinin receptor-2 in HAE-C1-INH (Fig. 1).

The safety and efficacy of icatibant were assessed in three randomized, double-blind, controlled prospective multicenter Phase III studies: two were placebo-controlled and in the third study, oral tranexamic acid served as the comparison. HAE patients presenting with cutaneous or abdominal attacks received 30 mg icatibant subcutaneously.

In the FAST-1 study (For Angioedema Subcutaneous Treatment), which was placebo-controlled and performed in 56 subjects, the primary endpoint was the median time to clinically significant relief of symptoms [26••].

Patients with symptoms of laryngeal attacks received open-label treatment with icatibant. Twenty-seven patients received icatibant and 29 patients received placebo. The primary endpoint was reached in 2.5 h with icatibant, vs. 4.6 h with placebo. The difference was not significant ($p=0.14$).

The FAST-2 study was performed in 72 subjects and was almost identical in design [26••]. Thirty-six patients received icatibant and 38 patients received tranexamic acid for comparison. The primary endpoint was reached in 2.0 h with icatibant versus 12.0 h with placebo. The difference was significant ($p<0.001$).

In FAST-1 and FAST-2, the treatment effect of icatibant was confirmed by secondary efficacy end points. Both studies showed significant differences in time to first symptom improvement in favor of icatibant (FAST-1: 0.8 h with icatibant versus 16.9 h with placebo; $p<0.001$; FAST-2: 0.8 h with icatibant versus 7.9 h with tranexamic acid; $p<0.001$). The median time to almost complete relief of symptoms for patients receiving icatibant was 8.5 h in FAST-1 and 10.0 h in FAST-2, compared with 19.4 h with the placebo in FAST-1 (not statistically significant), and 51.0 h with tranexamic acid in FAST-2 ($p<0.001$) [26••].

A total of 126 patients were treated in the open-label extension phase for a total of 714 separate attacks [27]. The efficacy results were similar to those seen in the controlled phase of the studies.

A total of 38 patients were treated for a total of 78 attacks of HAE affecting the larynx. The results were similar to patients with non-laryngeal attacks of HAE, with a median time to start of regression of symptoms of 0.6 h to 1.0 h (controlled phase) [27].

In a further randomized, double-blind, controlled prospective Phase III multicenter study (FAST-3), a total of 88 patients were randomized; 43 patients received icatibant and 45 patients received placebo [28]. The tool used to determine the primary efficacy endpoint differed from the FAST-1 and FAST-2 studies. The primary endpoint of FAST-3 was defined as the time to onset of symptom relief as measured by a composite visual analogue score (VAS-3 for non-laryngeal attacks). It was defined as the average of the three individual VAS scores for the symptoms of skin swelling, skin pain, and abdominal pain. The primary endpoint was reached in 2.0 h with icatibant versus 19.8 h with placebo. The difference was significant ($p<0.0001$) [28].

Recurrences or Worsening of HAE Attacks. In the initial open-label Phase II study, four of 15 patients with five attacks had recurrences of the swelling or new angioedema attacks starting 14, 17, 20, 20, and 27 h after an initially highly effective treatment with icatibant [25]. This occurred in two patients after intravenous (IV) treatment and in two other patients after sc treatment. In the FAST-1 study,

88.2 % of attacks, and in the FAST-2 study, 89.8 % of attacks, were treated with one dose of icatibant [27]. Approximately 10 % of patients required a second dose. In the three FAST-studies, 18 of 113 icatibant-treated patients (15.9 %) reported a worsening/recurrence of HAE within 48 h of icatibant administration [29]. The majority of these events were mild or moderate in severity. In a self-administration study (EASSI), 13 of 56 (23.2 %) patients experienced a recurrence or worsening of HAE after self-administration of icatibant [30]. The majority of the recurrences or worsening of HAE attacks were considered mild (five patients) and moderate (six patients) in severity, the other two patients had events that were considered severe [29]. Recently a series of 19 patients with HAE-C1-INH, who were treated with icatibant for acute attacks, were reported on. In 22 % of the attacks, a retreatment with icatibant or another medication was needed [31].

Safety. Local side effects at the site of the subcutaneous injection are very common (>1/10) including erythema, an urticarial wheal, and pain [25, 26••]. All injection site reactions observed until now resolved spontaneously and did not demand medical intervention.

Plasma Kallikrein Inhibitor

Ecallantide. In December 2009, ecallantide (Kalbitor®; Dyax Corp., Cambridge, Massachusetts, US), a kallikrein inhibitor, was granted market authorization by the FDA for the symptomatic treatment of acute attacks of HAE in adults. Ecallantide is a new principle of treatment in HAE due to C1-INH deficiency, inhibiting kallikrein.

Drug Properties. Ecallantide (DX-88) is a 60-amino acid protein of 7054 kDa. It is a potent and selective kallikrein inhibitor that acts by blocking its binding site. Ecallantide is produced as a recombinant protein in the *Pichia pastoris* strain of yeast. The plasma half-life is approximately 70 min when administered intravenously, and 2 h when administered subcutaneously.

Clinical Data. The safety and efficacy of ecallantide were evaluated in 168 patients, in two randomized, double-blind, placebo-controlled trials, termed EDEMA4 and EDEMA3 (EDEMA: Evaluation of DX-88's Effect in Mitigating Angioedema) [32, 33••]. Some patients participated in both trials. In both trials, patients having an attack of HAE at any anatomical location with at least one moderate or severe symptom, were treated with 30 mg subcutaneous ecallantide or placebo. The patients were randomized in a 1:1 ratio. The effects of ecallantide were evaluated using a mean symptom

complex severity (MSCS) score and a treatment outcome score (TOS).

Ninety-six patients were included in the EDEMA4 trial. The primary endpoint was the change from baseline in MSCS score at 4 h, and the TOS at 4 h was a key secondary end point. Patients treated with ecallantide demonstrated a greater mean decrease from baseline in the MSCS score than with placebo (−0.8 vs. −0.4, respectively), and a greater TOS than with placebo (53 vs. 8, respectively). At 24 h, patients treated with ecallantide also demonstrated a greater mean decrease from baseline in the MSCS score than with placebo (−1.5 vs. −1.1, respectively) and a greater TOS than with placebo (89 vs. 55, respectively). More patients in the placebo group (24 out of 48; 50 %) required medical intervention to treat unresolved symptoms within 24 h, compared with the group receiving ecallantide (16 out of 48; 33 %).

Seventy-two patients were included in the EDEMA3 trial. The primary endpoint was the TOS at 4 h, and the key secondary efficacy end point was the change from baseline in MSCS score at 4 h. At 4 h, patients treated with ecallantide showed a greater mean TOS than patients treated with placebo (63 vs. 36, respectively) and a greater mean decrease from baseline in the MSCS score than placebo (−1.1 vs. −0.6, respectively). In addition, more patients in the placebo group (13 out of 36; 36 %) required medical intervention to treat unresolved symptoms within 24 h, compared with the ecallantide-treated group (5 out of 36; 14 %).

In EDEMA4, an open-label dose of ecallantide was permitted between 4 and 24 h post-dosing for failure to respond, incomplete response, or relapse. Twenty-nine percent required a second dose [34].

Side Effects. In the EDEMA4 and the EDEMA3 trials, ten cases of anaphylaxis were reported; furthermore, rash, pruritus, and urticaria were reported in a few patients [34–37]. Some patients developed anti-ecallantide antibodies (IgG and IgE); the probability of seroconversion increased with the number of treated episodes [34].

Conestat Alfa. Recently, conestat alfa, a recombinant human C1-INH (rhC1INH) (Ruconest®/ Rhucin®, Pharming Group NV, Leiden, The Netherlands) has been developed for the treatment of HAE attacks and received marketing authorization in Europe in October 2010.

Ruconest is a recombinant human C1INH obtained from the milk of transgenic rabbits. The cloned human *C1INH* gene was inserted into a mammary gland-specific expression vector under the control of an S1 casein promoter. The construct was introduced into fertilized New Zealand white rabbit oocytes by microinjection, and a line expressing high levels of secreted rhC1INH was generated, yielding 12 mg/ml.

Rabbits have a short generation time and can produce sufficient quantities of rhC1INH.

Clinical Data. Two separate randomized, double-blind, placebo-controlled clinical trials were conducted in Europe and North America. The European randomized, double-blind, placebo-controlled Phase III study was conducted with 32 patients. Median time to the onset of symptom relief was 1 h, vs. 8 h in the placebo group, whereas median time to minimal symptoms was 6.1 h vs. 20.2 h, respectively. All instances of treatment with rhC1INH were successful, with no relapses. A second randomized, double-blind, placebo-controlled study with rhC1INH was conducted at several sites in the USA and Canada. In total, 38 acute HAE attacks (laryngeal, facial, abdominal, urogenital and peripheral) were treated in 38 patients, randomized to either of two doses of rhC1INH (100 or 50 U/kg), or to placebo. For the primary end point, intent-to-treat analysis demonstrated that patients who had received the 100-U/kg dose of rhC1INH reported onset of symptom relief at approximately 68 min (median), and those who had received placebo reported relief of symptoms at approximately 258 min. The time to minimal clinical symptoms (i.e. the secondary end point), reported by patients in the 100-U/kg, 50-U/kg, and placebo groups was approximately 245 min, 247 min, and 1098 min, respectively. The primary and secondary end point results obtained with both doses of rhC1INH were clinically meaningful and statistically significant relative to placebo with p-values of <0.01 [38••].

Therapeutic failure was reported in 11 % and 10 % of attacks treated with 50 and 100 U/kg, respectively [39].

Subtle differences in post-translational glycosylation result in a shorter half-life, compared with the human C1-INH concentrate. Since a healthy volunteer with an undisclosed rabbit allergy experienced an anaphylactic reaction after administration of rhC1-INH, the European Medicines Agency decided that Ruconest is contraindicated in all patients with known or suspected rabbit allergy, or with positive serum immunoglobulin E (IgE) antibodies against rabbit dander, due to the risk of major allergic reactions. Before initiating treatment, patients should be tested for the presence of IgE antibodies against rabbit allergens. Antibody testing should be repeated once a year or after ten treatments, whichever occurs first.

Long-Term Prophylaxis

Long-term prophylaxis can be achieved using androgens, anti-fibrinolytic agents, or C1-INH. Attenuated androgens are an effective treatment used worldwide in patients who have suffered numerous HAE attacks prior to commencing

treatment [40]. However, numerous side effects may be associated with attenuated androgens. Tranexamic acid may be less effective than attenuated androgens [41].

C1-INH Concentrate

Cinryze, Berinert P and Ceter have been used for this purpose. However, the available evidence about long-term prophylactic treatment with C1-INH concentrate has been sparse until now.

Cinryze. Cinryze (see above) is indicated for prophylaxis in adolescents and adults with a history of HAE attacks. Concerning prevention, Cinryze was evaluated for efficacy and safety in a multicenter, double-blind, placebo-controlled, crossover study [42••]. Patients were enrolled if they had been experiencing two or more HAE attacks per month. A total of 20 patients completed the study. The mean number of HAE attacks in each treatment period of 12 weeks was significantly lower for patients receiving Cinryze than for those receiving placebo. Significant reductions were also noted in the mean severity and duration of HAE attacks. It was concluded that Cinryze, given intravenously at a dose of 1,000 units (U), was effective in preventing or reducing the frequency of HAE attacks. Breakthrough attacks had to be treated by additional C1-INH injections. Two patients had more attacks during the treatment period than beforehand. The recommended dose of Cinryze is 1,000 U every 3–4 days.

Berinert. Berinert is currently not authorized for use in this indication. The first prophylactic application of Berinert P was described in 1989 in one patient with HAE-C1-INH; administration of 500 U of Berinert P every 4–5 days resulted in the patient remaining free of symptoms [43]. Subsequently, the successful use of Berinert P for long-term prophylaxis has been described in a number of patients with HAE-C1-INH [44, 45]. Recently, 14 patients were described who received one or more weekly intravenous injections of Berinert P for an average of nine years [46]. The most important benefit of this treatment was a reduction in symptom intensity: the vast majority of attacks were only mild or very mild. All patients reported that all or most of their attacks were considerably less severe than beforehand; the percentage of severe attacks was 93.3 % without prophylaxis, and 3.8 % with prophylaxis. At the end of the study, the monthly number of attacks was lower in eight patients, higher in five patients (considerably higher in some of these patients), and unchanged in one patient. In the opinion of most patients, the improvement in their quality of life due to weekly long-term treatment with Berinert P, compared with their disease burden before treatment, greatly outweighed the disadvantages. In some patients, an increased amount of Berinert P was required to control the

disease. Some patients reported rapidly developing attacks and skin swellings at multiple locations, which they had not experienced before commencing prophylaxis. This observation, and the necessity for regular administration of C1-INH concentrate once a week or more frequently, reflected an increased HAE-C1-INH activity in some patients. However, none of the patients reported any loss of effectiveness during the treatment with Berinert P.

Cetor. In 2006, the use of pasteurized C1-INH concentrate Cetor was assessed in long-term prophylaxis of HAE. Ten patients with HAE were reported to benefit from prophylactic treatment with C1-INH concentrate for a mean of 3.5 years [19]. Some of these patients simultaneously received other types of long-term prophylactic treatment.

Conclusions

In the last few years, a number of new drugs have been developed, either for treatment of acute attacks of hereditary angioedema or for long-term prophylaxis. Hopefully these drugs will diminish the burden of hereditary angioedema by reducing the risk of asphyxiation and by reducing the number of severe HAE attacks.

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