

German Guideline for Hereditary Angioedema due to C1-INH Deficiency

Guideline of the German Society for Angioedema Research (DGA), German Society of Internal Medicine (DGIM), German Society of Oto-Rhino-Laryngology, German Society of Allergology and Clinical Immunology (DGAKI), German Society of Paediatrics and Adolescent Medicine, German Dermatology Society (DDG) and the Society for Paediatric Allergology and Environmental Medicine (GPA)

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1. General information

Angioedema, formerly also termed angioneurotic edema or Quincke's edema, is a localized form of edema persisting for one up to seven days that recurs in irregular intervals. The organs affected include the skin, more rarely also the tongue, glottis or larynx, gastrointestinal tract, and very rarely other soft tissue organs. The same clinical sign and symptom "angioedema" is observed with various disease entities. Most commonly it is observed as a part of or equivalent of urticaria, with angioedema representing edema of the subcutis and hives representing edema of the dermis as far as location is concerned, with both being viewed as different forms of manifestation of a common basic pathomechanism (histamine-mediated angioedemas). An entirely different disease, also in terms of pathogenesis, clinical features and treatment, is recurrent

angioedema, the development of which can probably be largely ascribed to kinins and above all, bradykinin (kinin-mediated angioedemas). Certain forms of kinin-mediated angioedema are attributable to hereditary or acquired C1-inhibitor deficiency. The pathogenesis of other forms has not yet been adequately explained, but since they are not influenced by antihistamines they are also classified as kinin-mediated angioedemas. This applies to angioedema induced by angiotensin-converting-enzyme (ACE) inhibitors, a share of idiopathic angioedemas and hereditary angioedema with normal C1-INH (HAEnCI or HAE type III).

Hereditary angioedema (HAE) caused by a deficiency of C1-esterase inhibitor (C1-INH) is of particular importance, since numerous cases of asphyxiation have been reported with this condition and the quality of life of some patients is severely compromised by the frequent attacks of oedema. As a consequence, this guideline concentrates on HAE due to C1-INH deficiency (HAE-C1-INH).

Abbreviations used

ACE	Angiotensin-converting enzyme
ATII	Angiotensin II
BW	Body weight
C1-INH	C1-esterase inhibitor
EACA	Epsilon-aminocaproic acid
HAE	Hereditary angioedema
IgE	Immunoglobulin E
rh	Recombinant human

1.1 Epidemiology

The exact incidence of HAE-C1-INH not known, but is suggested to be approximately 1:50,000 with no known ethnic variation. Men and women are equally frequently affected.

1.2 Pathogenesis

There are two forms of HAE-C1-INH: HAE type I, the first and most common form (85% of patients), entails a defect in the synthesis of C1-INH, which is greatly reduced in quantity;

the second form, HAE type II (15% of patients), arises from a functional deficiency of C1-INH, though its plasma concentration is normal or even increased.

C1-INH is a glycoprotein with a molecular weight of 105,000 daltons. It is a single-chain protein consisting of 478 amino acids and is synthesised predominantly in hepatocytes, and to a lesser extent also in blood monocytes, skin fibroblasts and endothelial cells of the umbilical cord. C1-INH controls the spontaneous auto-activation of the first complement component (C1) and activated C1. Complement activation results from a deficiency of functional C1-INH. In 1963, Donaldson and Evans identified C1-INH deficiency as the cause of HAE [27]. Activation of the initial phase of the complement system leads to a permanent reduction of C4 in plasma.

Bradykinin is today believed to be the main mediator of increased vasopermeability of HAE-C1-INH. In HAE-C1-INH the C1-INH deficiency leads to activation of the kallikrein-kinin system, which is also known as the contact system. C1-INH is responsible for inhibiting the majority of plasma kallikrein and factor XIIa and so is the most important regulator when it comes to activating the kallikrein-kinin system. During acute episodes of HAE-C1-INH kallikrein is inadequately blocked on account of C1-INH deficiency and increased local production of bradykinin ensues at the end of the kallikrein-kinin cascade, ultimately resulting in swelling. However, the exact pathogenesis of HAE-C1-INH has not yet been explained exhaustively. There are a number of indications that bradykinin plays an important part in the emergence of edema associated with HAE-C1-INH:

- Bradykinin is found in increased plasma concentrations during an acute episode of HAE-C1-INH [39].
- The plasma concentration of bradykinin is higher in blood draining from angioedema sites compared to the systemic circulation [40]
- A knock-out mouse model revealed reduced vascular permeability [34] in mice deficient in C1-INH and the bradykinin B2 receptor, suggesting that both bradykinin and the bradykinin B2 receptor mediate the development of angioedema.
- Icatibant, a bradykinin B2 receptor antagonist, is therapeutically effective in acute episodes of HAE-C1-INH [9] (see below).

1.3 Genetics

HAE type I and II are inherited as autosomal dominant traits. The gene that codes C1-INH is located on the long arm of chromosome 11 in subregion q11.2-q13, and comprises eight

exons and seven introns. As a result of new techniques for identifying mutations, numerous mutants have now become known – to date, more than 200 [33, 41]. Each patient is heterozygous for the C1-INH defect and has one normal and one defective gene. Patients with HAE type I have a normally expressed C1-INH gene and an abnormal or deleted gene that is not expressed. Patients with HAE type II also have one normal gene; the other gene is abnormal and is expressed but gives rise to the synthesis of a dysfunctional C1-INH. HAE type II is brought about by point mutations in the C1-INH gene. New mutations are found in roughly 20% of patients.

1.4. Clinical symptoms

HAE-C1-INH is manifested clinically as episodic edema (attacks) or swelling of the skin, the gastrointestinal tract and – less frequently – the airways. Both types of HAE, namely type I and type II, do not differ in terms of clinical symptoms.

Prodromal symptoms: Fatigue, exhaustion, increased thirst, aggressiveness, depressive mood and erythema marginatum may precede the clinical symptoms.

Skin swellings: The skin swellings are usually tense, also less frequently soft, not erythematous but skin-coloured or pale, and mostly affect the face, hands and feet, as well as genitals. The skin swellings are hardly ever accompanied by itching, but rather only by a tight sensation and, less often, also pain. If advanced, the swellings can be very painful. They last one to three days on average, though may abate after just a few hours or only after seven days. Facial swellings tend to last longer than swellings on the extremities.

Usually, wheals or hives are not present in HAE-C1-INH.

Gastrointestinal attacks: In addition to skin swellings the majority of patients experience gastrointestinal attacks [20, 32], most often in the form of cramp-like abdominal pain and nausea, but also frequently with retching and vomiting. During a gastrointestinal attack, which usually lasts two to seven days, ascites develops not infrequently but resolves completely a few days later. Watery diarrhoea may occur due to an accumulation of fluid in the lumen of the edematous intestinal tract. Combined with the concomitant ascites, this may cause a considerable loss of fluid and so result in hemoconcentration and even shock [20]. In some patients the abdominal attacks occur in isolation, i.e. without skin symptoms,

or precede the onset of skin symptoms by a number of years. Due to the intense pain developing in gastrointestinal attacks, unnecessary exploratory laparatomies have sometimes been performed because of the suspicion of “acute abdomen” or appendicitis.

Laryngeal attacks: Some patients report involvement of the upper respiratory tract, laryngeal or supraglottic edema [12, 17]. The most common cause of death is asphyxiation from laryngeal attacks [19] which not infrequently arise due to trauma to the oral cavity or pharynx, particularly after dental surgery, tooth extraction or tonsillectomy [6].

Asphyxiation from laryngeal attacks: There have been repeated reports of death from asphyxiation [6, 19], often involving patients whose condition had gone undiagnosed. In other cases the diagnosis and necessary treatment were known, but for various reasons asphyxiation still occurred [19].

Other organs: A large number of other organs can less often be affected by attacks including the hypopharynx, oropharynx with soft palate and uvula, as well as the tongue [15]. Swellings in the efferent urinary tract can mimic infection.

1.5. Course

The manifestation of HAE-C1-INH most often ensues in the first decade of life, but also frequently in the second. In a few patients it develops later. Over the course of time, the attacks recur and are usually manifested as skin swellings and painful gastrointestinal attacks. The frequency of the attacks varies considerably from one patient to the next: it ranges from no episodes to episodes every few days. Even within one family the patients can be affected very differently. Women are generally more severely affected than men [15]. During pregnancy, the attacks may be more frequent, less frequent, or unchanged in number [26, 38]. During and shortly before childbirth, swelling is rare. The C1-INH laboratory values do not allow any inferences to be made about the frequency of the attacks.

With increased age, the attacks of HAE-C1-INH in some patients entail generally less pronounced symptoms or the attacks cease completely.

1.6. Triggers of edema attacks

Most attacks occur spontaneously without any identifiable trigger. The factors that trigger an attack primarily include pressure and trauma such as dental surgery, tonsillectomy, and intubation. Patients have also described stressful psychological situations and infectious diseases, such as flu-like infections or colds, as triggers. Menstruation and ovulation can likewise trigger attacks in certain patients.

The tendency to experience attacks can be markedly increased by the ingestion of ACE inhibitors. ACE inhibitors are contraindicated in HAE-C1-INH. Use of angiotensin (ATII) receptor blockers can sometimes also increase the number of attacks.

Similarly, attacks can occur at increased frequency in women using estrogen-based hormonal contraceptives or estrogens as hormone replacement therapy [2, 8].

2. Diagnosis

The laboratory diagnostic work-up in the event of clinically suspected HAE-C1-INH should cover the following parameters:

- C1-INH concentration,
- C1-INH activity,
- C4 concentration.

Plasma levels of these parameters are always low in patients with HAE type I. Values of less than 50% of the normal range for C1-INH activity and concentration is proof of a C1-INH deficiency. Very rarely, the plasma concentration of C4 may be normal. In HAE type II, C1-INH activity and C4 are low, whereas the C1-INH concentration is normal or even elevated.

A screening test with just one of these parameters will neither prove nor rule out HAE-C1-INH.

HAE-C1-INH is diagnosed from the following:

- Recurrent peripheral swellings on the skin and/or attacks of abdominal pain, and possibly laryngeal attacks,

- Possible positive family history (negative if the mutations are new, see above),
- Pertinent laboratory test results, i.e. reduced C1-INH activity and/or plasma concentration.

Genetic testing (screening for mutations in the C1-INH gene) is conducted commercially at various genetic laboratories, offering a detection rate of 90% to 95%. If the clinical and laboratory findings are unequivocal, such testing is not necessary. It is strongly recommended, however, in patients in whom a precise diagnosis cannot be made due to contradictory plasma test results.

Since the complement values fluctuate in the first year of life, the three plasma parameters are reliable at the end of the first year of life at the earliest.

Family screening, namely testing blood relatives for the above-mentioned three parameters, is necessary. New mutations (see above) are possible. In such a case, the plasma parameters will be normal in the parents and siblings.

Differential diagnosis includes acquired angioedema due to C1-INH deficiency (no familial occurrence, plasma C1q often reduced, sometimes auto-antibodies to C1-INH present) as well as HAE with normal C1-INH (HAE type III; very rare, almost only ever affecting women, normal C1-INH concentration, C1-INH activity and plasma C4 concentration) and other acquired forms of angioedema [4] that are not attributable to C1-INH deficiency.

3. Treatment

Due to the potential risk of asphyxiation, it is a tremendous responsibility to manage the treatment of a patient with HAE-C1-INH. It is essential that the patient be provided with comprehensive, detailed explanations of the symptoms – especially the initial signs – of laryngeal attacks. The patient must also be given a plan of what to do if these symptoms develop. Similarly, the patient's family should be informed about the disease and the action that needs to be taken. Patients with the disease should be issued with an emergency ID card (see below). Since all of these activities are very important and also time-consuming, it is advisable to utilise the long-standing experience of an HAE treatment center and introduce the patient to such a service. HAE-C1-INH patients are generally

provided with care locally by their general practitioner or non-hospital-based specialist, usually in close cooperation with an HAE treatment center.

3.1. Treatment of acute attacks

3.1.1. Indication

In the treatment of acute attacks of HAE-C1-INH, mild swellings of the hands and feet do not necessarily require treatment – for example if only the backs of the hands are affected. It is wise to treat skin swellings which are extensive or causing functional restrictions, such as swelling of an entire extremity or swelling that is routinely followed by involvement of other parts of the body. Facial swelling from HAE-C1-INH should be treated since it quite often leads to a laryngeal attack. Treatment with antispasmodic suppositories (containing butylscopolammonium bromide) may suffice for mild abdominal attacks. Most abdominal attacks are so painful, however, that treatment with C1-INH concentrate or icatibant will be necessary. Patients with HAE-C1-INH attacks of the head with edema of the pharynx or larynx represent emergency cases due to the risk of asphyxiation and should be hospitalised immediately for treatment and monitoring. Treatment for laryngeal attacks depends on how far the laryngeal attack has progressed. If life-threatening dyspnoea develops, immediate intubation (including fiberoptic) or, in extreme emergency, cricothyrotomy or tracheotomy should be performed. In all cases, immediate treatment with a C1-INH concentrate or icatibant is the pharmacological therapy of choice.

3.1.2. Discontinuation of medication that exacerbates the disease

Estrogens (oral contraceptives, hormone replacement therapy), ACE inhibitors, and sometimes sartans, may increase the frequency and severity of HAE-C1-INH attacks considerably. They should be discontinued and avoided in the future.

3.1.3. Pharmacotherapy for acute attacks

3.1.3.1. C1-inhibitor concentrate

Efficacy: The administration of C1-INH concentrate, i.e. the protein that is genetically missing or not fully functional in the patient, will block the exaggerated kallikrein-kinin cascade in the event of an acute attack (see above).

Human C1-INH concentrate has proved highly effective in the management of acute attacks. Such a concentrate was licensed in Germany in 1979 for intravenous injection under the name *C1-Inaktivator Behringwerke* and since 1985 has been available as a pasteurised, virus-inactivated presentation under the name *C1-Inaktivator Behring*, later changed to *Beriner[®] P* (CSL Behring GmbH, Marburg, Germany) in 2001. More than 30 years' experience has therefore been gained with this concentrate in Germany in the management of acute HAE attacks [3]. Various non-placebo-controlled studies have demonstrated efficacy in the treatment of laryngeal attacks [5, 12], attacks of abdominal pain [14] and skin swelling [21] from HAE-C1-INH. A randomised, double-blind, placebo-controlled study investigating the efficacy of a vapour-heated C1-INH concentrate by the company Baxter/Immuno was published in 1996 [44]. The time to first symptom improvement was 55 minutes in 22 patients with acute HAE attacks at all sites as opposed to 563 minutes in those patients treated with placebo. Despite proof of efficacy, the C1-INH concentrate was removed from the market by Baxter/Immuno in 2003. Within the scope of the marketing authorisation of *Beriner[®]* in the USA, a randomised, double-blind, placebo-controlled study was performed from 2005 to 2007 in 125 patients with HAE type I or II, revealing statistically significant superiority for *Beriner[®]* (20 U/kg BW) over placebo [25]. At the given dosage, the symptoms were alleviated after 30 minutes irrespective of the severity of the facial or abdominal attacks. The goal should be to treat an attack as early as possible [14, 35].

The rapid recurrence of swelling after an injection, known as a rebound phenomenon, has not been observed on treatment with C1-INH concentrate.

In June 2011, the C1-INH concentrate *Cinryze[®]* (ViroPharma Inc., USA) was licensed in Europe for the treatment of acute attacks.

Dosage: In the double-blind study with *Beriner[®]* mentioned above [25], treatment for acute facial and abdominal attacks at a dose of 20 U/kg BW was statistically significantly superior to placebo. Though treatment with 10 U/kg BW was effective compared against placebo, the difference was not statistically significant. In this regard, the outcome of this

study contradicts the practical and published experience gained previously with C1-INH concentrate in thousands of patients, including the patients in the 1996 randomised, double-blind study in the USA [44]. According to these studies, 500 U – or 7.1 mg/kg BW – was very effective in a patient with a body weight of 70 kg in by far the majority of cases. Some of the attacks and patients required 1000 U (14.2 mg/kg BW), but hardly ever any more. In one observational study in 61 patients, 468 cases required 500 U Berinert[®] P, and only nine cases (2%) 1000 U [28]. In other studies, 500 U sufficed to treat effectively 68.6% of the 4834 abdominal attacks in 75 patients [14], 81% of the 2104 cases of skin swelling in 47 patients [21], and 24.9% of the 193 cases of laryngeal oedema in 18 patients [6].

It is not clear why the results of the latest Berinert[®] study contradict all the previous findings. One reason could be the high placebo effect in HAE-C1-INH attacks not treated with Berinert[®], as reported by other studies. The patients with abdominal attacks were hospitalised and the study setting did not reflect that of “everyday life”. The study was partly conducted in the USA, i.e. a country which by that time had no previous experience in the management of acute attacks (except for treatment with fresh frozen plasma). Results from randomised, double-blind, placebo-controlled studies deliver the highest level of evidence. The results of the randomised, double-blind study published in 2009 led to the marketing authorisation of the 20 U/kg BW dose, i.e. 1400 U (almost three vials of Berinert[®]), in Australia, Canada, the USA and many European countries for the treatment of acute attacks in patients with a body weight of 70 kg.

A Berinert[®] dose of 20 U/kg BW should be selected for treatment of laryngeal attacks, since a laryngeal attack in itself is potentially life-threatening. If the attacks HAE-C1-INH are not life-threatening, i.e. they affect the skin or abdomen (which constitute about 99% of acute attacks), it is perfectly justifiable to be guided by the patient’s needs and therefore choose a dose of 500 U or, if this is not sufficient, 1000 U Berinert[®] per attack.

The manufacturer of Cinryze[®] recommends a dose of 1000 U for treatment of an acute attack of HAE-C1-INH.

Safety: The safety profile of C1-INH concentrate (Berinert[®] P) is extraordinarily good. Anaphylactic reactions have been reported in extremely rare cases. In some patients there have been reports of an unexpected increase in disease activity after frequent use of C1-

INH concentrate during long-term therapy [10, 11]. No virus transmission has been reported.

As with all patients receiving plasma derivatives, hepatitis B immunisation (active immunisation) is advisable, especially if multiple doses of C1-INH concentrate are to be administered.

Timing of the injection: Early injection is recommended for acute attacks. An initial improvement is usually seen within 30 to 60 minutes after the intravenous injection.

Self-administration and home treatment: Many patients are now injecting themselves with Berinert[®] or having the injections administered by a close relative, after receiving appropriate training in intravenous injection techniques (home treatment) [37]. Berinert[®] is licensed for home treatment by the Paul Ehrlich Institute. The C1-INH concentrate Cinryze[®] was also licensed for self-administration in Europe in June 2011. The responsibility for home self-treatment remains with the treating physician.

3.1.3.2. Icatibant

Efficacy: Icatibant, also formerly known as HOE-140, was synthesized in 1991. Icatibant is a synthetic decapeptide with a structure similar to bradykinin, but contains five non-proteinogenic amino acids (D-Arg, L-Hyp, L-Thi, D-Tic and L-Oic). It is stable and is not degraded by those enzymes responsible for the degradation of bradykinin, such as carboxypeptidase N (kininase I) and the angiotensin-converting enzyme (ACE or kininase II). By preventing bradykinin from binding to the bradykinin B2 receptor on endothelial cells, it is possible to treat an acute attack of HAE due to C1-INH deficiency. Antagonism of bradykinin is a novel therapeutic approach. A phase II study demonstrated that icatibant was very effective in treating acute attacks of HAE-C1-INH [9]. Two extensive multicenter, randomised, double-blind phase III studies (FAST-1 and FAST-2) likewise found icatibant to be very effective and safe in the treatment of HAE-related skin swelling and abdominal attacks compared to placebo or tranexamic acid [23]. The primary endpoint was not achieved in the FAST-1 study, since significance in the abdominal attacks was inadequate. Icatibant also proved very effective in laryngeal attacks. According to the results of the FAST-1 and FAST-2 studies, swelling recurred six or more hours after the injection (rebound phenomenon) and a second or third injection of icatibant was necessary in about

10% of the treated attacks. Icatibant was authorised in July 2008 in Germany as a symptomatic treatment for acute attacks HAE-C1-INH in adults, under the trade name Firazyr[®] (Shire, UK).

Dosage: Icatibant is injected subcutaneously. One 3 ml vial contains 30 mg icatibant. One vial of Firazyr[®] is usually sufficient. In case of insufficient relief or recurrence of symptoms (see above), a second injection can be administered after six hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection can be administered after a further six hours. No more than three subcutaneous injections of 30 mg icatibant each should be administered in a 24-hour period.

Safety: The safety profile of icatibant, based on experience so far, is good. Short-term erythema, urticaria and burning are very common at the injection site. Systemic side effects include exhaustion and weakness. Pivotal studies observed a rebound phenomenon in 10% of the treated attacks (see above).

Timing of the injection: Early injection is recommended for acute attacks. An initial improvement will mostly be seen within 30 to 60 minutes after the injection.

Self-administration and home treatment: Firazyr[®] has been licensed for self-injection by patients since March 2011. The responsibility for home self-treatment remains with the treating physician.

3.1.3.3. Conestat alfa

Efficacy: Conestat alfa is a recombinant human (rh) C1 inhibitor (Ruconest[™]/Rhucin[®], Pharming Group NV, Netherlands) developed for the treatment of HAE-C1-INH attacks. Recombinant DNA technology is used to produce rhC1-INH in the mammary glands of transgenic rabbits. In clinical studies, rhC1-INH proved to be highly effective in the treatment of acute HAE-C1-INH attacks [45]. Differences in post-translational glycosylation result in a markedly shortened half-life compared to C1-INH in human plasma. Ruconest[™] was licensed in Europe in October 2010 for the treatment of HAE-C1-INH attacks in adults.

Dosage: Ruconest[™] is injected intravenously. According to the manufacturer, adults with a body weight of up to 84 kg are given 50 units/kg BW, and those weighing more receive 4200 units (two vials).

Safety: The most common adverse reaction to Ruconest[™] is headache. Because a healthy volunteer who had not disclosed an allergy to rabbits experienced an anaphylactic reaction after receiving rhC1-INH, the European Medicines Agency decided that, on account of the risk of an allergic reaction, Ruconest[™] is contraindicated in patients with a known or suspected rabbit allergy or positive for immunoglobulin E (IgE) against rabbit allergens. The IgE antibody test should be repeated after ten treatments, but once annually as a minimum.

3.1.3.4. Fresh frozen plasma

Due to its content of C1-INH, fresh frozen plasma is also effective in treating acute attacks of HAE-C1-INH. There have been a number of individual observations, but no controlled studies. In addition to coagulation factors, fresh frozen plasma also contains proteins of the kallikrein-kinin system, meaning that an increased concentration of bradykinin could develop. This could result in a worsening of acute attacks in certain patients [42]. Fresh frozen plasma is not virus-inactivated. Virus-inactivated products are also available, however.

3.1.3.5. Ineffective medications

Corticosteroids, antihistamines, adrenaline and adrenaline derivatives are not effective in the treatment of HAE-C1-INH!

3.1.4. Which medication for an acute attack?

Five medicinal products are now available in Germany: Berinert[®] (C1-INH concentrate), Firazyr[®] (icatibant), Ruconest[™] (recombinant human C1-INH), Cinryze[®] (C1-INH concentrate) and fresh frozen plasma. All are appropriate for treating acute attacks in adults. The strengths and weaknesses of the medications are described above. To date there have been no publications on the experience gained from treating large numbers of patients with Firazyr[®], Ruconest[™] and Cinryze[®] in daily practice. Weighting is not possible,

therefore, on the basis of the data available so far. Fresh frozen plasma should only be used if in an emergency situation Berinert[®], Firazyr[®], Ruconest[™] or Cinryze[®] is not available. Androgens and tranexamic acid are not suitable as treatments for acute attacks due to their delayed onset of effect. Consideration should also be given to cost-effectiveness when selecting an appropriate treatment.

3.1.5. Treatment of acute attacks during pregnancy and lactation

Berinert[®] P is very suitable for treating acute attacks in pregnant and nursing women, as confirmed by several observational studies [26, 38].

The treatment of acute attacks during pregnancy with Firazyr[®] is not recommended at present since there has been insufficient experience with use in humans. It is not known whether Firazyr[®] is excreted in human milk.

3.1.6. Treatment of acute attacks in children

Berinert[®] P is licensed for the treatment of acute attacks in children, who should be given the same dose as adults. Cinryze[®] is authorised for use in adolescents and adults. There are limitations to the use of Firazyr[®] in children and adolescents due to a lack of experience.

3.2. Long-term pharmacological prophylaxis

Treatment for an acute attack should take preference over long-term prophylaxis. Long-term prophylaxis should be considered if attacks are frequent, e.g. if severe attacks occur more than 12 times per year or last for more than 24 days with associated HAE-C1-INH symptoms, despite optimal treatment of the acute attacks.

3.2.1. Attenuated androgens

Androgen derivatives, above all danazol, stanozolol and oxandrolone, can provide successful long-term prophylaxis. The indication for long-term pharmacological prophylaxis must take the risks related to androgens and the personal situation of the patient into account. Androgens are highly effective. A double-blind, randomised, crossover study with

danazol (600 mg/kg) vs placebo demonstrated that danazol decreases the number of attacks significantly (2.2% vs 93.6%) [31]. Such a high dose of danazol is no longer recommended at present, however. In a study published in 2008, 46% of the patients on danazol were entirely free of symptoms or had one or fewer attacks per year [7]. The attacks experienced during danazol treatment were much milder than before or after treatment. Not all patients respond to androgen therapy, and in some patients the efficacy may weaken after a number of years [30].

Attenuated androgens do have adverse effects that should not be underestimated, however. The benefits and risks must therefore be taken into consideration. Weight gain, menstrual disorders and virilisation in female patients, as well as hepatotoxicity, depression and arterial hypertension on long-term use, are particularly common amongst the many other adverse reactions [7, 24, 47]. Hepatocellular adenomas have been reported [16, 18], plus hepatocellular carcinoma in two patients. Regular hepatic function tests as well as ultrasound scans of the liver are necessary, in addition to monitoring for other potential adverse effects [7].

The above-named androgens are not licensed in Germany for HAE-C1-INH so must be sourced from an international pharmacy. Anyone administering androgen treatment to an HAE-C1-INH patient must ensure that the requisite monitoring for adverse effects is also guaranteed.

Particularly frequent attacks (more than one to two per month) or multiple episodes of laryngeal attacks are potential indications for attenuated androgens.

For all the reasons stated, it is advisable to introduce such treatment at an HAE treatment center, also because androgens were in the past often used in the wrong indication and at too high a dose, thereby leading to the respective complications.

Dosage: Danazol: 200 mg or less per day. Individual dose adjustment as far as the lowest possible dose that suffices for suppressing the symptoms.

Contraindications: Pregnancy, lactation, childhood, prostate carcinoma.

3.2.2. Tranexamic acid

Two antifibrinolytic agents have proved effective in HAE-C1-INH: epsilon-aminocaproic acid (EACA) and tranexamic acid. A double-blind, placebo-controlled, crossover study of 16 g EACA daily versus placebo revealed EACA to be significantly effective in four patients [29]. Another placebo-controlled, crossover study of tranexamic acid found HAE-C1-INH to be clearly improved by tranexamic acid in most patients [43]. Tranexamic acid, the tolerability of which is better than that of EACA, has been used since 1972 in the long-term treatment of HAE-C1-INH [1]. The efficacy of tranexamic acid in adults is generally much lower than that of attenuated androgens. Due to milder adverse effects, it is frequently used in children with HAE-C1-INH. Being an antifibrinolytic, the adverse reactions can entail thromboembolic events. Patients with a predisposition to thrombosis should not be treated with tranexamic acid. Colour sense can also be impaired; hence the ocular fundus should be monitored regularly during long-term treatment.

Dosage: The starting dose is 20-50 mg/kg BW up to a maximum of 3 g in adults. The daily dose should be down-titrated to the lowest effective dose.

Contraindications: Pregnancy, renal failure, acute thrombosis or thromboembolic processes. Use is strictly limited if there is a family history of thrombophilia or acute thromboembolic events.

3.2.3. C1-INH concentrate

C1-INH concentrate can also be used for long-term prophylaxis. The first HAE-C1-INH patient to be treated in this way was in 1989, with remarkable success [22]. Further studies demonstrated good results in terms of efficacy and tolerability [10, 36, 44]. The weekly regimen constitutes two doses of 500 U C1-INH concentrate or more. In a double-blind, placebo-controlled, crossover study (22 patients over two 12-week periods), the nano-filtered C1-INH concentrate Cinryze[®] reduced the number of HAE attacks from 12.7 to 6.3 at a dose of two times 1000 U/week [46]. Cinryze[®] was licensed in October 2008 in the USA and in June 2011 in Europe for long-term prophylaxis of HAE-C1-INH.

An increase in disease activity occurs in some patients receiving frequent injections of C1-INH concentrate, including as long-term prophylaxis. This is identifiable from an increase

in the number of attacks, an increased need for C1-INH concentrate and/or the occurrence of rapidly developing, multilocular attacks [10].

4. Prognosis

Until suitable diagnostic and therapeutic options were developed, lethality was high in HAE-C1-INH, reaching 25% to 50% of family members in some families. The cause of death is almost always asphyxiation from a laryngeal attack. Though now very rarely, deaths do still result from this disease [19]. Patients at most risk are those in whom the occurrence of a laryngeal attack is unexpected by them and those around them. If the diagnosis and thus the risk of the disease are known, appropriate precautions can be taken – including detailed information in particular about the disease, but above all about the initial symptoms of attacks, the triggering factors and emergency measures.

Aside from the risk of asphyxiation, the everyday as well as working lives of patients with HAE-C1-INH are often severely adversely affected. Clear improvement can be offered by adequate and effective treatment of the symptoms.

5. Practical recommendations

Every patient with HAE-C1-INH should be provided with an emergency ID card. Such a card (multilingual) can be obtained, for example, from the company CSL Behring GmbH, Philipp-Reis-Str. 2, 65795 Hattersheim, Germany.

Patients with HAE-C1-INH should keep stocks of Berinert® or Firazyr® sufficient for two doses at home as emergency medication and carry it with them when travelling. The nearest hospital should be familiar with the patient and the condition.

In the case of school children, teachers should be informed that acute attacks can develop.

Patients with HAE-C1-INH should be administered 500-1000 U Berinert[®] P one hour prior to dental surgery, including tooth extractions, or other oropharyngeal operations [13]. Cinryze[®] has also been licensed for short-term prophylaxis since June 2011.

6. Patient organization

Patients with hereditary angioedema can find support from the following patient organization:

HAE-Vereinigung e.V.

Lucia Schauf

Mühlenstraße 42 c, 52457 Aldenhoven, Germany

www.hae-online.de

References

1. Blohmé, G. (1972). "Treatment of hereditary angioneurotic oedema with tranexamic acid. A random double-blind cross-over study." Acta Med Scand **192**(4): 293-8.
2. Böckers, M. and K. Bork (1987). "Kontrazeption und Schwangerschaft beim hereditären Angioödem." Dtsch Med Wochenschr **112**(13): 507-9.
3. Bork, K. (2008). "Pasteurized C1 inhibitor concentrate in hereditary angioedema: pharmacology, safety, efficacy and future directions." Expert Review of Clinical Immunology **4**(1; 4): 13-20.
4. Bork, K. (2010). "Recurrent angioedema and the threat of asphyxiation." Dtsch Arztebl Int **107**(23): 408-14.
5. Bork, K. and S. E. Barnstedt (2001). "Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema." Arch Intern Med **161**(5): 714-8.
6. Bork, K. and S. E. Barnstedt (2003). "Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema." J Am Dent Assoc **134**(8): 1088-94.
7. Bork, K., A. Bygum, et al. (2008). "Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients." Ann Allergy Asthma Immunol **100**(2): 153-61.
8. Bork, K., B. Fischer, et al. (2003). "Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy." Am J Med **114**(4): 294-8.
9. Bork, K., J. Frank, et al. (2007). "Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant)." J Allergy Clin Immunol **119**(6): 1497-503.
10. Bork, K. and J. Hardt (2011). "Hereditary Angioedema: Long-Term Treatment with One or More Injections of C1 Inhibitor Concentrate per Week." Int Arch Allergy Immunol **154**(1): 81-88.
11. Bork, K. and J. Hardt (2009). "Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate." Am J Med **122**(8): 780-3.
12. Bork, K., J. Hardt, et al. (2003). "Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to c1 esterase inhibitor deficiency." Arch Intern Med **163**(10): 1229-35.
13. Bork, K., J. Hardt, et al. "Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **112**(1): 58-64.
14. Bork, K., G. Meng, et al. (2005). "Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema." Transfusion **45**(11): 1774-84.

15. Bork, K., G. Meng, et al. (2006). "Hereditary angioedema: new findings concerning symptoms, affected organs, and course." Am J Med **119**(3): 267-74.
16. Bork, K., M. Pitton, et al. (1999). "Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema." Lancet **353**(9158): 1066-7.
17. Bork, K. and N. Ressel (2003). "Sudden upper airway obstruction in patients with hereditary angioedema." Transfus Apheresis Sci **29**(3): 235-8.
18. Bork, K. and V. Schneiders (2002). "Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema." J Hepatol **36**(5): 707-9.
19. Bork, K., K. Siedlecki, et al. (2000). "Asphyxiation by laryngeal edema in patients with hereditary angioedema." Mayo Clin Proc **75**(4): 349-54.
20. Bork, K., P. Staubach, et al. (2006). "Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency." Am J Gastroenterol **101**(3): 619-27.
21. Bork, K., P. Staubach, et al. (2008). "Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema." Allergy **63**(6): 751-7.
22. Bork, K. and G. Witzke (1989). "Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency." J Allergy Clin Immunol **83**(3): 677-82.
23. Cicardi, M., A. Banerji, et al. "Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema." N Engl J Med **363**(6): 532-41.
24. Cicardi, M., R. Castelli, et al. (1997). "Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients." J Allergy Clin Immunol **99**(2): 194-6.
25. Craig, T. J., R. J. Levy, et al. (2009). "Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks." J Allergy Clin Immunol **124**(4): 801-8.
26. Czaller, I., B. Visy, et al. (2010). "The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey." Eur J Obstet Gynecol Reprod Biol **152**(1): 44-9.
27. Donaldson, V. H. and R. R. Evans (1963). "A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase." Am J Med **35**: 37-44.
28. Farkas, H., L. Jakab, et al. (2007). "Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy." J Allergy Clin Immunol **120**(4): 941-7.
29. Frank, M. M., J. S. Sergent, et al. (1972). "Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study." N Engl J Med **286**(15): 808-12.
30. Fust, G., H. Farkas, et al. (2011). "Long-term efficacy of danazol treatment in hereditary angioedema." Eur J Clin Invest **41**(3): 256-62.

31. Gelfand, J. A., R. J. Sherins, et al. (1976). "Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities." N Engl J Med **295**(26): 1444-8.
32. Göring, H. D., K. Bork, et al. (1998). "Untersuchungen zum hereditären Angioödem im deutschsprachigen Raum." Hautarzt **49**(2): 114-22.
33. Gösswein, T., A. Kocot, et al. (2008). "Mutational spectrum of the C1INH (SERPING1) gene in patients with hereditary angioedema." Cytogenet Genome Res **121**(3-4): 181-8.
34. Han, E. D., R. C. MacFarlane, et al. (2002). "Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor." J Clin Invest **109**(8): 1057-63.
35. Kreuz, W., I. Martinez-Saguer, et al. (2009). "C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis." Transfusion **49**(9): 1987-95.
36. Levi, M., G. Choi, et al. (2006). "Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency." J Allergy Clin Immunol **117**(4): 904-8.
37. Longhurst, H. J. and K. Bork (2006). "Hereditary angioedema: causes, manifestations and treatment." Br J Hosp Med (Lond) **67**(12): 654-7.
38. Martinez-Saguer, I., E. Rusicke, et al. (2010). "Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate." Am J Obstet Gynecol **203**(2): 131 e1-7.
39. Nussberger, J., M. Cugno, et al. (1998). "Plasma bradykinin in angio-oedema." Lancet **351**(9117): 1693-7.
40. Nussberger, J., M. Cugno, et al. (1999). "Local bradykinin generation in hereditary angioedema." J Allergy Clin Immunol **104**(6): 1321-2.
41. Pappalardo, E., S. Caccia, et al. (2008). "Mutation screening of C1 inhibitor gene in 108 unrelated families with hereditary angioedema: functional and structural correlates." Mol Immunol **45**(13): 3536-44.
42. Prematta, M., J. G. Gibbs, et al. (2007). "Fresh frozen plasma for the treatment of hereditary angioedema." Ann Allergy Asthma Immunol **98**(4): 383-8.
43. Sheffer, A. L., K. F. Austen, et al. (1972). "Tranexamic acid therapy in hereditary angioneurotic edema." N Engl J Med **287**(9): 452-4.
44. Waytes, A. T., F. S. Rosen, et al. (1996). "Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate." N Engl J Med **334**(25): 1630-4.
45. Zuraw, B., M. Cicardi, et al. (2010). "Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema." J Allergy Clin Immunol **126**(4): 821-827 e14.

46. Zuraw, B. L., P. J. Busse, et al. (2010). "Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema." N Engl J Med **363**(6): 513-22.
47. Zurlo, J. J. and M. M. Frank (1990). "The long-term safety of danazol in women with hereditary angioedema." Fertil Steril **54**(1): 64-72.

German Guidelines for Hereditary Angioedema due to C1-INH Deficiency

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Participating associations

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- German Society of Internal Medicine (DGIM e.V.) (Dr. Emel Aygören-Pürsün)
- German Society for Oto-Rhino-Laryngology (PD Dr. Murat Bas)
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